


(With D. Potter.)


II. Alveolar (Lobar) Pneumonia. Page 83.
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(With H. J. R. Kirkpatrick and W. S. Craig.)

A case of sagittal sinus thrombosis and subdural abscess following nasal sinusitis. 1935. J. Laryngol. and Otol. 1, 600.
(With A. Brownlee Smith.)


(With W. A. Alexander.)
Tuberculosis of the central nervous system, with special reference to tuberculous meningitis. 1937. J. Path. and Bact. xlv, 613.

(With C. A. Green.)


(With W. C. Wilson and C. P. Stewart.)
A STUDY OF TUBERCULOSIS IN CHILDHOOD, BASED UPON A REVIEW OF FORTY-TWO POST-MORTEM CASES.

By AGNES R. MACGREGOR, M.B., Ch.B., Assistant to the Professor of Pathology, University of Edinburgh; Pathologist to the Royal Edinburgh Hospital for Sick Children.

The material upon which this study is based was derived from a series of autopsies performed by the writer at the Royal Edinburgh Hospital for Sick Children, during the period between July 1922 and December 1924. The cases are not strictly consecutive, as there were several periods of absence, the cases occurring during which were not included; but as they are entirely unselected, they have the same value as consecutive cases.

During the period under review, 194 post-mortem examinations were performed in the hospital. All of the cases were children under 12 years of age. Approximately one-half of them were under 1 year. All except 17 were under 5 years.

Tuberculous lesions were found in 42 of the 194 cases, or 22 per cent. The ages of the tuberculous children ranged from 4 months to 10 years, the average age being 2 years and 9 months; 7 were under 1 year, 4 over 5 years, and 31 between 1 and 5 years of age.

Death was due to tuberculosis in 33 of the 194 cases, or 17 per cent. Of the 9 tuberculous cases in which death was due to other causes, 3 were under treatment for tuberculosis in glands or bone, at the time of death. Thus there were only 6 cases, or 3 per cent., in which unsuspected tubercle was found at autopsy. This figure must not be accepted as indisputably accurate, as minute tuberculous lesions might have been over-
looked, exhaustive microscopic examination not having been made in all cases. Yet, gross lesions would certainly have been found, had they been present; and the small number of these young children in whom undeclared tuberculosis was found after death, is in striking contrast to the frequency of such lesions in older subjects. Further reference is made to this question later.

Tuberculosis is pre-eminently a focal infection, the bacilli being established in the body in certain localised areas, most commonly in one or more groups of lymphatic glands, or in the lungs, bones, or other sites. From the primary focus, infection spreads at a subsequent date, by various channels, and manifests itself in new situations by the formation of fresh foci. Tuberculosis practically never takes the form of a general infection, in the sense in which streptococcal septicæmia is a general infection. Although the bacilli may be transported by the blood stream, their survival and multiplication in the body are apparently dependent upon their ability to establish themselves in foci. Otherwise they perish, or are excreted. Nor is tuberculosis commonly a general infection, even in the sense that every tissue and organ in the body is invaded by foci; for certain tissues, notably muscle, are notoriously immune from this invasion. The term “general tuberculosis” must therefore be recognised as a relative term, used to denote a widespread dissemination of foci, and not a general infection in the strict sense.

It is a well-recognised fact, that in children the lymphatic glands are peculiarly prone to form a nidus for the development, and a centre for the dissemination, of tuberculous infection. In every case in the present series, lesions were found in one or other of the three principal groups of lymphatic glands (cervical, thoracic, mesenteric), which were probably the primary, and certainly the most advanced, lesions in the body.

The tendency to extension from the primary focus varies with each site. The first object of this study is to assess the risks, and the nature, of dissemination of infection from the three principal groups of lymphatic glands.

In the tables which follow, the percentages are given as the most convenient means of comparison, although it is recognised that the practice of reckoning in percentages, when relatively small numbers of cases are being considered, is apt to be misleading.
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In the 42 cases of tuberculosis, the distribution of advanced lesions in the three groups of glands was as follows:—

<table>
<thead>
<tr>
<th>Group</th>
<th>Total cases</th>
<th>Fatal cases</th>
<th>Per cent. fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical glands</td>
<td>2 cases</td>
<td>1</td>
<td>50.0</td>
</tr>
<tr>
<td>Thoracic glands</td>
<td>21 cases</td>
<td>19</td>
<td>90.5</td>
</tr>
<tr>
<td>Mesenteric glands</td>
<td>22 cases</td>
<td>16</td>
<td>73.0</td>
</tr>
</tbody>
</table>

In 3 of the cases advanced caseous lesions were found in more than one group, thus:—

- In cervical and thoracic, equally. 1 case
- In thoracic and mesenteric, thoracic older. 1 case
- In thoracic and mesenteric, mesenteric older. 1 case

When the 33 fatal cases only are considered, the distribution of advanced lesions in the three groups is found to be as follows:—

<table>
<thead>
<tr>
<th>Group</th>
<th>Total cases</th>
<th>Fatal cases</th>
<th>Per cent. fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical glands</td>
<td>1 case</td>
<td>3</td>
<td>3 per cent.</td>
</tr>
<tr>
<td>Thoracic glands</td>
<td>19 cases</td>
<td>19</td>
<td>58</td>
</tr>
<tr>
<td>Mesenteric glands</td>
<td>16 cases</td>
<td>16</td>
<td>49</td>
</tr>
</tbody>
</table>

Consideration of the proportion of cases with advanced caseateion in the various gland groups, which terminated in fatal tuberculosis, gives the following results:—

- Acute miliary tuberculosis and meningitis. 21 cases
- Pulmonary, without generalisation. 1 case
- Peritonitis. 7 cases
- Intestinal. 4 cases

The very large proportion of the cases to come under the heading of miliary tuberculosis and meningitis (50 per cent. of the total, and 65.5 per cent. of the fatal), brings out clearly a notable characteristic of tuberculosis in early life, namely, a strong tendency for extension to be widespread by the blood stream, and to assume this acute and rapidly fatal form, which is much less common in adults.

In the 21 cases of acute miliary tuberculosis and meningitis,
advanced caseous lesions were found in the glands as indicated below. This table is intended only as a comparison between the three groups of glands, and no indication is given as to the presence or absence of advanced lesions elsewhere, for example in lungs, intestine, or peritoneum.

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced lesions in thoracic glands</td>
<td>18</td>
<td>86</td>
</tr>
<tr>
<td>Most advanced lesions in thoracic glands</td>
<td>16</td>
<td>76</td>
</tr>
<tr>
<td>Advanced lesions in thoracic glands only</td>
<td>15</td>
<td>71</td>
</tr>
<tr>
<td>Advanced lesions in mesenteric glands</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>Most advanced lesions in mesenteric glands</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Advanced lesions in mesenteric glands only</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Advanced lesions in cervical glands</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Most advanced lesions in cervical glands</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Advanced lesions in cervical glands only</td>
<td>0</td>
<td>...</td>
</tr>
</tbody>
</table>

Consideration of the proportion of cases with advanced caseation in the various gland groups, which fall into the category of acute miliary tuberculosis and meningitis, gives the following results:

<table>
<thead>
<tr>
<th>Group</th>
<th>Total cases</th>
<th>Meningitis</th>
<th>Per cent. meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>2</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Thoracic</td>
<td>21</td>
<td>18</td>
<td>86</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>22</td>
<td>5</td>
<td>23</td>
</tr>
</tbody>
</table>

From these figures emerges the striking fact that, in this series, acute miliary tuberculosis and meningitis were very much more often associated with advanced caseation in the thoracic glands, than in any other group. The conspicuous position occupied by the thoracic group in both the foregoing tables is even more remarkable, when it is noted that the one cervical, and two of the mesenteric cases, which became generalised, had associated advanced caseation in the thoracic glands. Thus it appears that in only 3 of 21 cases did miliary tuberculosis occur without the presence of advanced caseous lesions in the thoracic glands; and in only 3 of 21 cases in which caseous thoracic glands were present, did miliary tuberculosis fail to occur.

A very pronounced tendency for the infection to become widely disseminated by the blood stream when the thoracic glands are extensively caseous, is thus brought out in a most striking manner. In the abdominal group, only 3 of 20 cases in which caseation of thoracic glands was not associated
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with the mesenteric lesions, became thus disseminated; and in the cervical group, none.

The following brief summary of the 21 thoracic cases emphasises further the fatal character of these lesions, and the constancy with which the disease extended beyond the primary nidus in the thoracic glands.

<table>
<thead>
<tr>
<th>Fatal Cases</th>
<th>No.</th>
<th>Per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miliary and meningitis</td>
<td>18</td>
<td>86.0</td>
</tr>
<tr>
<td>Pulmonary, without general</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>90.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-fatal Cases</th>
<th>No.</th>
<th>Per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>With tubercle in lungs</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>With tubercle in bone</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>In glands only</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>9.5</td>
</tr>
</tbody>
</table>

In seeking an explanation of this difference between the thoracic and other groups of lymphatic glands, two obvious possibilities have first to be considered. In the first place, owing to their connection with the respiratory tract, the thoracic glands are infected with the human type of tubercle bacillus in the majority of cases. In the present series the bacilli were not typed; but in cases investigated by other workers, notably in a large number collected by C. Y. Wang, the predominance of the human type in tuberculosis of the thoracic glands is amply demonstrated; whereas cervical cases are frequently, and mesenteric cases usually, bovine. It is possible that, owing to higher virulence, the human bacillus is more liable to extend by the blood stream, and to cause miliary tuberculosis and meningitis, than is the case with the bovine bacillus; that is to say, that human infections in any situation would generalise more readily than bovine in the same situation. Wang's work certainly shows that the great majority of cases of tuberculous meningitis and generalised tuberculosis are caused by the human bacillus. But the explanation suggested above is purely hypothetical, and unsatisfactorily vague, and would be difficult to prove with any degree of certainty. A second, and perhaps more satisfactory explanation of the frequency with which thoracic gland tuberculosis extends in this way, is found in the close relationship of these glands to the lungs, the frequency of associated pulmonary lesions, and the liability of these pulmonary lesions to be the source
of heavy infection of the blood. On this view, the predominance of human infection in miliary tuberculosis would be explained by the fact that the human bacilli, being usually inhaled, gain access more readily than the bovine, to the danger spot in the thorax.

With this possibility in view, the cases of the present series were reviewed with the object of determining the frequency, and the nature, of associated pulmonary lesions.

Of 21 cases with caseous thoracic glands, tuberculous lesions were found in the lungs in 20 (95 per cent.). It was thus found to be very rare for advanced tubercle to exist in the thoracic glands without infection of the lungs taking place. The chronological relationship of the pulmonary and glandular lesions is discussed later.

On examination of the 18 cases of miliary tuberculosis with caseous thoracic glands, it was found that pulmonary lesions, obviously preceding the terminal blood-spread infection, were present in 14, or 78 per cent. These lesions took the form of more or less large caseous foci (8), cavities (2), tuberculous bronchopneumonia (2), or obvious lymphatic extension from the glands (10). This observation suggests that the formation of tuberculous foci in the lungs is an important, but not an essential, step in the progress of the disease towards generalisation of the infection by the blood stream. Further reference to other problems in connection with the relationship between pulmonary and glandular lesions, and blood infection, is made later.

In view of the old-established controversy as to whether the disease develops first in the thoracic glands or in the lungs, the cases were reviewed to determine in what proportion lesions were found in the lungs, which appeared to be as old as, or older than, those in the thoracic glands. Such lesions took the form of caseous nodules of some size and standing, and cavities with formed walls.

Of 21 cases with caseous thoracic glands, lesions of this type were found in the lungs in 13, or 62 per cent. In none of these was the pulmonary lesion obviously older than the glandular. In the remaining 8 cases (38 per cent.) pulmonary lesions, when present, were obviously secondary to the glandular; taking the form of a very recent, blood-spread infection, part of the terminal miliary tuberculosis, in 4 cases; recent lymphatic spread tubercles in 3; and being entirely absent in 1.
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It would appear, therefore, that in this series, infection of the thoracic glands not infrequently preceded infection of the lungs; while primary infection of the lungs was possible in nearly two-thirds of the cases, but was proved in none.

A further observation which perhaps supports the view that infection of the thoracic glands very often preceded infection of the lungs, is that, in most of the cases in this series, the greatest enlargement, and the most complete caseation, were found in the glands related to the bifurcation of the trachea, and not in the root glands, as might naturally be expected, were the infection of the glands usually secondary to foci in the lungs.

With regard to the mode of infection of the thoracic glands in cases where the primary lesion is clearly not in the lungs, there are several possibilities. The two most obvious and most generally accepted are:

1. By inhalation of the bacilli into the trachea or larger bronchi, and their passage by way of lymphatic channels to the tracheo-bronchial glands.

2. By way of the cervical glands, from an infection entering by the tonsils, or elsewhere in the pharynx.

Infections occurring by the first route would be mostly, if not all, of human type. Those occurring by the second might be either human or bovine. The fact, stated above, that the human bacillus is found much more often than the bovine in this type of case, suggests the first route as probably the more common. But the second cannot be excluded, and may be of great importance.

The cases were therefore reviewed to determine the frequency with which lesions were present in the cervical glands, in the 21 cases with caseous thoracic glands.

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>No. of cases</th>
<th>Per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete caseation with gross enlargement</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Discrete caseous tubercles</td>
<td>5</td>
<td>...</td>
</tr>
<tr>
<td>Grey miliary tubercles only</td>
<td>2</td>
<td>...</td>
</tr>
<tr>
<td>Total with lesions</td>
<td>8</td>
<td>38</td>
</tr>
<tr>
<td>Without lesions</td>
<td>13</td>
<td>62</td>
</tr>
</tbody>
</table>

Most of the 13 negative cases were examined microscopically, the tonsils being included in the examination. Macroscopic tubercle was never found in the tonsils, but in all cases with visible involvement of cervical glands, in which the tonsils were examined microscopically, small tubercles were found.

In all the cases, except one, in which lesions were found...
in the cervical glands, these lesions were much less advanced than those in the thoracic glands. This is capable of interpretation in two ways.

1. That tuberculous infection of the thoracic glands occurs usually independently of the cervical glands, as already suggested.

2. That tubercle bacilli are liable to pass through the tonsils and cervical glands, forming either no lesions at all, or only small foci, without conspicuous enlargement, and produce their principal disturbance in the thoracic glands.

By typing the bacilli, an estimate might be formed of the probabilities as between these two, but as this was not done in the present series, no statement can be made upon this subject. Yet it appears not unlikely that, in certain of the cases in which microscopic tubercles were found in the tonsils, and small caseous foci, with or without minor, almost negligible, enlargement, in the cervical glands, the second interpretation may be the correct one.

Another important point which emerges from the study of the cervical lesions in this series, is the remarkable rarity of generalised infection in children with obviously enlarged and caseous cervical glands. There was only one such case in this series, and in it there was associated caseation of the thoracic glands. The inconspicuous part played by the cervical glands in this series is the more remarkable, considering the excessive prevalence of tuberculous cervical lymphadenitis among Edinburgh children. It would appear, therefore, that the greatest risk of general dissemination of the infection exists, not when the cervical glands react, and become enlarged and obviously tuberculous, but in cases in which these glands fail to arrest the infection, and allow it to pass through to the thoracic glands, a position from which generalisation is very much more liable to occur.

There is, however, a third possible route by which tuberculous infection may reach the thoracic glands. The glands of the tracheo-bronchial group are regional glands of the lungs. They may therefore be said to be regional glands of the pulmonary circulation, and thereby occupy a unique relation to the general blood circulation. They are for that reason exposed to infection by organisms borne by the blood stream, to a greater extent than the glands of any other group. It is possible, therefore, that the thoracic glands may be the site of
primary foci formed by bacilli which have been brought in the blood to the lungs, from a portal of entry anywhere in the body. These, filtered out of the circulation, probably in most cases without forming any foci in the lungs, are carried in lymphatic vessels to the tracheo-bronchial glands.

This special relation of the thoracic glands to the circulation is interesting and suggestive, in view of the frequency with which wide extension by the blood occurs, when these glands are the principal site of infection. The possibility cannot be altogether ignored, that the very fact that these glands are infected, may indicate, in certain cases, a peculiar liability, dependent upon factors at present beyond our knowledge, for the bacilli to invade and travel by the circulation, as soon as they enter the body. Assuming the infection from the outside to occur repeatedly, and more or less continuously—as must happen when a child is taking milk infected with virulent bacilli, or associating with a person suffering from phthisis—the bacilli would be at first arrested in the lungs, transferred to the pulmonary glands, and thereby prevented from further dissemination by the blood. At a later stage, after the lymphatic apparatus had been damaged by disease, this arrest would no longer occur, and infection would be permitted to pass to the systemic circulation.

From this it would follow that, in the absence of disease of the thoracic glands, impairing the defensive power of the lungs, a much more massive infection of the blood would be required to set up widespread miliary tuberculosis, than would be the case in the presence of such disease. This may explain the comparative infrequency of miliary extension from caseous cervical and abdominal glands, in the absence of disease in the thoracic group. Further, on similar grounds, it would follow that foci would be much more easily established in the lungs when the pulmonary lymphatic apparatus is disabled by tuberculous disease in the glands, than when this most important defensive mechanism is in full health and efficiency. This would be equally true by whatever route the infection might reach the lungs, whether by direct inhalation, by "retrograde" lymphatic extension from the larger bronchi, or by any other possible path. This may explain the frequency with which infection of the glands appears to precede the formation of foci in the lungs. Both these suggestions receive some support from the observations on this series, already recorded; but the
number of cases is not sufficient to justify the drawing of positive conclusions.

Full discussion of the many problems which arise in this connection, is beyond the scope of this paper; but the whole question is one which merits investigation, and which it is hoped to make the subject of further study in the future.

The hypothesis that primary foci of tuberculous infection may be formed by bacilli carried to the primary site by the blood, is at variance with the more generally accepted view, which holds that the primary focus is formed at or near the site of entry of the bacilli, and that invasion of the blood is always secondary. But this less orthodox view received strong support from the work of Ribbert and Calmette, and it may explain some of the many mysteries met with in the study of the distribution of tuberculous lesions.

Localised foci, which may be the only tuberculous lesions in the body, are not infrequently found in situations to which access can have been gained only by means of the circulation. Familiar examples are foci in bones; tuberculoma of the brain; primary renal tuberculosis, and tuberculous epididymitis, which are said to be blood borne infections. Perhaps more remarkable was a case, seen by the writer, of tuberculous meningitis in a child of three years, in which, not only was no old-standing lesion found as a source of the infection, but, in spite of exhaustive search, both at the post-mortem and with the microscope, not a sign of any tuberculous focus of any kind was found anywhere in the body, except in the meninges. There seems to be no feasible explanation, except that in this case the initial infection entered the blood straightway, and localised itself first and only in the meninges.

The whole question of blood borne infection in tuberculosis is one of great interest and complexity. Bacilli, in all probability, enter the circulation much more frequently than is commonly supposed. In addition to the possibility of blood transport of the initial infection to the site of the primary focus, there is a strong probability that invasion of the blood stream occurs, more or less continuously, in all cases in which active tuberculous lesions are present. It is, indeed, difficult to understand how this can fail to be so, where, for example, active foci in lymphatic glands must surely be discharging virulent bacilli constantly into their efferent vessels, and so, via the thoracic duct, into the circulation, in addition to the risk of invasion of veins at
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the site of the foci. Everyone who has studied the subject must be familiar with the fact that, in cases of pulmonary tuberculosis in adults, which have never assumed the "miliary" form, a few scattered foci are found, almost constantly, in the liver and spleen, and perhaps elsewhere, which are obviously blood borne, and which are usually, quite evidently, of various ages. Further examples of limited blood infection are found in those cases of tuberculoma of the brain, bone, and genito-urinary tuberculosis, in which the apparent primary site is in lymphatic glands far removed from the solitary secondary foci.

Although in the present series of cases, dissemination by the blood tended usually to be widespread and fatal, evidence was found in certain cases, of limited extension by the blood having occurred at some stage of the disease. In 3 cases of miliary tuberculosis there were caseous masses in the brain, obviously much older than the miliary foci formed by the terminal spread; and in several similar cases, caseous tubercles, older than the general miliary foci, existed in liver and spleen. The one case of pulmonary tuberculosis, without meningitis, or miliary tuberculosis in the usual sense, showed a small number of tubercles in the liver and spleen. There was one case of tuberculous osteomyelitis of the humerus, with caseous thoracic glands, which probably comes into this category. In several of the abdominal cases, tubercles, apparently, though perhaps not certainly, blood-spread, were found in the liver and spleen, and in one case in the kidneys, though there was no blood-spread extension beyond the abdomen. One of the cases of meningitis was an interesting example of limited extension by the blood, though in this case it was fatal, there being, in addition to the meningitis, caseous mesenteric glands, and no tubercles detectable either macroscopically or microscopically, in any other organ.

The small number of examples of blood extension which remained strictly limited in its distribution, obtainable in this series, is probably due to the very tender age of the majority of the patients, any tuberculous infection which occurs at this age tending towards a wide and fatal extension. In older children and adults far more numerous examples are found. Thus, although in this series the fatal extensions are necessarily conspicuous, even greater interest attaches to the question of limited and non-fatal extensions by the blood stream, and the factors determining their limitations. On this subject, and on
Agnes R. Macgregor

the general question of the relation of the circulation to the distribution of tuberculous infection, it is hoped to publish further observations at a later date.

Abdominal Cases.—There were in the series 22 cases with advanced caseation in the mesenteric glands. Of these, 16 were fatal from tuberculosis, or 73 per cent. The fatal cases were as follows:—

<table>
<thead>
<tr>
<th>Disease</th>
<th>No.</th>
<th>Per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miliary tuberculosis and meningitis</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>Intestinal</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16</td>
<td>73</td>
</tr>
</tbody>
</table>

Of the 5 cases of meningitis, 2 had associated caseous thoracic glands, in one of which the thoracic lesions were obviously older. Thus only 4 of 21 cases of miliary tuberculosis and meningitis, or 19 per cent., were primary in the abdomen, and only 3 of these occurred without preliminary spread to the thoracic glands.

In 2 of these 5 cases intestinal ulcers were present, but in only one did they appear to be other than very recent. The other 3 showed no lesions in the bowel, and general tuberculous peritonitis was present in none of the five.

Of the cases of peritonitis, 5 were of the dry type, with dense, universal adhesions; 2 of the ascitic type. Intestinal ulceration was demonstrated in 5 of the 7. In none of these 7 cases, and in none of the 4 cases of intestinal ulceration without general involvement of the peritoneum, was evidence found of any spread of the infection by the blood stream beyond the abdomen, though in 4 of the cases of peritonitis the pleuræ were involved by a lymphatic extension through the diaphragm.

Six cases occurred in which the mesenteric glands were caseous, and no tuberculous lesions were found anywhere else in the body, except, in one case, one caseous cervical gland.

A summary of the 22 mesenteric cases is given below.

<table>
<thead>
<tr>
<th>Disease</th>
<th>No.</th>
<th>Per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatal Cases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miliary and meningitis</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>Intestinal</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16</td>
<td>73</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>No.</th>
<th>Per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>With tubercles in cervical gland</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>In mesenteric glands only</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6</td>
<td>27</td>
</tr>
</tbody>
</table>

It appears from this study that tuberculosis of mesenteric glands tends chiefly to spread by the lymphatic system, locally
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in the abdomen, and extends by the blood stream much less constantly than does tuberculosis of thoracic glands. The chance of the infection remaining confined to the mesenteric glands is much greater than in the case of the thoracic group.

Healed Tubercle in Children.—In view of the frequency with which calcified foci, indicating healed tubercle, are met with in autopsies on adults, it is interesting to note the incidence of calcified tubercles in young children. In the present series, such foci were found in 3 cases, viz.:

- Mediastinal glands and lungs . . 1 case, aged 4 years.
- Mesenteric glands . . . 2 cases, aged 4 and 5 years.

In one other case mesenteric glands, which were the only tuberculous lesions found in the body, were partially fibrosed, and appeared to be quiescent.

The rarity of even partially healed tubercle in this series, compared with its frequent occurrence in adults, is an impressive indication of the inability of the tissues of young children successfully to combat the disease, if infection occur. In the whole series of cases in which tuberculous infection was proved to have occurred, the lesions were obviously active in over 90 per cent., and actually fatal in 76.5 per cent. It would appear from these observations, and from the fact that only once in 194 post-mortems were tuberculous lesions found in the lungs of a child not dead from tuberculosis, that the foci which give rise to those apical scars and other evidences of healed tubercle found so frequently in adult lungs, result from infection acquired in most instances at an age later than that of the majority of these cases.

Nutritional and Degenerative Effects.—An important aspect of tuberculosis, which is apt to receive less attention than it deserves from pathologists, and perhaps also from clinicians, is the toxæmic element, which must always be present in greater or less degree, when active tuberculous lesions exist. Its importance hardly requires emphasis, if it be realised that, in the majority of adult patients suffering from tuberculosis, most of the symptoms, and the fatal issue, when it occurs, are due, not to the direct effects of the presence of tuberculous lesions in the body, but to the absorption of toxins therefrom, which cause wasting, muscular weakness and atrophy, and all the complex phenomena of failing metabolism, known as cachexia.

From the standpoint of the morbid anatomist, the most obvious evidence of this toxic action is found in the state of
general nutrition, and in the presence of degenerative changes in the organs, of which the most conspicuous and characteristic is fatty change in the liver. With a view to determining the part played by the toxæmic element in tuberculosis of childhood, a study was made of the state of nutrition in the present series of cases, and the presence and extent of degenerative changes in the organs, with particular attention to fatty change in the liver.

In the group of cases of meningitis, nutrition was good or fair in 8 of the 21 cases. Pronounced emaciation was present in 9; slight emaciation in 4. It is doubtful whether, in cases of meningitis, emaciation can legitimately be attributed entirely to general toxic action. Wasting occurs rapidly after the onset of meningeal symptoms, and is probably in large part due to trophic disturbances consequent upon meningitis, and to the persistent vomiting which is an almost constant feature. Emaciation was always most pronounced, however, in those cases in which there was a history of ill health for some time preceding the onset of meningitis, and in which there was post-mortem evidence of a considerable extension of the disease before the terminal phase.

Degenerative changes in the liver were absent or slight in 16 of the 21 cases, pronounced in 4, and extreme in 1. This case is referred to again below. When present, the fatty change corresponded in degree fairly accurately to the severity of emaciation.

In the abdominal cases, nutritional and degenerative changes were more conspicuous. In only 2 of the 7 cases of peritonitis was the general nutrition other than extremely poor. One of these two died from acute intestinal obstruction, the other from perforation of an ulcer and acute peritonitis; so that in both death may be said to have occurred accidentally, as it were, before the disease had evolved to its natural termination. Fatty change in the liver was more or less in proportion to the degree of emaciation, and was very striking in most cases.

The cases of intestinal ulceration, without generalised peritonitis, were very similar in this respect, severe emaciation, and extreme fatty change being present in 3 of the 4 cases, and a moderate degree of both in the fourth.

The degree of fatty change found in the liver in these abdominal cases was remarkable. Nothing comparable to it was ever seen in any of the autopsies on cases dead from
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diseases other than tuberculosis; and the only case of tuberculous meningitis which showed the extreme fatty change so common in the purely abdominal cases, was one with chronic ulcers in the bowel and caseous mesenteric glands.

It appears, therefore, that nutritional and degenerative changes attributable to the action of tuberculous toxins, were most constant and most severe in the abdominal cases. This is doubtless due to the longer course run by this form of tuberculosis, and also to the large area from which absorption of toxins takes place in cases of peritonitis; while the anatomical connection between the area of toxic absorption in abdominal tuberculosis, and the liver, through the portal vein, must also play an important part in the causation of the degenerative changes in that organ, which were so conspicuous in this series.

Cases which end with meningitis are cut short relatively early in the course of the disease, because foci are formed in a situation in which they are directly and fatally dangerous to life. It is only when this fatal extension occurs relatively late in such cases, that the toxæmic element becomes really conspicuous; and only when the extension of the foci of infection is not in itself fatal, that the toxæmic factor assumes in children the rôle which it plays in the majority of adult cases, and appears as the actual and direct cause of death.

In this series, the actual cause of death being meningitis in 21 cases, while 4 of the abdominal cases died as a result of accidents in the course of the disease, such as perforation of ulcers, and acute intestinal obstruction (each in 2 cases), death can be attributed directly to the general effects of the tuberculous toxins in only a small number of the patients. This fact again emphasises the more active and deadly character of the actual tuberculous lesions in young children, as compared with adults. Nevertheless, the toxæmic element is far from being inconspicuous, and must be recognised as being of the utmost importance.

Conclusions.—1. In this series, a great majority of the cases of acute miliary tuberculosis and meningitis showed advanced caseous tuberculosis in the thoracic glands.

2. A great majority of the cases with advanced caseous tuberculosis in the thoracic glands terminated with miliary tuberculosis.

3. The association of acute miliary tuberculosis with advanced caseous tuberculosis in other groups of lymphatic glands was
much less frequent and constant than in the case of the thoracic group.
4. Almost all cases with advanced caseous tuberculosis of the thoracic glands had associated pulmonary lesions. The pulmonary lesions may be frequently the source of the miliary extension.
5. Infection of the thoracic glands preceded infection of the lungs, certainly in over one-third of the cases, and probably more often. Infection of the lungs was never found to be obviously of longer standing than that of the thoracic glands.
6. The probability of infection of the thoracic from the cervical glands is discussed.
7. In this series, acute miliary tuberculosis was very seldom associated with advanced caseous tuberculosis of the cervical glands.
8. In cases where the infection enters the circulation prior to the formation of foci, the thoracic glands would be liable to be the site of the primary lesions.
9. There is evidence in support of the view that disablement of the pulmonary lymphatic apparatus is of great importance as a preliminary both to the formation of foci in the lungs, and to the passage of blood-borne bacilli from elsewhere in the body through the lungs into the general circulation.
10. Blood-borne extensions in young children tend to be widespread and fatal, but there is evidence that limited extension by the blood stream is of frequent occurrence.
11. Caseous tuberculosis in the mesenteric glands was relatively seldom associated with acute miliary tuberculosis but tended rather to spread locally in the abdomen, or to remain confined to the glands.
12. Calcified tubercles were rarely found in this series. The evidence derived from this study indicates that, when tuberculous infection occurs in young children, the lesions usually assume an active, and often a fatal, character.
13. Toxaemic manifestations in tuberculosis are of great importance, but are the actual cause of death in children less often than in adults.
14. Nutritional and degenerative changes, due to general toxic action, were most constant and most severe in the abdominal cases.

CASES OF CONGENITAL CARDIAC DEFECT IN CHILDREN.

By AGNES R. MACGREGOR, M.B. Ch.B., from the Royal Hospital for Sick Children, Edinburgh.

CONGENITAL malformations of the heart are of great interest from the standpoint of the embryologist, because often, by the study of deviations from the normal, light is thrown upon the problems of development. They are of no less interest to the clinician, in view of the fact that numerous cases have been reported of persons living for weeks, months, or years, with very extreme developmental defects of the heart. Sometimes, moreover, the recognition of the presence of cardiac malformations is less easy than might be expected; while a diagnosis of the exact condition is seldom arrived at with any certainty.

Within recent months, three examples of somewhat rare congenital cardiac abnormalities have come to my notice. The first of these is described below. For permission to publish the case, and for the use of the clinical record, I am indebted to Dr Norman Carmichael.

CASE I.—E. F., an illegitimate female child, aged 3 weeks, was brought to the Royal Hospital for Sick Children on 27th June 1923, by a woman in whose charge it had been left, five days previously, by the mother, who told her that the baby was a normal, healthy child. The woman stated that she had thought it looked slightly blue at times, but that it had been perfectly well until the morning of admission, when it had a "fit." It became almost black, and gasped for breath; and she brought it to hospital at once.

On admission, the child was small, but adequately nourished. There was extreme cyanosis; breathing was difficult, gasping, and rapid; pulse feeble; temperature 100° F. The heart was thought to be enlarged. There were no audible murmurs. The child responded to treatment with stimulants. The breathing soon became easier, and cyanosis decreased gradually. By evening the colour was normal.

For three or four days the condition remained fairly satisfactory. Occasionally the face and lips became cyanosed, but there was no attack as severe as that on the day of admission. In the intervals, the colour was fairly good. On 2nd July, however, there was an
attack similar to the first. Response to treatment was again good, and all symptoms passed off in three hours. The following day there was a third attack, which proved fatal.

Post-mortem Report.—Apart from the presence of a small quantity of clear, serous fluid in both pleural sacs, and some enlargement and congestion of the liver, nothing of pathological interest was found in the body, except in the heart. There were no other congenital malformations.

Description of the Heart.—The heart was much enlarged, but was normally situated. The enlargement was mainly due to increase in the size of the right ventricle. This chamber was both hypertrophied and dilated. From it arose the aorta. The aortic valve had three well-formed cusps, two anterior, one posterior. The right coronary artery arose from the posterior sinus, passed forward between the aorta and the right auricular appendix, and pursued its usual course. The left coronary artery arose from the left anterior sinus, and divided at once into its two branches, which were distributed in the usual manner. The aorta, which was of normal calibre, passed almost vertically upwards to the arch, anterior to, and to the right of, the pulmonary artery, and, turning backwards and to the left, descended in its usual position. Its branches were given off in normal sequence and position.

The cavity of the left ventricle was considerably smaller than that of the right, but its walls were of much the same thickness. From it arose the pulmonary artery. The pulmonary valve had three perfect cusps, one anterior, two posterior. The pulmonary artery, which was of normal calibre, passed vertically upwards, posterior to, and to the left of, the aorta, and at a distance of 1.5 cm. above the valve, divided into its right and left branches, the right passing beneath the aortic arch. The pulmonary artery and aorta were thus placed parallel to each other, and did not cross, as is normally the case. The ductus arteriosus was patent, admitting a large probe, and was placed in its usual position, arising from the left pulmonary artery, immediately after the bifurcation, and entering the lower aspect of the aortic arch distal to the origin of the great arteries of the neck.

The tricuspid and mitral valves were normal, and the interventricular septum was complete.

The great veins were found in their normal positions, the vena cavae entering the right atrium, and the four pulmonary veins the left. Neither atrium showed either hypertrophy or dilatation to any important extent. The foramen ovale was patent. The aperture, though not very wide, was not of a valvular character, and was filled with post-mortem blood clot, which passed through it from one atrium to the other.
Transposition of the primary vessels, such as was found in this case, is due to an abnormality in the development of the aortic septum. This septum is formed by the fusion of two ridge-like projections from opposite walls of the truncus arteriosus, and divides the tube into two vessels, aorta and pulmonary artery. The separation is completed by the formation of a short septum in the bulbus cordis, which unites with the aortic septum above, and with the ventricular septum below; and by the appearance of endocardial cushions at the proximal end of the truncus, from which the semilunar valves are developed. Owing to twisting of the tube upon itself during this period of development, the aortic septum normally takes a spiral course, so that the pulmonary artery lies to the left of the aorta above, but in front and to the right of it near the heart. Thus when union takes place between the aortic and ventricular septa, the aorta is brought into communication with the left ventricle, and the pulmonary artery with the right.

A reversal of the position of the two great vessels might be brought about either by a reversal of the direction of the spiral twist of the aortic septum, or by this twist being incomplete, thereby bringing the aortic portion of the truncus into communication with the right ventricle, and the pulmonary portion with the left. Which of these alternatives is responsible for this abnormality appears to be a matter of some doubt among embryologists. Each may account for certain of the cases. In the present case, the parallel disposition of the two vessels perhaps suggests that the septum took a practically straight course, instead of developing the usual spiral.

Cases of transposition of the aorta and pulmonary artery have been reported by a number of authors. This malformation was first described by Baillie in 1797. Farre\(^1\) quotes two cases in addition to Baillie's, which appear to be identical with that just described, while several similar cases, reported by various authors, are mentioned by Peacock.\(^2\) Transposition of the primary vessels may be associated with various other abnormalities in the heart. Several of the reported cases have had a defect in the interventricular septum; examples of this have been described by Peacock, and by Sanders\(^3\) and others; but according to the former authority, the ventricular septum is entire in the majority of cases.

The question of how the circulation was maintained in this case is an interesting one. Aeration of the blood in the systemic
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circulation was rendered possible only by the presence of a patent foramen ovale and ductus arteriosus. Otherwise, blood entering the right atrium from the venae cavae, would have been despatched back to the systemic circulation through the aorta; while that returning from the lungs to the left atrium would have been sent back whence it came, through the pulmonary artery. Further, had the blood flow through the foramen ovale been, as in the fetus, from right to left, aerated blood could have reached the aorta only through the ductus arteriosus. This would mean the exclusion of the head and upper limbs from all supply of oxygenated blood, which would appear to be an impossible state of affairs, and incredible in view of the fact that there was practically no cyanosis, except during the attacks. If, however, the flow had been from left to right through the foramen ovale, the head and upper limbs would have received a share of arterial blood, while venous blood would have been transmitted to the lungs by the ductus arteriosus. It seems probable, then, that there was a flow of blood through the foramen and ductus, in a direction opposite to that which obtains during fetal life. Considering the large amount of venous blood which, even under the most favourable circumstances possible, must have been present in this child's systemic arteries, the fact that she lived even as long as three weeks, without symptoms or very obvious cyanosis, is sufficiently remarkable.

The exact cause of the intermittent attacks of cyanosis is doubtful. Attacks of this kind are of frequent occurrence in congenital heart cases. They may have been due simply to failure of the myocardium. But in this case it is possible that the cause was some interference with the circulation through the foramen ovale and ductus, upon which so much depended. The condition of the foramen was such that strong contraction of the musculature in the region of the annulus might conceivably have occluded the aperture. This would inevitably have caused derangement and embarrassment of the whole circulation, and cut off the supply of arterial blood to the upper part of the body and the brain.

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Cases of Congenital Cardiac Defect in Children

BY

AGNES R. MACGREGOR, M.B., Ch.B.

From the Royal Hospital for Sick Children, Edinburgh

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CASES OF CONGENITAL CARDIAC DEFECT IN CHILDREN.

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III.

CASE III.—Baby F., aged 2 days, male, was admitted to the Royal Hospital for Sick Children on 28th June 1923, under the charge of Mr. John Fraser, on account of spina bifida in the lumbo-sacral region. The skin over the swelling had ulcerated, and there was some discharge of cerebro-spinal fluid from the sac. The infant was deeply cyanosed and obviously very ill. It was therefore decided not to attempt surgical treatment. He died in a fit on the fourth day after birth.

The baby, who was born after the death of his father, was the eleventh child. Nine of the older children were alive and well.

Post-mortem Examination.—The child was undersized, but quite well nourished. The whole body was livid. The blood was of a very dark colour, and all the organs were cyanotic.

Description of the Heart.—In size the heart was somewhat above the average for the size and age of the child. This was due to enlargement of the right ventricle, which was both hypertrophied and dilated. A single large arterial trunk arose from the right ventricle, in the normal position of the pulmonary artery. Its calibre was not larger than that of a normal aorta at birth. The valve at its root was provided with two semilunar cusps of approximately equal size, placed anteriorly and posteriorly. From the sinus opposite the anterior cusp the right coronary artery arose, and was distributed in the usual manner. The left coronary artery arose from the sinus opposite the posterior cusp, and passing forwards between the arterial trunk and the left auricular appendix, divided into its two branches, which pursued their usual course. At a distance of 1.5 cm. above the valve, from the posterior aspect of the arterial trunk, a vessel was given off, which passed backwards and downwards for about 1 cm. and then divided into two branches, which were distributed to the lungs. The calibre of the pulmonary stem was not more than half that of a normal pulmonary artery, and its main branches were of correspondingly small size. After giving off the pulmonary artery, the primary vessel continued as the aorta, giving off branches in the usual sequence, and occupying the normal position of the aorta. There was no ductus arteriosus.
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No vessel arose from the left ventricle, which was of considerably smaller size than the right, and had much thinner walls. There was a defect in the upper or membranous part of the septum ventriculorum, through which there was a free communication between the two ventricles. It measured about 0.75 cm. from above downwards, and had the smooth, concave lower margin usually found in these defects. The foramen ovale was patent to the extent usual in new-born infants. The tricuspid and mitral valves were normal.

The arrest of development exemplified in this case, whereby the aortic septum, which divides the truncus arteriosus into an aortic and a pulmonary portion, fails to form, is not a very rare one. A considerable number of examples can be found in the literature. A case closely resembling the present one, except in that the two pulmonary branches arose separately from the common trunk, and the valve had three cusps, was reported by Power. The septum ventriculorum is always defective in these cases, as its closure is prevented by the absence of any outlet from the left ventricle, other than that provided by a septal defect. In a considerable number of the specimens described, the septum ventriculorum was absent, so that there was only one ventricle, and, not infrequently, a single atrium also. Cases of this kind were reported by Crisp, Ramsbotham, Forster, and Clark. The majority of the patients lived only a few days.

It is of interest to note that, unlike the two cases previously reported in the present series, this child was deeply cyanosed at birth, whereas the other two patients showed no cyanosis for several weeks, although there must have been just as much mixing of arterial and venous blood in them as in this infant. There was, however, in this case, one feature which was absent from the other two, namely, a great reduction in the calibre of the pulmonary artery, which must have seriously restricted the supply of blood to the lungs. It is probable that this, rather than the mixing of blood, was responsible for the intensity of cyanosis which characterised this case from birth.

I am indebted to Professor John Fraser for the use of the clinical notes.

CASES OF CONGENITAL CARDIAC DEFECT IN CHILDREN.

By AGNES R. MACGREGOR, M.B., Ch.B., from the Royal Hospital for Sick Children, Edinburgh.

II.

Perhaps the most interesting case of my series is that recorded below. The developmental abnormalities found in this heart appear to be distinctly rare, and in spite of their extreme nature, no cardiac defect was suspected until the day of death.

Case II.—D. H., a female child, aged 7 weeks, was brought to the Royal Edinburgh Hospital for Sick Children on 3rd September 1924, in a moribund condition. The history was that she had been perfectly well and of a normal colour until that morning, when the breathing quite suddenly became extremely difficult, and the child began to perspire freely and collapsed almost lifeless. The doctor who saw her at home and sent her to hospital, thought that he detected a pulmonary murmur.

On examination in hospital, the child was seen to be small but well nourished. There was cyanosis of the face and ears, and the extremities were cold. The pulse was feeble and rapid, but regular. Respiration was difficult and gasping. No cardiac murmurs were audible. The temperature was 103° F.

Stimulants were applied without avail, and the child died in the evening of the day of admission to hospital.

Post-mortem Examination.—There was a small excess of clear fluid in all the serous sacs, and the liver was congested and displaced downwards, but not enlarged to any important extent. The other organs, with the exception of the heart, were healthy. There were no other congenital malformations.

Description of the Heart.—The heart was situated in the normal position, but was greatly enlarged, this being due chiefly to the unusual size of the left ventricle. Both atria were markedly dilated, and they communicated freely with each other through the foramen ovale, which was widely patent, the aperture readily admitting the middle finger. The great veins were of normal calibre, and entered the atria in the usual positions. There was no communication between the right atrium and the right ventricle, the right atrio-ventricular orifice and tricuspid valve being entirely absent. There was thus no outlet from the right atrium except through the foramen ovale. The right...
ventricle was small in proportion to the size of the heart, but of average dimensions as compared with the normal. Its wall was of average thickness, and its muscular trabeculae were well developed, but the papillary muscles and chordae tendineae were absent. The pulmonary artery arose from it in the usual position, possessed a perfectly normal valve, and was of the usual calibre.

The left atrio-ventricular orifice was somewhat wider than usual, but was in the natural position, and possessed a valve with two cusps, exactly resembling a normal mitral valve. The cavity of the left ventricle was remarkably dilated, and its wall hypertrophied in great degree. The aorta was normal in every respect, as was also its valve. The ductus arteriosus was perversus, but very narrow, and obviously in process of obliteration.

In the interventricular septum there were two apertures. The larger, which readily admitted the forefinger, was situated in the upper part of the septum, immediately below the aortic valve, and communicated with the infundibular portion of the right ventricle. The other, which was barely half as large, was situated near the apex, the two apertures being separated from each other by a thick band of muscular substance.

The interesting features of this heart are, firstly, the absence of the right atrio-ventricular orifice, and secondly, the defects in the interauricular and interventricular septa. The first is due to misplacement of the septum intermedium, which normally divides into two parts the atrial canal, between the atrial and ventricular portions of the developing heart, and which in this case, being formed too far to the right, shut off the communication between the right atrium and right ventricle. This defect, in combination with other abnormalities in the heart, has been described by several authors in the past. In some of the specimens described, there was a single ventricle, the septum ventriculorum being absent, or represented only by a muscular ridge. An example of this was reported by Thore,¹ and Peacock² mentions a similar specimen in the Museum of St Thomas' Hospital, in which there was, in addition, transposition of the great vessels. Peacock also quotes cases reported by Worthington, Favell, and Sieveking, of which the last most closely resembles the present case. In a specimen described by Boyer³ there was a single atrio-ventricular orifice, with transposition of the atra. A slightly different condition, though similar in its effect upon the circulation, is that in which both the atrio-ventricular orifices open into the left ventricle. Holmes⁴ describes a remarkable case
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of this condition in a man who lived to the age of twenty-one years. A very similar case in an infant was recorded by Valleix, and quoted by Peacock, who also mentions examples of absence of the mitral valve.

The defects in the auricular and ventricular septa in this case may be regarded as consequent upon the absence of the tricuspid orifice. They were necessary for the maintenance of the circulation, and were doubtless the direct result of the abnormal conditions present in the heart. The foramen ovale being the only outlet for the blood from the right atrium, a constant current had to pass through it, which would render its closure impossible. It must be remembered that a degree of patency of the foramen ovale is commonly found at all ages; and at the age of this child, complete closure is the exception rather than the rule. But the defect present here was much larger than that usually found even in new-born infants, and must be regarded as definitely abnormal.

A defect in the interventricular septum was also a necessity for the maintenance of the circulation, as only in this way could the blood reach the right ventricle; and it is probable that the constant over-distension of the left ventricle, caused by its receiving the whole volume of blood entering both atria, was the cause of the failure of the septum to close. In all the cases of absence of the right atrio-ventricular orifice found in a fairly extensive search through the literature, the septum ventriculorum was either defective or entirely absent.

The usual site of defects in the interventricular septum is at the base, immediately below the aortic valve; that is to say, in that part of the septum which is the last to be closed, and which is known as the pars membranacea, or undefended space. Instances of apertures in this position are numerous in the literature, with or without other malformations. A frequent accompaniment is contraction of the pulmonary orifice, which, by obstructing the outflow from the right ventricle, appears to interfere with the closure of the septum. When unaccompanied by other gross abnormalities, this defect in the septum is compatible with life, and even with good health, for a number of years.

A defect at the apex is much less common. In 1876, Dyce Duckworth reported as probably unique a case in which an aperture in the septum ventriculorum near the apex of the heart was the only abnormality present; while Peacock...
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mentions the occurrence of defects at the apex, but quotes no cases, other than one of tricuspid stenosis in which there were two apertures in the septum, the position of the lower not being stated. It is extremely difficult to account for the occurrence of a defect at the apex, as the septum grows upward from below, and how or why an aperture should be formed in this situation is unknown.

Although examples have been found in the literature illustrating the various abnormalities present in this case, I have been unable to find any record of a heart exactly similar.

The course of the circulation must have been as follows.

Blood entering the right atrium from the venae cavae would pass through the foramen ovale into the left atrium, where it would mix with arterial blood returned from the lungs. Mixed arterial and venous blood would pass into the left ventricle, and thence into the aorta, and also through the septal defects to the right ventricle and pulmonary artery. There must have been a very great mixing of blood, and this being so, the absence of cyanosis for seven weeks is surprising. There appears to be little doubt that restriction of the amount of blood passing to the lungs is of more importance in producing cyanosis than the presence of a proportion of venous blood in the systemic arteries, and the most extreme cyanosis is found when the calibre of the pulmonary artery or its orifice is greatly reduced. But mixing of blood to the extent which must have occurred here, necessarily restricts the amount of venous blood passing to the lungs at each systole, as a considerable proportion of the blood in the right ventricle must have been arterial. It is probable that cyanosis could be absent, under these circumstances, only during early infancy, while the child was doing nothing requiring much exertion.

The “pulmonary murmur” suspected by the doctor was doubtless caused by the passage of blood through the defects in the septum ventriculorum.

My thanks are due to Dr Norman Carmichael for permission to publish this case.

ACUTE PNEUMONIA IN EARLY CHILDHOOD.

PATHOLOGY OF ACUTE PNEUMONIA IN EARLY CHILDHOOD.*

BY

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DIFFERENTIATION between lobar pneumonia and broncho-pneumonia by pathological examination in fatal cases is usually a matter of no great difficulty, for most cases exhibit well defined features which enable them to be placed in one or other of these two classes. Occasional cases, however, possess atypical characters and present difficulty in classification.

Definition of Terms.

The term "lobar pneumonia" is applied to cases in which there is a circumscribed area of lung tissue completely and uniformly consolidated. The area may be of the extent of one complete lobe, or more, or less. Scattered patches of pneumonia in addition to the main area are absent. Bronchitis is usually little in evidence.

The term "broncho-pneumonia" is applied to cases in which pneumonia occurs in patches surrounding bronchi and bronchioles, either without or with confluence; the latter may lead to massive consolidation of parts of the lungs. Inflammation is more intense in alveoli closely related to bronchi. The bronchi themselves are much inflamed.

Differences in the character of the exudate are of small value in distinguishing the types. While as a rule the exudate of lobar pneumonia is more fibrinous and that of broncho-pneumonia richer in cells, this difference is not constant.

Incidence of the Types.

The incidence of the types in 100 consecutive cases of pneumonia in children examined post mortem at the Royal Edinburgh Hospital for Sick Children was as follows:

Lobar Pneumonia.—This group was represented by 11 cases, of which 8 were typical, 3 being somewhat

* A paper read in the Section of Diseases of Children at the Annual Meeting of the British Medical Association, Edinburgh, 1927.

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atyypical but possessing chiefly the features of lobar pneumonia. Of the 11 cases 3 were bilateral. The eldest patient was 4$\frac{3}{4}$ years of age, the youngest 6 months; the average age was 17 months. Six were under 1 year, 3 between 1 and 2 years.

Broncho-pneumonia,—This group was represented by 89 cases, of which 3 were somewhat atypical. Of the 89 cases 79 were bilateral; in 11 of these one of the lungs was relatively slightly affected, and in 63 the disease was extensive in both lungs; 69 showed massive confluence in one or more lobes; 20 showed no confluence in any considerable area. The eldest patient was 5 years of age; the youngest 3 weeks; the average age was 14$\frac{1}{2}$ months. Forty-three were under 1 year; 29 between 1 and 2 years.

These figures show that in a series of fatal cases: (i) 81 per cent. of all the cases were in children under two years of age; (ii) 89 per cent. were cases of broncho-pneumonia; (iii) 89 per cent. of the cases of broncho-pneumonia were bilateral, while less than one-third of the cases of lobar pneumonia were bilateral; (iv) 77.5 per cent. of the cases of broncho-pneumonia were of the confluent type and exhibited massive consolidation in at least one lobe. This is an outstanding difference between broncho-pneumonia in children and in adults, confluent consolidation being relatively uncommon in the latter. It is important from the clinical point of view, as it introduces a difficulty in differential diagnosis during life.

At autopsy confluent broncho-pneumonia is distinguished from lobar pneumonia chiefly by the following features: (1) The massive airless portion is usually of less uniform consistency in broncho-pneumonia, and is produced by a combination of consolidation and collapse. (2) On section its appearance is not uniform; it shows mottling, usually yellow, around the bronchi. (3) Usually it is defined less sharply than is the case in lobar pneumonia, and shades off into indefinite patches at the edges. (4) In addition, discrete patches of broncho-pneumonia are present in other parts. (5) There is a more or less diffuse acute bronchitis.

A fact which ought to be emphasized is that broncho-pneumonia, at least in fatal cases, is of very much more widespread distribution than the average fatal case of lobar pneumonia. Often lobar pneumonia is confined to one lobe of the five. Broncho-pneumonia, whether with or without confluence, usually attacks all five lobes, and the inflammation is at different stages in the various parts. The very extensive involvement of the terminal airways which results accounts for the severe respiratory embarrassment which characterizes the clinical picture of broncho-pneumonia.

Microscopic Pathology.

During the course of the research on which this communication is based a series of cases has been studied with the aid of paraffin sections extending to a whole lung. These sections can be examined under high powers of the micro-
scope, and they are of great value in the investigation of the distribution of inflammatory changes in various forms of pneumonia. The conclusions which are here stated have been drawn largely from a study of these sections. This study has revealed certain important differences between lobar pneumonia and broncho-pneumonia.

In lobar pneumonia, as seen in the human subject, the freedom of the connective tissue framework and lymphatic system of the lungs from inflammatory infiltration is a remarkable feature. There is no persistent lymphangitis; the inflammation is located in the alveoli, whose walls possess no lymphatics. The alveolar septa show congestion, oedema, desquamation of epithelium, but the exudate is poured out into the alveolar spaces, and the walls do not suffer disorganization. When recovery occurs the products of inflammation are removed by resolution. There is no occasion for a process of reorganization, which would bring about permanent changes in structure and inevitable disablement of function.

In broncho-pneumonia it is usual to find a large amount of inflammatory infiltration of the substance of bronchial walls and of alveolar walls in the centre of pneumatic patches. In the area of an early lesion a bronchiole is present, with catarrhal contents in its lumen and inflammatory infiltration in its walls and in the peribronchial lymphatics (in the severer cases the infiltrating cells are mostly polymorphs). This is surrounded by a group of consolidated alveoli, whose walls are also infiltrated; and often infiltration of the walls seems to precede consolidation of the lumen, and extends beyond the edge of the consolidated patch. It is therefore evident that infection reaches these alveoli through the bronchus wall and along the alveolar septa, and not by continuity of lumen. Acute interstitial inflammation is an essential part of the process.

There may be in addition, directly connected with this by continuity of lumen, consolidation in the terminal alveolar expansions of the central bronchiole. When there is confluence this is always present, but the interstitial inflammation persists in the peribronchial zone, and produces the mottled appearance noted on naked-eye examination.

Cases exhibiting acute interstitial inflammation and lymphangitis have been described by some authors as a special type, which they call acute interstitial pneumonia. We have found it to be practically constant in our cases, and have come to regard it as the characteristic lesion of broncho-pneumonia. We believe that the cases described under this name are those in which interstitial inflammation is particularly obvious and alveolar inflammation more or less in abeyance, but that the difference between these and other cases is merely one of degree, and that the presence and importance of acute interstitial inflammation in all cases of broncho-pneumonia have not been sufficiently recognized.

In the involvement of the framework of the lungs
lymphangitis plays an important part. In ordinary cases of acute broncho-pneumonia it appears as a crowding of lymphatic channels with inflammatory cells, sometimes causing enormous dilatation of the larger vessels. It begins in peribronchial lymphatics, but soon spreads to perivascular and septal lymphatics also, and extends gradually in progressive fashion to all parts of the lungs.

We believe that the existence of progressive lymphangitis in broncho-pneumonia accounts for the firm hold which the infection gains upon the lungs; and that the absence of it in typical lobar pneumonia favours rapid and perfect recovery from the effects of inflammation.

It has, however, been claimed by Blake and Cecil that lobar pneumonia experimentally produced in monkeys begins as a primary lymphangitis to which alveolar inflammation is secondary. Further, they state that this lymphangitis passes off with the onset of lobar consolidation of the alveoli. The application of this result to human cases has yet to be demonstrated, but if it be correct it would seem to follow that broncho-pneumonia results from persistence of the primary lymphangitis.

The question arises whether all cases in which the features of confluent broncho-pneumonia are present at the time of death have possessed those features from the outset. This is important in connexion with the problem of differential diagnosis of lobar pneumonia and broncho-pneumonia during life, and the difficulty of placing certain cases in one or other of the two groups. It seems not unlikely that the lymphangitis which leads to broncho-pneumonia might develop either from bronchitis or from a localized patch of primary pneumonia. In certain cases of localized pneumonia of lobar type lymphangitis may supervene as a later development, and lead to a subsequent spread of inflammation throughout the lungs, after the manner of broncho-pneumonia. Such a case would be classed as confluent broncho-pneumonia at necropsy; and some fatal cases of primary pneumonia which clinically are thought to be lobar, but at post-mortem examination are found to be confluent broncho-pneumonia, may perhaps be explained in this way.

To sum up: we regard acute broncho-pneumonia as the result of progressive invasion of the lymphatic system and interstitial framework of the lungs by the infective agent; in other words, as the result of failure of the lymphatic apparatus to defend itself against invasion.

Some Further Effects of Lymphangitis.

It is widely recognized that broncho-pneumonia is more apt than lobar pneumonia to cause serious damage to the lungs, and to be followed by various undesirable results. Among the most important of these are suppuration, bronchiectasis, and fibrosis of the lungs. All these may be directly attributed to effects of lymphangitis.
1. Suppuration within the Lungs.

As a development of broncho-pneumonia this occurs in two distinct forms.

(a) Originating in bronchial walls, as a direct result of suppurative lymphangitis in peribronchial lymphatics. This seems to be not very uncommon in fatal cases. In our series it has been most often associated with empyema. We believe that the interference with lymphatic drainage which results from compression of the lung by a pleural effusion definitely favours the development of suppuration in the lymphatics. Suppurative lymphangitis, though most common in peribronchial lymphatics, may also cause diffuse suppuration along lymphatic paths throughout the lungs.

(b) In some cases areas of necrosis are formed in the lungs, and in these suppuration proceeds apace and gangrene may supervene. The necrosis is often associated with, and appears to be caused by, septic thrombosis in the blood vessels; and for this perivascular lymphangitis may be held primarily responsible.

2. Bronchiectasis.

This important occasional outcome of acute broncho-pneumonia is usually attributed either to the persistence of chronic smouldering inflammation in the bronchi which weakens their walls and leads to dilatation, or to fibrosis of the lung substance exercising traction upon them. Observations on certain cases among our series have served to throw some light upon the sequence of changes which results in bronchiectasis following acute broncho-pneumonia.

The earliest stages of the process are met with in cases of severe broncho-pneumonia, with purulent bronchitis and lymphangitis particularly well marked. The acute peribronchial lymphangitis with associated inflammation of the bronchial walls leads to complete destruction of the whole thickness of the wall in a part or the whole of the circumference of the bronchus. The destruction may extend to and involve some neighbouring alveoli. The result is the formation of a cavity whose lumen is surrounded by exposed alveoli, which are likely to be consolidated but are usually not in a state of suppuration. In fact, the cavity is often singularly clean-cut. Every vestige of the original structure of the bronchus wall—cartilage, muscle, elastic tissue—may disappear. If only a part of the circumference of the bronchus be affected, the rest of the wall remaining intact, the result is an irregular, somewhat saccular enlargement of the lumen.

Later healing occurs in the walls of these cavities, by means of which a new bronchus wall is constituted. Granulation tissue springs from among the surrounding alveoli; the cavity comes to be enclosed by a layer of young fibrous tissue; epithelium surviving in neighbouring parts of the bronchus proliferates and clothes this fibrous wall
with new epithelium, which is usually of a modified type, composed of low cubical cells. When the process of healing is complete the bronchus is reconstituted with a new wall composed entirely of fibrous tissue in which no remnant of the original structure is left.

If the initial acute process causes destruction of a considerable amount of tissue there will be, when healing is complete, an increase in the size of the lumen of affected bronchi—that is, the end-result is bronchiectasis. The conclusion to be drawn from this is that bronchiectasis following acute broncho-pneumonia is not always the result of a slow smouldering inflammation which leads to gradual dilatation, but is sometimes an acute and active process of excavation, followed by the formation of a new fibrous wall around a lumen which has been enlarged by actual loss of tissue. Obviously the new fibrous wall must lack the strength conferred upon the normal bronchus wall by its muscle and elastic tissue. Therefore there is likely to follow a gradual progressive enlargement of the lumen by dilatation; and even cases where there is at first no evident bronchiectasis are probably liable to develop it in course of time.

3. **Fibrosis of the Lungs.**

I do not propose to consider those cases in which fibrosis originates in the pleura. There is a group in which fibrosis of the lungs occurs after broncho-pneumonia, independently of pleurisy. In some of them it may be simply the result of persistence in a chronic form of that inflammation of bronchial and alveolar walls which is so conspicuous in the acute stage of broncho-pneumonia. But in some at least, and perhaps in most, the underlying pathological process is apparently the same as that which has just been described leading to bronchiectasis. If the smaller bronchi be affected in this way the result is different from that in the case of the larger bronchi. For just as a small abscess is by healing converted into a fibrous scar, or a small phthisical cavity closed by fibrosis, so a small bronchus whose wall is utterly destroyed may be obliterated by proliferation of granulation tissue in its lumen. The permanent obliteration of many small bronchi by this process must inevitably lead to permanent obliteration by fibrosis of large tracts of alveolar tissue.

We suggest that the pathological process underlying many cases of chronic pneumonia which go on to fibrosis and retraction of the lungs is this obliterative bronchiolitis, which starts with wholesale destruction of the walls of small bronchi and ends with obliteration by fibrosis of those bronchioles and of the whole of their associated alveoli. As fibrosis of the lungs and bronchiectasis can thus be traced to a common source, it is to be expected that the two conditions will usually be present together. If, however, in any case the damage were confined to the small bronchi, fibrosis might result unaccompanied by bronchiectasis.
After this brief review it is evident that the extension of the inflammatory infection from bronchial lumen to surrounding lymphatics is the cause of the characteristic changes of both acute and chronic broncho-pneumonia.

We have still to explain why the infection in this form of pneumonia results in a massive invasion of the lymphatics. Of conditions which offer a possible explanation, the one most generally recognized is that broncho-pneumonia is often a sequel to some definite infective fever such as measles. In these cases there are two infections, and that of the primary fever is in some sense a preparation for the subsequent inroad of the pneumonic infection. The primary predisposes to the secondary infection.

On the other hand, it must also be recognized that in children broncho-pneumonia is often primary and without a preparatory antecedent infection. The infection settled in the bronchi simply invades the lymphatics; there is no obvious sequence of another infection. For the interpretation of these facts various suggestions have been offered, postulating separately or together (a) a virus of specific quality and possibly of special virulence also; and (b) a condition of the patient, non-infective and yet preparing the way for pneumonia. In favour of the latter suggestion is the fact that it still maintains, though in a new form, the general principle of predisposition in broncho-pneumonia.

The conditions advanced on this hypothesis are such as (1) age—less than 2 years; (2) bottle-feeding; (3) undergrowth; (4) poverty; (5) lack of care in upbringing; (6) rickets.

Should it be shown that certain forms of virus have a special relation to broncho-pneumonia of the primary type, it will probably nevertheless be found that these conditions are still predisposing in their effect.

The importance of the consideration of predisposition as an etiological factor is that, should the hypothesis be proved, it would follow as a general conclusion that the elimination of broncho-pneumonia from the child community will depend to a corresponding extent on the application of preventive measures for the removal of the predisposing conditions.

REFERENCE.

CHARLES McNEIL, AGNES R. MACGREGOR AND W. ALISTER ALEXANDER.

STUDIES OF PNEUMONIA IN CHILDHOOD
STUDIES OF PNEUMONIA IN CHILDHOOD.

I. STATISTICAL ANALYSIS OF PNEUMONIA AND BRONCHITIS.


(From the Royal Edinburgh Hospital for Sick Children, and the Laboratory of the Royal College of Physicians, Edinburgh).

Introduction.—In a series of papers the subject of pneumonia in childhood will be presented mainly from the standpoint of morbid anatomy and histology, but with reference also to its clinical aspects. Bacteriology will not be dealt with.

In the first place, it will be an advantage to obtain a general view of the subject by means of a statistical analysis of a large series of cases, and the present paper will be devoted to this purpose. The subsequent papers will deal with the so-called lobar type of pneumonia; broncho-pneumonia; bronchiectasis; and empyema. In these studies large thin sections of the entire lung have been used, and illustrations of these will be shown. These large sections give not only an extensive view in one plane of the morbid anatomy, but also permit an accurate microscopic study of the pathological processes over a wide extent of lung.

STATISTICAL ANALYSIS OF PNEUMONIA AND BRONCHITIS.

This analysis includes two distinct series of statistics, 648 cases of pneumonia and 244 autopsies in the same disease. The age period in both was from birth to twelve years.

The 648 cases in the clinical series were admitted to one ward of the Edinburgh Children's Hospital between January, 1921, and October, 1928, a period of almost eight years. Because of the close connection between bronchitis and pneumonia in the early years of childhood, we have placed alongside this series all cases of bronchitis admitted during the same period. A third group, bronchiectasis, includes cases where as the sequel of pneumonia or severe bronchitis there was serious and lasting damage to the bronchial walls, with bronchial dilatation in most cases and with marked fibroid change in the lung in a smaller number.

All these cases have been under one medical charge, (C. McN.). In order to secure full co-operation and exchange of views between clinician and pathologist, we have studied many of them together both in the ward and in the post-mortem room. Moreover, for the purpose of this survey, all the records have been read together by two of us, and the diagnosis and other points carefully reviewed. This revision has resulted in not a few changes.
in some instances the original diagnosis of the type of pneumonia has been modified, and doubtful cases have been excluded from the group. By this selection of a large number of cases from a single medical charge, by co-operation, and by a thorough revision of all the records, we have tried to secure uniform and consistent standards and as much accuracy as possible.

The 244 autopsies have been made and recorded throughout by one of us (A. R. M.). They include 83 examinations from the above series of 648 cases of pneumonia, and 161 examinations in cases from other wards in the hospital. The total (244) represents all cases of pneumonia examined post mortem during a period from 1st July, 1922, to 31st October, 1928.

Main Groups in Clinical Series.—The totals of cases and deaths in the clinical groups are shown in Table I.

TABLE I.
MAIN GROUPS IN CLINICAL SERIES.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases</th>
<th>Deaths</th>
<th>Death-rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis</td>
<td>231</td>
<td>6</td>
<td>2.5%</td>
</tr>
<tr>
<td>Pneumonia (all types and including empyema)</td>
<td>648</td>
<td>163</td>
<td>25.0%</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>33</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>912</td>
<td>169</td>
<td>18.5%</td>
</tr>
</tbody>
</table>

This aggregate of 912 excludes all other respiratory diseases, e.g., asthma and asthmatic bronchitis, pulmonary tuberculosis, tuberculous and rheumatic pleurisy. These figures for bronchitis and pneumonia are compared with those for all other diseases treated in the ward during the same period in Table II.

TABLE II.
PRESENT SERIES COMPARED WITH TOTAL ADMISSIONS.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases</th>
<th>Deaths</th>
<th>Death-rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis, pneumonia, bronchiectasis</td>
<td>912</td>
<td>169</td>
<td>18.5%</td>
</tr>
<tr>
<td>All other cases</td>
<td>1,964</td>
<td>380</td>
<td>19.5%</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>2,876</td>
<td>549</td>
<td>19%</td>
</tr>
</tbody>
</table>

Thus the bronchitis, pneumonia, bronchiectasis group formed 31.5 per cent. of all cases admitted. The death-rate in the same combined group was slightly lower than in the group of all other cases; while if the pneumonia group be taken alone, its death-rate was somewhat higher than in the 'all other' group.

Twenty years ago Dunlop, in the same hospital and ward, collected and analysed 500 cases of pneumonia exclusive of empyema; the total admissions
STUDIES OF PNEUMONIA IN CHILDHOOD.

during the same period were 3,300. A comparison with Dunlop's figures can be made by subtracting the cases of empyema from the pneumonia cases in our series (Table III).

### TABLE III.

**Present Series compared with Series recorded in 1908.**

<table>
<thead>
<tr>
<th>Pneumonia</th>
<th>Total Admissions</th>
<th>Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunlop (1908)</td>
<td>500</td>
<td>104</td>
</tr>
<tr>
<td>Present Series</td>
<td>559</td>
<td>127</td>
</tr>
</tbody>
</table>

This shows that in the present series the incidence and death-rate of pneumonia were slightly higher than in a similar Edinburgh series collected some twenty years ago.

### Types of Pneumonia.

The types of pneumonia have been studied in two series of cases: a clinical series and a post-mortem series.

**Types of Pneumonia: Clinical Series.**

Table IV shows the division of the inclusive pneumonia group into its different sub-groups, giving for each the total cases and the numbers of deaths.

### TABLE IV.

**Classification: Inclusive Pneumonia Group (Clinical Series).**

<table>
<thead>
<tr>
<th>Type</th>
<th>Cases.</th>
<th>Deaths.</th>
<th>Death-rate.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar (Lobar or Croupous) Pneumonia</td>
<td>386</td>
<td>26</td>
<td>7%</td>
</tr>
<tr>
<td>Broncho-pneumonia</td>
<td>144</td>
<td>78</td>
<td>54%</td>
</tr>
<tr>
<td>Empyema</td>
<td>89</td>
<td>36</td>
<td>40-5%</td>
</tr>
<tr>
<td>Miscellaneous Group</td>
<td>21</td>
<td>21</td>
<td>100%</td>
</tr>
<tr>
<td>Acute Pleurisy</td>
<td>8</td>
<td>2</td>
<td>25%</td>
</tr>
<tr>
<td>Totals</td>
<td>648</td>
<td>163</td>
<td>25%</td>
</tr>
</tbody>
</table>

Table IV is important and requires some explanation and discussion, especially of the clinical and pathological criteria which determined the classification. The death-rates refer to all ages between birth and twelve years and, while they are of some interest, their importance when studied in smaller age periods is much greater.

The term 'alveolar pneumonia' will be used throughout this and succeeding papers instead of 'lobar or croupous pneumonia.' The reasons for this will be given later.
The outstanding feature of the above table is the large preponderance of cases of alveolar (lobar) pneumonia over those of broncho-pneumonia. This is contrary to the majority of collected statistics of pneumonia in children. Crozer Griffith, in a recent paper, has compared a number of statistical analyses on this point and some of these may be quoted. For example, in Dunlop’s series of 265 cases of pneumonia under 2 years of age, the ratio between alveolar (lobar) and broncho-pneumonia was 1 to 5; in a similar series by Holt (322 cases) the ratio was 1 to 3. The comparable ratio in the present series (256) is 1-3 to 1. This discrepancy in results from different observers may depend partly upon climatic conditions or the type of case admitted to certain hospitals, but it is probable that a more important factor is a difference in the standards of differential diagnosis between these two types of pneumonia. It is therefore necessary to explain the standards that have been employed in the present analysis.

**Differentiation of Alveolar (lobar) and Broncho-pneumonia.** The separation of these two types of pneumonia is determined by pathological and clinical data. No bacteriological test is available. The differentiation can be made with certainty only at autopsy: during life it is more difficult and uncertain. Standard text books (e.g., Holt, Thomson) give tables of symptoms and signs by which these two types may be distinguished in life. These criteria are sufficient in many cases, but in a considerable number they fail, and may even mislead, for the reason that the description of lobar pneumonia is based on the adult type, whereas the morbid anatomy of this type of pneumonia in the child often does not conform to that in the adult. In the latter, consolidation usually involves the whole of one lobe, but in children, and especially in young children, it often occupies only a small portion of a lobe. The word ‘lobar’ is therefore unsuited to many cases of this type in children. The pathological process, however, corresponds in its essential characters to the lobar pneumonia of the adult. The inflammation occurs in the alveoli, producing complete consolidation of a definite area; there is very little involvement of the interstitial tissue; bronchitis, if present, is no more than a trivial and superficial catarrh. We suggest that ‘alveolar pneumonia’ is a term which accurately describes this type of pneumonia, and that in children it is preferable to the term ‘lobar’ because in them the inflammation is not necessarily lobar in extent. In broncho-pneumonia, the changes are of an entirely different character. Severe bronchitis is an essential feature, with inflammatory infiltration of the bronchial wall and interstitial framework of the lung; the consolidation occurs in patches, following the distribution of the bronchial tree, with or without confluence over areas of considerable size. The word broncho-pneumonia is thus a correct description of the pathological changes in this type of pneumonia.

Does this real difference of pathological process in these two types of pneumonia manifest itself in different clinical features? The physical signs of auscultation and percussion are essential in the discovery of consolidation, and without evidence of consolidation a diagnosis of pneumonia cannot be made. A ‘dry’ consolidation localized in one lobe gives physical signs
STUDIES OF PNEUMONIA IN CHILDHOOD.

characteristic of alveolar pneumonia; scattered patches of consolidation over both lower lobes, accompanied by many moist sounds, are diagnostic of broncho-pneumonia. But in two kinds of case the physical signs may be misleading. First, cases of alveolar pneumonia are met with, in which the area of consolidation is small and there are accompaniments around the pneumonic patch, and occasionally also over both roots and bases, indicating a slight catarrhal process; in such cases the physical signs closely resemble those of broncho-pneumonia. Secondly, in rapidly confluent and massive broncho-pneumonia the physical signs are very similar to those of an extensive alveolar (lobar) pneumonia. It would therefore be true to state that in the differentiation of the type of pneumonia physical signs in many cases may be of little service and may, indeed, lead to error. The manner of onset in both types may be sudden and immediately grave. It is nearly always so in alveolar pneumonia, while in broncho-pneumonia it is more often progressive; but this difference is not constant or striking. So also for the type of dyspnea and the presence of cyanosis; they may be helpful and corroborative, but they are too inconstant to have a decisive value.

There remain, however, three things, the character of the cough, the duration of high fever and especially the type of decline of fever. These are the most important clinical features by which the two types may be distinguished. In alveolar pneumonia, the cough may be absent; it is, however, generally present, but it is seldom conspicuous; it is a short single cough, which may be suppressed and painful if pleurisy is present. The duration of the fever does not exceed two weeks in the great majority of cases; its level is high but not always sustained. The decline of fever is by crisis or occasionally by lysis, and is followed in most cases by equally dramatic improvement in the general condition and by rapid resolution of the exudate. In broncho-pneumonia, the cough is generally prominent, occurs in bouts and paroxysms, and is harsh and loud. The fever in all severe cases extends over several, and perhaps many, weeks; throughout, the temperature is apt to be irregularly remittent, although in the early stages of rapidly confluent pneumonia it may be high and sustained; in the later stages of severe cases it drops gradually and irregularly to the normal level, about which it may fluctuate for some time. We believe that in this type of pneumonia the fever almost never terminates by crisis, and only rarely by regular lysis.

These three features, the type of decline of fever, the character of the cough, and the duration of the fever, in this order of importance, have been the principal criteria by which, in doubtful cases, we have determined the type of pneumonia. Other signs and symptoms have also been of service, especially the physical signs of auscultation and percussion. The latter are, of course, necessary for the diagnosis of pneumonia, but we wish to repeat that in the differentiation of the type of pneumonia, particularly in children under two years of age, they are not seldom indecisive and misleading. And it is in these first two years, when about half of the cases of alveolar and nearly all the cases of broncho-pneumonia occur, that this separation of the two types has to be made. Whether our main clinical criteria are of the primary importance we
have assigned to them is a matter for discussion. They have been consistently applied to the present series of cases shown in Table IV, and it is probably due to them, and to the secondary place given to physical signs, that the high figures for alveolar pneumonia have been obtained.

One or two other points may be noted here. In Table I a large group of cases of bronchitis (231) is shown; of these, 192 were cases of acute bronchitis, the remainder being chronic bronchitis, laryngitis, and tracheitis. The acute cases were all febrile illnesses with cough and physical signs of bronchitis. The standards of diagnosis, in addition to the above, were the absence of consolidation and a short duration of fever. The presence of rapid and difficult respiration for a few days was not accepted as sufficient evidence of pneumonia. These more severe cases of bronchitis might, however, be regarded by other clinicians as cases of broncho-pneumonia, and in our revision we transferred from the broncho-pneumonia group to the bronchitis group a number of such cases. It must therefore be emphasized that the broncho-pneumonia group in our series has shed off into the alveolar pneumonia group on the one hand, and into the bronchitis group on the other, a number of cases that other observers with different standards would have retained within it.

**Cases of Slowly Resolving Pneumonia.** Included in the alveolar pneumonia group were 46 cases in which the process of resolution was slow, lasting from two months up to one year, or even longer in one or two instances. It might be argued that these, or some of them, were cases of broncho-pneumonia. They were carefully considered during our revision and have been retained meantime as a sub-group of alveolar pneumonia. In their onset and early course they were of the alveolar type, showing a definite, and sometimes massive, consolidation confined to one lobe or lung, but with little or no cough. In the later stages their course was almost afebrile with a satisfactory general condition. The death-rate was trifling, viz., one case. Nevertheless, it seems likely that the interstitial framework had become the seat of a degree of chronic inflammation. They form an interesting group which deserves further study.

**Empyema Group.** It is hardly necessary to justify the inclusion of cases of empyema in the general consideration of a large series of cases of pneumonia in childhood, although in some published series this has not been done. In our survey we have taken out of the main groups of alveolar and broncho-pneumonia, and placed in the group of empyema, all cases in which pus or seropurulent fluid, even in small amount, was found free in the pleural cavity before or after death. Only in this way can an accurate estimate of the frequency of this complication in pneumonia be obtained. Even so, the incidence of empyema will be under-stated by the omission of a few recovered cases in which, undetected, a slight purulent effusion had taken place and had been absorbed, and of a larger number of fatal cases in which no autopsy was made. The frequency of empyema in our aggregate group of pneumonias was 1 in 7 (89 to 648). The attempt was made to determine for all these cases of
empyema, whether the original pneumonia had been alveolar or broncho-
pneumonia. In 31 cases it was not possible to say; in the remaining 58
cases, the type was presumed to be alveolar in 45 and broncho-pneumonia
in 13.

The death-rate in our cases of empyema at all ages was 40.5 per cent.
This, however, is not a true estimate. The point will be discussed in a later
section when the frequency and the death-rate of empyema over smaller age
periods will be given, but the fallacy may be briefly alluded to now. In many
cases of fatal empyema in infants the purulent effusion is only incidental, and
the death of the child is really due to the predominant and severe pneumonia
which accompanies it. For this reason the death-rate for empyema just given
is inaccurate, and is too high.

Pleurisy. This was a small group where there was a fibrinous pleurisy
without evidence of pneumonia. In several of these, pneumonia was suspected,
but no convincing evidence was obtained either clinically or post-mortem. The
smallness of the group is interesting, and shows how uncommon is the occur-
rence of primary pleurisy apart from associated inflammation of the lung.

Miscellaneous Group. All these were fatal cases and included various
small sub-groups, terminal pneumonia, early fatal pneumonia, and other
indefinite cases. These various sub-groups will be more suitably discussed in
the section dealing with the post-mortem series.

Types of Pneumonia: Post-mortem Series.

During the period from 1st July, 1922, to 31st October, 1928, the total
number of post-mortem examinations carried out in the hospital was 946.
Pneumonia was present in 233 of these, and empyema without recognizable
pneumonia in an additional 11 cases. The total number of cases of pneumonia
and empyema was therefore 244, almost 26 per cent. of all autopsies.

An attempt has been made to classify the 233 cases of pneumonia according
to type. In doing this both macroscopic and microscopic characters have been
considered in a large number of the cases. In others, microscopic material
not being available, it was necessary to rely upon the gross characters alone;
but as few cases of doubtful type were among these and very careful records
had been kept, it is perhaps legitimate to claim that even these could be
classified with reasonable confidence. In a large series of cases occurring after
the end of 1925, in addition to ordinary microscopic material, paraffin sections
of whole lungs have been used. The result is shown in Table V.

We do not intend to discuss fully in this paper the pathological grounds on
which the types have been distinguished, because that will form an important
part of later communications. A brief reference has already been made to the
chief pathological features of alveolar and broncho-pneumonia (p. 15).

Broncho-pneumonia. The immense preponderance of broncho-pneumonia
over all other forms is a striking illustration of the fatal character of this type.
It is not, however, to be regarded as proving that this is the commonest type
of pneumonia at any age period. It must not be forgotten that the cases
included in any post-mortem series are in a sense selected cases, selected, that
is to say, by the fatality of the disease. The frequency with which any type of pneumonia is seen in the post-mortem room is no measure of its actual incidence. Nevertheless this group must be regarded as the most important, because it is clear from a consideration of the figures presented in Table V, that the pressing problem of pneumonia mortality is in very large measure a problem of broncho-pneumonia.

**TABLE V.**

**Classification : All Cases (Post-mortem Series).**

<table>
<thead>
<tr>
<th>Type</th>
<th>Number.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broncho-pneumonia</td>
<td>140</td>
</tr>
<tr>
<td>Alveolar (lobar) pneumonia</td>
<td>23</td>
</tr>
<tr>
<td>Terminal pneumonia</td>
<td>29</td>
</tr>
<tr>
<td>Miscellaneous group</td>
<td>15</td>
</tr>
<tr>
<td>Chronic pneumonia</td>
<td>5</td>
</tr>
<tr>
<td>Septic (pyemic) pneumonia</td>
<td>4</td>
</tr>
<tr>
<td>Unclassified</td>
<td>17</td>
</tr>
<tr>
<td>Empyema without pneumonia</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>244</strong></td>
</tr>
</tbody>
</table>

*Alveolar (lobar) pneumonia* was represented by a small group of 23 cases. This is in striking contrast to the numerical superiority of this type in our clinical series. The relatively low mortality of alveolar pneumonia in children causes it to occupy a subsidiary place in a series of post-mortem cases.

There were several cases in which appearances characteristic both of alveolar and of broncho-pneumonia were present in different parts of the lungs. These have been classed as broncho-pneumonia.

*Terminal pneumonia.* The cases classed as terminal pneumonia might be regarded as a sub-group of broncho-pneumonia, with which they had certain features in common. They were mostly cases of hypostatic pneumonia in marasmic infants or debilitated children with enteritis or other wasting diseases. In most instances clinical manifestations of pneumonia were not present; consolidation was posterior and basal in distribution, somewhat indefinite in character, and associated with marked passive congestion and oedema.

*Miscellaneous Group.* Although the great majority of the acute cases fell into one of the above groups, there were a few whose characters did not justify their inclusion under the name of either alveolar or broncho-pneumonia. These are included in Table V in a miscellaneous group which embraces cases of three different types, as follows:—
First, there was a group of four cases, all in infants under one month old, in which the microscopic changes consisted of very intense generalized congestion and rather massive consolidation in both lungs, without much inflammation of the bronchi. The appearance resembled that of the condition which Gaskell\(^5\) has called 'milary pneumonia' and ascribes to an infection reaching the lungs via the blood stream. Microscopically, the presence of a copious exudate of polymorphonuclear leucocytes was somewhat at variance with Gaskell's description. Whether or not these cases may be regarded as examples of this blood-spread type of pneumonia, they were certainly not ordinary broncho-pneumonia; nor could they be legitiately classed as alveolar pneumonia.

Secondly, there were five cases which resembled those described by M'Gowan and McNeil\(^6\) in 1913. In all of these the illness lasted less than twenty-four hours; the symptoms were those of an acute respiratory infection; the lungs showed quite an extraordinary degree of active hyperemia, some oedema, but no consolidation; and in four of the five cases there was general hyperplasia of lymphoid tissue throughout the body, with or without enlargement of the thymus gland.

Thirdly, six cases showed widespread patches of consolidation in both lungs, not obviously related to the distribution of bronchi, and an absence of generalized bronchitis and of interstitial inflammation of the bronchial walls and pulmonary stroma. The appearance was that of the so-called 'lobular' or 'primary disseminated pneumonia.' Holt\(^4\), who describes this type fully, states that it is the commonest form of pneumonia in infancy and is attended by a mortality of about sixty per cent. in the first two years of life. In view of this, we have been surprised to find in our series so few cases corresponding to his description. It would seem that either the incidence or the mortality of this type must be much less in this locality than in Holt's experience.

The small group called chronic pneumonia includes cases of organising pneumonia, pulmonary fibrosis and bronchiectasis. The septic or pyemic pneumonias were cases of septicaemia and pyaemia in which pneumonia occurred as a secondary manifestation of a general pyogenic infection.

The seventeen unclassified cases showed remnants of pneumonia post mortem, but it was impossible to determine with reasonable accuracy of what type the pneumonia had been. Most of them were cases of empyema, or of death from other complications or sequelae, such as pericarditis, in which the original pneumonia had all but completely resolved.

The Influence of Age on the Incidence and Death-rate of Pneumonia and Bronchitis.

The factor of age is of great importance and interest. As regards the clinical series, its influence is shown graphically in Chart I. In it the numbers of cases of pneumonia and of bronchitis, and also the deaths, are represented for one-yearly periods throughout childhood. All types of pneumonia and empyema, as set out in Table IV, are merged into one inclusive group.
CHART I.

AGE INCIDENCE: ALL CASES (CLINICAL SERIES).

- = Pneumonia.
- = Bronchitis.
- = Fatal Cases.
STUDIES OF PNEUMONIA IN CHILDHOOD.

Taking pneumonia, it will be seen that the totals reach their highest peaks in the first two years; they then fall rapidly until the fifth year and more slowly in subsequent years. The deaths from pneumonia are concentrated in the first two years in a remarkable way; indeed, in the first year the number of deaths is almost three times, and in the second year it is quite twice, the total from 2 to 12 years. The cases of bronchitis, numbering 231, show a similar distribution over the yearly age periods, the great mass being found in the first two years. This parallel behaviour of the two diseases, bronchitis and pneumonia, is most significant and interesting.

The influence of age in pneumonia and bronchitis can be emphasized by grouping the twelve one-yearly periods into three larger ones, birth to 2 years, 2 to 5 years, and 5 to 12 years. When this is done, the figures shown in Table VI are obtained.

**TABLE VI.**
**Age-groups in Clinical Series.**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pneumonia</th>
<th>Bronchitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Deaths</td>
</tr>
<tr>
<td>Birth—2 years</td>
<td>310</td>
<td>138</td>
</tr>
<tr>
<td>2—5 years</td>
<td>184</td>
<td>18</td>
</tr>
<tr>
<td>5—12 years</td>
<td>154</td>
<td>9</td>
</tr>
<tr>
<td>Birth—12 years</td>
<td>648</td>
<td>163</td>
</tr>
</tbody>
</table>

This grouping brings into prominence the period of the first two years, when the remarkable concentration of cases of pneumonia and of deaths therefrom is apparent. One half of all cases of pneumonia and five-sixths of the deaths occur at this time. It is again worth noting that in this grouping the behaviour of bronchitis is closely parallel, two-thirds of the cases and five of the six deaths falling within the first two years. This period therefore stands out as one of special susceptibility to bronchitis and pneumonia, and of high mortality from the latter.

These facts regarding the influence of age on mortality receive striking confirmation from a study of the age incidence in the post-mortem series, which comprises a larger number of fatal cases than the clinical series. Chart II represents the number of deaths in the combined group of pneumonia and empyema in one-yearly periods.

In Table VII, the deaths are grouped in the three larger age-periods.

**TABLE VII.**
**Age-groups: Post-mortem Series.**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Deaths</th>
<th>Percentage of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 2 years</td>
<td>196</td>
<td>80.5%</td>
</tr>
<tr>
<td>2 to 5 years</td>
<td>36</td>
<td>15%</td>
</tr>
<tr>
<td>5 to 12 years</td>
<td>11</td>
<td>4.5%</td>
</tr>
<tr>
<td>Birth to 12 years</td>
<td>243</td>
<td>—</td>
</tr>
</tbody>
</table>
The high mortality in the first two years and the rapid decrease in the later age periods are very clearly shown. In Chart II it may be noted that almost one half of all the deaths occurred in the first year.

It is worth while tracing in half-yearly periods the death-rates for pneumonia in the clinical series through this critical time of the first two years (Table VIII).

**TABLE VIII.**

**Inclusive Pneumonia Group (Clinical Series).**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cases</th>
<th>Deaths</th>
<th>Death-rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 6 months</td>
<td>45</td>
<td>40</td>
<td>89%</td>
</tr>
<tr>
<td>6 to 12 months</td>
<td>89</td>
<td>39</td>
<td>45%</td>
</tr>
<tr>
<td>1 to 1½ years</td>
<td>91</td>
<td>34</td>
<td>37-5%</td>
</tr>
<tr>
<td>1½ to 2 years</td>
<td>85</td>
<td>23</td>
<td>27%</td>
</tr>
<tr>
<td>2 to 3 years</td>
<td>90</td>
<td>9</td>
<td>10%</td>
</tr>
</tbody>
</table>
The numbers of cases in each period are sufficient to allow comparison by a percentage death-rate. The rate shows a regular decline from a very high figure in the first six months. In the third year the rate has dropped to 10 per cent., which is that of the whole period 2 to 5 years.

Table IX shows the number of deaths from pneumonia and empyema in the post-mortem series in the first four half-yearly periods.

**TABLE IX.**

**AGE GROUPS: PNEUMONIA AND EMPYEMA (POST-MORTEM SERIES).**

<table>
<thead>
<tr>
<th>Age Period</th>
<th>Deaths</th>
<th>Percentage of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 6 months</td>
<td>64</td>
<td>26%</td>
</tr>
<tr>
<td>6 to 12 months</td>
<td>57</td>
<td>23.5%</td>
</tr>
<tr>
<td>1 to 1½ years</td>
<td>55</td>
<td>23%</td>
</tr>
<tr>
<td>1½ to 2 years</td>
<td>20</td>
<td>8%</td>
</tr>
</tbody>
</table>

These figures are in agreement with those of the clinical series. The largest number of fatal cases was in the first half-year and a steady fall occurred thereafter. There was a remarkable decrease in numbers after the age of eighteen months.

*Alveolar and Broncho-pneumonia.* The influence of age in these separate groups in the clinical series is illustrated in Chart III. It should be noted that they do not contain cases of empyema or of the miscellaneous group.

**Chart III.**
The broncho-pneumonia group may be taken first. Here the broad result is simple and striking: the great majority both of cases and deaths occurred in the first two years—about 80 per cent. of the cases and 84 per cent. of the deaths. There were only three cases after the fifth year, all of them fatal. Thus, in the clinical series the death-rate for this type of pneumonia was high throughout the whole period of childhood.

The results for alveolar pneumonia are different, both in case-incidence and death-rates. Considerably less than half the cases occurred in the first two years (38 per cent.). This type, indeed, was fairly common throughout childhood, although the numbers, measured in yearly periods, fell off after the fourth year. With regard to deaths, although again the great majority (about 80 per cent.) occurred in the first two years, the death-rate for this period was trifling (14.5 per cent.) as compared with that for broncho-pneumonia (61 per cent.); thereafter, it at once fell to a low level, at which it remained throughout childhood.

These broad results can be shown clearly in figures by the use of larger age periods (Table X).

TABLE X.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Alveolar Pneumonia</th>
<th>Broncho-pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 2 years</td>
<td>143</td>
<td>21</td>
</tr>
<tr>
<td>2 to 5 years</td>
<td>131</td>
<td>2</td>
</tr>
<tr>
<td>5 to 12 years</td>
<td>112</td>
<td>3</td>
</tr>
<tr>
<td>Birth to 12 years</td>
<td>386</td>
<td>26</td>
</tr>
</tbody>
</table>

It should be mentioned that the death-rates given above are lower than they should be, especially for broncho-pneumonia, by the omission of cases of empyema and of the miscellaneous group.

Chart IV represents the age incidence in the post-mortem series of alveolar and broncho-pneumonia in yearly periods.

It confirms the facts obtained from the clinical series. In the earlier age periods the fatal cases of broncho-pneumonia show a vast preponderance over those of alveolar pneumonia. Nevertheless, the two curves are not materially different in form. Further, in both types of pneumonia, the period of greatest mortality is the first year.
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CHART IV.


Empyema. The standards of selection for this group have already been explained. The aim was to include all cases in which any pus or sero-purulent fluid, discovered by needle-aspiration during life or by post-mortem examination, had been poured out into the pleural cavity. The total was 89, but as the number for annual periods were small, the influence of age will be better shown by taking the longer periods previously used (Table XI).

TABLE XI.

AGE GROUPS: EMPYEMA (CLINICAL SERIES).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cases</th>
<th>Deaths</th>
<th>Death-rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 2 years</td>
<td>36</td>
<td>27</td>
<td>75%</td>
</tr>
<tr>
<td>2 to 5 years</td>
<td>10</td>
<td>6</td>
<td>31-5%</td>
</tr>
<tr>
<td>5 to 12 years</td>
<td>34</td>
<td>3</td>
<td>8-5%</td>
</tr>
<tr>
<td>Birth to 12 years</td>
<td>89</td>
<td>36</td>
<td>40-5%</td>
</tr>
</tbody>
</table>
The incidence of empyema would appear by Table XI to be fairly equal in the three periods. It must be remembered, however, that empyema is not an independent disease, but a complication of pneumonia. What it is really important to ascertain is the frequency of its occurrence in pneumonia; and to do this, the figures for empyema must be set alongside those for pneumonia in the same age periods. This comparison is made in Table XII.

**TABLE XII.**

<table>
<thead>
<tr>
<th>Age Groups: (Clinical Series)</th>
<th>Pneumonia (all cases including empyema)</th>
<th>Emphyema</th>
<th>Emphyema percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 2 years</td>
<td>310</td>
<td>36</td>
<td>11.5%</td>
</tr>
<tr>
<td>2 to 5 years</td>
<td>184</td>
<td>19</td>
<td>10.5%</td>
</tr>
<tr>
<td>5 to 12 years</td>
<td>154</td>
<td>34</td>
<td>22%</td>
</tr>
<tr>
<td>Birth to 12 years</td>
<td>648</td>
<td>89</td>
<td>13.5%</td>
</tr>
</tbody>
</table>

The result brought out by these figures is definite. The complication of empyema is twice as frequent in pneumonia after five years as before that age. In the present series empyema occurred once in every five cases of pneumonia over five years of age. Some allowance must, however, be made for fatal cases of pneumonia where empyema was undetected during life and where no post-mortem examination was made; but even if this is done, the broad statement is probably true that the complication of empyema is decidedly commoner in pneumonia after five years of age than before it. Over the whole period, the frequency of empyema in pneumonia was about one in seven.

With regard to the death-rates for empyema in these age periods, it must be repeated that empyema is a complication of an acute and death-producing disease, and that in early childhood the death-rate from pneumonia alone is very high. Therefore, the figures for the first two years in Table XI do not accurately express death-rates from empyema. No doubt the occurrence of empyema is an added risk of death, but the risk from the existing pneumonia is already great. In the period 5 to 12 years, when the death-rate from pneumonia is trifling, the death-rate for empyema given above is approximately accurate.

**SEX INCIDENCE.**

The influence of sex is shown in Tables XII and XIII.

**TABLE XII.**

<table>
<thead>
<tr>
<th>Type</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis</td>
<td>126</td>
<td>105</td>
</tr>
<tr>
<td>Alveolar pneumonia</td>
<td>230</td>
<td>156</td>
</tr>
<tr>
<td>Broncho-pneumonia</td>
<td>79</td>
<td>65</td>
</tr>
<tr>
<td>Miscellaneous group</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Empyema</td>
<td>53</td>
<td>36</td>
</tr>
<tr>
<td>Pleurisy</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>526</td>
<td>392</td>
</tr>
</tbody>
</table>
STUDIES OF PNEUMONIA IN CHILDHOOD.

TABLE XIII.

SEX INCIDENCE: ALL CASES (POST-MORTEM SERIES).

<table>
<thead>
<tr>
<th>Types</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar pneumonia</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Broncho-pneumonia</td>
<td>78</td>
<td>62</td>
</tr>
<tr>
<td>Terminal pneumonia</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Miscellaneous group</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Chronic pneumonia</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Septic (pyemic) pneumonia</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Unclassified</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Empyema (no pneumonia)</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Totals</td>
<td>149</td>
<td>95</td>
</tr>
</tbody>
</table>

The noteworthy feature of these figures is the preponderance of males. It is remarkably consistent throughout the different groups. The total for males for both series is 669 as against 487 for females, a ratio of 1.37 to 1. The only exceptions are found in the bronchiectasis group in the clinical series, and in the chronic pneumonia group in the post-mortem series; it is interesting and perhaps significant that these two are the only chronic groups represented in the tables.

SEASONAL INCIDENCE.

Charts V, VI and VII illustrate the influence of season. The figures in Charts V and VI include cases admitted till the end of 1928, thus bringing a period of eight complete years under review and differing slightly from the remainder of the clinical statistics which do not go beyond 31st October, 1928.

Chart V shows the quarterly incidence of pneumonia (all types and including empyema) in each of the eight years. From it the total yearly incidence can be roughly judged and it is seen that there is no very significant difference between the years, the totals ranging from a minimum of 63 in 1921 to a maximum of 105 in 1924. This chart and the succeeding one (Chart VI), which includes bronchitis in addition to pneumonia, also illustrate the relative importance of the seasons. The numbers of cases of both pneumonia and bronchitis were, of course, greater in the autumn and winter months, but it is to be noted that throughout the period of eight years the incidence of these two acute respiratory diseases never became negligible in any one month or quarter of the year.

When the figures are further considered over quarterly periods, it is found that in the case of pneumonia the average is highest in the fourth (October-December) and is only slightly less in the first (January-March) quarter; it is lowest in the third (July-September) quarter. A similar variation is shown in the post-mortem series (Chart VII). It is perhaps worthy of remark that the first quarter of the year, which can be regarded as the second half of the winter, might have been expected to provide the greatest number of cases, and especially of fatal cases, of pneumonia.
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CHART V.

QUARTERLY INCIDENCE: PNEUMONIA (CLINICAL SERIES).

CHART VI.

TOTAL MONTHLY INCIDENCE (CLINICAL SERIES).
Chart VI gives the total monthly incidence of pneumonia and bronchitis over the whole period of eight years. Of the individual months in this (clinical) series, November shows the highest, and July and September the lowest incidence of pneumonia. The seasonal occurrence of bronchitis is slightly different: the rate is highest in January and February, with the result that the first quarter (January—March) shows the greatest number of cases.

**Chart VII.**

**TOTAL MONTHLY INCIDENCE (POST-MORTEM SERIES).**

Chart VII illustrates the total monthly incidence of fatal cases in the post-mortem series. In order to enable six complete years to be reviewed, the period 1st November, 1922, to 31st October, 1928, has been taken: it differs slightly from that covered by the remainder of the post-mortem statistics (1st July, 1922 to 31st October, 1928). This Chart is more striking than the similar clinical one (Chart VI) and the contrasts are greater. The two correspond, as has already been mentioned, in that in both the fourth (October—December) quarter shows the highest figures. While, however, in the clinical series November had the highest incidence of pneumonia, December was the month in which autopsies were most numerous.

In conclusion we wish to express our thanks to our colleagues, Dr. N. S. Carmichael and Dr. L. H. F. Thatcher, for their courtesy in putting at our disposal a number of their fatal cases of pneumonia. These have been included in the post-mortem series dealt with in this paper. In subsequent papers we shall again be indebted to them for clinical records and post-mortem material in other cases that were under their care.

**REFERENCES.**

ARCHIVES OF DISEASE IN CHILDHOOD

APPENDIX.

The three following Tables contain a detailed statement regarding age incidence in both the clinical and post-mortem series: and facts regarding the site of consolidation in the post-mortem series.

TABLE XIV.

**Age Incidence: All Cases (Clinical Series).**

<table>
<thead>
<tr>
<th>Type</th>
<th>Age in years</th>
<th>0-1</th>
<th>1-1½</th>
<th>1-2</th>
<th>2-3</th>
<th>3-4</th>
<th>4-5</th>
<th>5-6</th>
<th>6-7</th>
<th>7-8</th>
<th>8-9</th>
<th>9-10</th>
<th>10-11</th>
<th>11-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis</td>
<td>Total Deaths</td>
<td>56</td>
<td>47</td>
<td>33</td>
<td>19</td>
<td>33</td>
<td>13</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>3</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alveolar pneumonia</td>
<td>Total Deaths</td>
<td>8</td>
<td>40</td>
<td>47</td>
<td>53</td>
<td>45</td>
<td>46</td>
<td>30</td>
<td>30</td>
<td>15</td>
<td>24</td>
<td>11</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>1</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
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TABLE XV.

**Age Incidence: All Cases (Post-mortem Series).**

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Total: 37 33 174
CHARLES McNEIL, AGNES R. MACGREGOR & W. ALISTER ALEXANDER.

STUDIES OF PNEUMONIA IN CHILDHOOD.
II. ALVEOLAR (LOBAR) PNEUMONIA.
STUDIES OF PNEUMONIA IN CHILDHOOD.

II. ALVEOLAR (LOBAR) PNEUMONIA.

BY


(From the Royal Edinburgh Hospital for Sick Children, and the Laboratory of the Royal College of Physicians, Edinburgh).

In the first paper of the series, a statistical analysis of pneumonia and bronchitis in childhood was presented, based on two series of cases, clinical and post-mortem. These were reviewed and classified into various types. The present paper deals with that type of pneumonia usually called lobar, giving a general account of its morbid anatomy and histology, and a report of three cases. It is advisable to explain that we use the term 'alveolar' instead of 'lobar' to designate this type of pneumonia. The reasons for this preference have been given in the preceding paper and will again be alluded to in the course of this paper.

After Barthez and Rilliet had clearly differentiated the type broncho-pneumonia in infants and young children, its great frequency was established, and the view was held by many that at this early period of life croupous or lobar pneumonia scarcely ever occurred. Thus Gairdner1 in 1853 referred to this controversy on the relative frequency of lobular and lobar pneumonia in early childhood in the following passage:—

Some of the earliest writers on the subject distinctly state that of the two forms of pneumonia, the lobular and the lobar, the former alone is to be found in early infancy, the latter alone beyond that age. The latest authorities, in some instances at least, will be found to maintain the same opinion, and notwithstanding the distinct observations of Barthez and Rilliet, Legendre and Bailly, Friendlèben and others as to the occurrence of lobar hepatisation in young infants.

In 1888 Henoch2 summed up the prevailing contemporary view of the controversy as follows:—

Although catarhal or broncho-pneumonia is the commonest inflammatory affection of the lung in childhood, yet the view which formerly obtained as to the rareness of the croupous form has long been done away with, and rightly too. Between the third and the twelfth years this disease is indeed very common, and also in the first two years of life it is by no means rare.

The weight of clinical opinion at the present day seems to take the same view. Table I shows the relative numbers of cases of alveolar (croupous, lobar) pneumonia occurring in childhood before and after two years as reported by various authors.

1853

22029
TABLE I.
ALVEOLAR (LOBAR) PNEUMONIA.

<table>
<thead>
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<th>Author</th>
<th>Date</th>
<th>No. of cases</th>
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<td>Dunlop</td>
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<tr>
<td>Hutchison</td>
<td>1926</td>
<td>70</td>
<td>35</td>
<td>50%</td>
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<td>McNeil, Macgregor, and Alexander</td>
<td>1929</td>
<td>386</td>
<td>164</td>
<td>45.2%</td>
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These views, old and new, are, however, largely based on clinical diagnosis, corrected to some extent by post-mortem evidence. In a recent discussion on the subject, Findlay strongly reasserted the old doctrine. He maintained that practically all cases of primary pneumonia under the age of three years belonged to the type broncho-pneumonia and based this statement on the evidence of 65 consecutive autopsies of pneumonia in children. In a recent number of this journal, Olive Somerville has published a detailed analysis of this post-mortem material. Out of the total, only one typical lobar pneumonia was found and that in a child aged five years. There were two other cases, both in children under two years, which might be classed as lobar pneumonia but which presented atypical features. The principal criterion of diagnosis in this investigation was the microscopic examination of relatively small pieces of lung tissue.

Although the question in dispute cannot be completely settled by post-mortem evidence, Findlay's results, if confirmed, would go far to overthrow this long preponderant view that alveolar or lobar pneumonia occurs throughout childhood and is fairly common even in infancy. We therefore present a series of fatal cases of alveolar (lobar) pneumonia, the majority of them in children under two years, in which the post-mortem appearances are described, and in which we offer macroscopic and microscopic evidence in justification of the diagnosis of this type of pneumonia.

PATHOLOGICAL STUDY.

Alveolar (lobar) pneumonia is comparatively seldom seen in the post-mortem room of a children's hospital. In uncomplicated cases the mortality is low. The cases which come to autopsy are, as a general rule, those of unusual extent or severity, those in which some dangerous complication has developed, or those in which some pre-existent abnormality has prejudiced the patient's chances of survival. Opportunities of studying the pathology of this disease in straightforward uncomplicated cases of the kind which usually recover are therefore relatively few. This fact occasions some difficulty in determining exactly what are the usual pathological characters of alveolar pneumonia in childhood and infancy, and is responsible for the uncertainty concerning the frequency of this type.
In our previous paper it was stated that of a series of 945 autopsies in cases of death from all causes performed in the Royal Edinburgh Hospital for Sick Children during the period from July, 1922, to October, 1928, inclusive, 23 (2.5 per cent.) were cases of alveolar pneumonia, and 140 (14.8 per cent.) were cases of broncho-pneumonia. There were also examples of other types, the characters and number of which were stated. A short survey of these 23 cases of alveolar pneumonia may be of some interest as an introduction to a study of the morbid anatomy and histology of this type.

Age.—The ages of the children ranged from 4 months to 4 years and 9 months. Twelve were under one year old; six were between one and two years. Thus more than three-quarters of all the cases were in children under two years of age.

Sex.—There were seventeen boys and six girls. Although the number of cases is far too small to warrant any drawing of conclusions with regard to sex incidence, the preponderance of males is striking, and is in agreement with the figures derived from a much larger series of clinical cases which was reviewed in our previous paper.

Complications.—The incidence of serious complications was very high in this series. In 15 of the 23 cases the pneumonia was accompanied by some complicating condition (either resulting directly from the pneumonic infection or pre-existent), which greatly increased the gravity of the illness, and was in some instances certainly the actual cause of death.

The nature and frequency of these complications were as follows:—empyema, 8; pericarditis, 3; meningitis, 3; abscess in lung, 3; peritonitis, 1; acute nephritis, 1; suppurative pyelonephritis, 1; congenital defect of the heart, 1.

Morbid Anatomy.

Site and extent of consolidation.—In 8 of the 23 cases, the right lung only was affected; in 8, the left lung only; in 7, both lungs were involved.

In 10 cases, the pneumonia was confined to one lobe. In 13 cases, more than one lobe was wholly or partly consolidated. The order of frequency with which the various lobes were affected was as follows:—left lower lobe, 9; right upper lobe, 5; right lower lobe, 8; left upper lobe, 4; right middle lobe, 4.

In ten cases the area of consolidation extended to one whole lobe or more. In eight cases the pneumonia was present in a single patch the extent of which was less than one lobe. In the remaining five cases, pneumonia was present in more than one lobe, but affected only a part of each. In no case was an entire lung consolidated, although there were instances in which the unaffected part was very small (Plate II, Fig. 5).

In those cases in which the pneumonic area was less than a whole lobe, it was, as a general rule, of considerable size, often about half a lobe (Plate II, Fig. 6); but in certain instances no more than a patch about an inch in diameter was consolidated (Plate II, Fig. 7).
When consolidation affected only a part of a lobe, its position in the lobe was very variable. It was more often posterior than anterior. It very seldom failed to reach the pleural surface at some point. In two cases it was situated deeply near the root, without having extended to the surface. Sometimes its position was peripheral, so that it did not approach the root (Plate II, Fig. 7.)

It is evident from these observations that, although this disease is commonly called lobar pneumonia, involvement of a whole lobe or nearly a whole lobe is not an essential character of alveolar pneumonia in children. In our experience, it is more usual to find consolidation of a part of a lobe or lobes. There is far more variation in the extent of consolidation in the alveolar pneumonia of childhood than in the corresponding disease (lobar pneumonia) of adult life. While it may be very extensive, the pneumonic area is often relatively smaller in children than is usual in adults. If this be true of fatal cases, it is likely to be even more often true of the slighter cases which recover; and this is confirmed by clinical experience. At the same time, it should be pointed out that a majority of our cases showed pneumonia in more than one lobe; but it does not follow, of course, that this is of equally frequent occurrence in non-fatal cases. It is apparently rather unusual for an entire lung to be completely consolidated.

Appearance of the pneumonic area.—When pneumonia in a child is encountered at autopsy, the problem which confronts the pathologist is the diagnosis between alveolar pneumonia and confluent broncho-pneumonia. In typical cases the question is not a difficult one, for an area of alveolar pneumonia presents certain well-defined macroscopic characters by which it may be distinguished from confluent broncho-pneumonia.

The affected part, no matter of what extent, is massively and completely consolidated. As every alveolus is filled with exudate, no collapse is present within the area, which accordingly projects well above the level of neighbouring unconsolidated lung. Its consistence is solid, firm, and uniform. It lacks the nodular character and somewhat rubber-like resilience which in most broncho-pneumonic lungs, even of the most confluent type, are produced by an alternation of zones of complete consolidation with zones of partial collapse within the affected part. Where the pneumonic area abuts upon aerated lung substance, the margin is usually extremely definite (Plate II, Figs. 6 and 7). This also is a point of difference between alveolar pneumonia and confluent broncho-pneumonia.

Should the pneumonia extend to the surface of the lung, the pleura overlying it is invariably inflamed. Usually there is only a thin layer of dry fibrinous exudate, and this may or may not be present beyond the limits of the pneumonic area. Apart from the cases in which empyema had developed, we have rarely seen either a copious fibrinous exudeate or a pleurisy with effusion. It is probably true to say that in childhood cases, in which the pleurisy is severe, usually go on to empyema.

On section, the appearance of the pneumonic area naturally depends upon the stage which has been reached. If resolution has not begun, the cut
surface has a dry, dull appearance and the projection of plugs of exudate from the alveoli often imparts to it a finely granular character. This differs from the appearance of a broncho-pneumonic lung, which on section usually presents a moist and shiny surface.

The colour varies from red to grey according to the stage of the disease. Most of our cases were at the stage of early grey hepatization at the time of death, but there were several examples of red hepatization. The colour of the cut surface is usually fairly uniform, but rarely perfectly so. Alternations of red and grey are often present throughout the patch due to differences in the composition of the exudate; but these variations in colour are independent of the distribution of bronchi, and the appearance of motting produced by them is quite different from the definite peri-bronchial motting which is characteristic of broncho-pneumonia. In early cases there is often a zone of intense haemorrhagic congestion at the spreading edge of the patch.

Bronchi and bronchioles within the pneumonic area are not conspicuous; do not show inflammatory thickening of their walls; are not noticeably dilated; and do not contain large quantities of pus, although a certain amount of exudate is present in them. In unconsolidated parts of the lungs the bronchi are healthy. The absence of bronchitis, especially of the smaller tubes, in those parts where there is no consolidation is an important feature of typical alveolar pneumonia. Some hyperemia of the mucous membrane of the large bronchi and of the trachea, and the presence therein of exudate derived from the pneumonic area, are usual.

Apart from the definite patch or patches of pneumonia, the lungs are free from consolidation. There is usually some general congestion, and a degree of acute vesicular emphysema may be present, but usually very much less than in broncho-pneumonia. Interstitial emphysema, which is of common occurrence in broncho-pneumonia, we have never seen in a case of alveolar pneumonia.

The tracheo-bronchial and root glands show swelling and active hyperæmia (Plate I, Fig. 3), but the very great enlargement and intense inflammation of these glands, so often associated with broncho-pneumonia (Plate II, Fig. 8), have not been found in any case in our series.

Morbid Histology.

In the pneumonic area complete consolidation of the whole part affected is a constant feature. Every alveolus is filled with exudate, and areas of collapsed or partially collapsed alveoli are not present.

The exudate.—There is considerable variation in different cases in the composition of the exudate which fills the alveoli, depending partly, but not entirely, upon the stage of the disease. There would seem to be a tendency for the exudate to be of a more cellular and relatively less fibrinous character in children than in adults. This is true especially in very young children, in whom departure from the typical standard of the adult case is apt to be greater in this and in other respects. Nevertheless, this rule is not of universal
application, for even in infants the exudate may be composed mostly of fibrin. Fig. 9 (Plate III), which is taken from the lung of a male infant, aged 9 months, shows an exudate in which fibrin greatly preponderates.

There is always some variation in the composition of the exudate in different parts of the pneumonic area; and, as in adult cases also, the more cellular parts are often those nearest to the terminal bronchiole, the outlying alveoli of the lobule containing a more fibrinous exudate. In certain cases, which in other respects conform to the alveolar type, there is very little formation of fibrin, and the exudate is almost entirely composed of polymorphonuclear leucoocytes. We are of opinion that the amount of fibrin in the exudate is not a reliable guide in differentiating alveolar pneumonia from bronchopneumonia, especially when only small sections are used, and the microscopic examination is thus confined to a limited portion of the consolidated part. Most lungs with confluent broncho-pneumonia contain areas in which fibrin is as plentiful in the alveoli as in any case of croupous pneumonia in child or adult.

The alveolar walls.—It is characteristic of alveolar pneumonia that the products of inflammation are thrown out into the alveolar spaces and that the walls do not show any marked degree of infiltration with inflammatory cells (Plate III, Fig. 10). Congestion of capillaries in the early stages, and sometimes swelling of the lining epithelium before it is cast off, may cause the walls to look somewhat thicker than in health (Plate III, Fig. 9); but the dense infiltration with inflammatory cells, which so greatly obscures the alveolar walls in broncho-pneumonia, is characteristically absent in the alveolar type.

The bronchi.—Within the pneumonic area the bronchi always contain inflammatory exudate which resembles that present in the alveoli, although it is often relatively richer in leucoocytes. When the alveolar exudate is fibrinous, the bronchi are often plugged with fibrino-cellular exudate, a condition rarely seen in broncho-pneumonia. When the exudate in the alveoli is of a very cellular type, in the bronchi it may have an almost purulent character. Evidence of severe inflammation of the bronchi themselves is, however, absent in typical cases. If it be present, the case is either atypical, or the diagnosis of alveolar pneumonia is mistaken. The blood vessels of the bronchial wall may share to some extent in the general hyperaemia of the part; but the wall is not significantly swollen, nor infiltrated with polymorphonuclear cells, and quite often even the epithelial lining remains surprisingly intact (Plate III, Fig. 11). The healthy condition of small bronchi in the midst of an area of consolidation is clearly shown in Fig. 12 (Plate III).

In some of our cases, especially those of young children, a certain amount of lymphocytic infiltration has been found in the bronchial walls in the pneumonic area. Some observers hold that this is characteristic of broncho-pneumonia, and would classify as such any case in which it was found. Our experience has been that in broncho-pneumonia the cellular infiltration of the bronchial walls is much more severe; that among the infiltrating cells polymorphonuclear leucoocytes rather than lymphocytes predominate; that the walls are greatly swollen in addition to being infiltrated; and that the lining epithelium is usually destroyed. In the absence of other evidence of acute
inflammation of the bronchial wall, a certain amount of lymphocyte infiltration need not be regarded as inconsistent with a diagnosis of alveolar pneumonia. The lymphocytes are probably derived from the microscopic lymph nodes which occur normally in the walls of bronchi and readily undergo hyperplasia in the presence of any inflammation in their neighbourhood.

*Interlobular septa and perivascular stroma.*—There are often large deposits of fibrin in the interlobular septa, causing them to be greatly broadened out so that they form a conspicuous feature of the section (Plate III, Fig. 13). A certain number of polymorphonuclear leucocytes may be entangled in the fibrin meshwork. Dense aggregations of leucocytes in the septa are unusual. We have found this fibrin deposit in the septa very frequently in cases of alveolar pneumonia, and comparatively seldom in broncho-pneumonia, even where there has been extensive confluence. The perivascular fibrous tissue may show the same condition, but often it is remarkably free from any inflammatory change (Plate III, Fig. 12). Sub-pleural and septal lymphatic vessels may be dilated and filled with a fibrinous coagulum. The pleura practically always shows an exudate, usually scanty and mostly fibrinous except when empyema is present.

The margin of the pneumonic area. When the area of pneumonia abuts upon unconsolidated lung, the edge is a fairly definite one (Plate II, Fig. 6). Sometimes the consolidated patch is bounded in part by interlobular septa, but a boundary of that kind is rarely complete along the whole extent of the patch. If the pneumonia be still spreading at the time of death, there may be a narrow zone of intense congestion and haemorrhage at the edge of the consolidated area. Sometimes there is merely a zone in which the capillaries in the alveolar walls are congested and the spaces contain an oedematosus material. In either case the appearances at the spreading edge suggest an extension of the inflammation by continuity from alveolus to alveolus in a more or less uniform manner all along the margin of the patch. This is quite different from the manner of spread in broncho-pneumonia, which is by way of the bronchi, so that beyond the edge of an area of confluent broncho-pneumonia outcrops of consolidation appear in small patches surrounding bronchioles (Plate II, Fig. 8).

In unconsolidated parts of the lungs the alveoli and bronchi alike are free from inflammatory exudate. Apart from some general hyperæmia and perhaps slight acute vesicular emphysema, the parts of the lungs which are not consolidated are healthy. This is exceedingly characteristic of typical alveolar pneumonia (Plate I, Figs. 2 and 4, and Plate II, Fig. 6), and is in sharp contrast to the state of affairs in confluent broncho-pneumonia (Plate II, Fig. 8).

**Discussion.**

The features of alveolar pneumonia to which special importance is attached in distinguishing it from confluent broncho-pneumonia are the following:—the localization of consolidation to a certain definite area; the absence of generalized bronchitis; the absence of anything more than a very trivial
inflammation of the bronchi within the pneumatic area; the freedom of the bronchial and alveolar walls and stroma generally from damage by infiltration with inflammatory cells.

The last of these deserves special emphasis. Alveolar pneumonia, in marked contrast to broncho-pneumonia, is a disease in which the inflammatory reaction results in the throwing out of the products of inflammation upon the surface (i.e., the alveolar spaces), and in which the substance of the lung shows no severe or persistent involvement. A reason for this immunity of the interstitial framework may be found in the fact that the infection is located in the alveoli, whose walls possess no lymphatics. Invasion of the lymphatics of the lungs by the infection, with consequent lymphangitis and acute interstitial inflammation, is therefore not liable to occur. In broncho-pneumonia, on the contrary, where the infection is centred chiefly in the bronchi whose walls possess a rich network of lymphatic vessels which are readily invaded, the occurrence of lymphangitis and acute interstitial inflammation is obviously a strong probability.

According to Blake and Cecil, however, lobar pneumonia experimentally produced in monkeys begins as a lymphangitis in the walls of bronchi which is followed by alveolar inflammation; and with the onset of consolidation of the alveoli, this lymphangitis passes off. The application of this result to human cases has yet to be demonstrated, but if it be correct, it is significant that the lymphangitis is not persistent or progressive, but a transient affair which disappears when the inflammatory reaction is fully established and the infection passes out into the alveolar spaces.

The absence of persistent lymphangitis and inflammatory involvement of the interstitial framework of the lungs in alveolar pneumonia is a significant pathological feature which has an important bearing upon certain clinical features of the disease. The relatively short course, the abrupt termination of serious symptoms, and the rapid return of the lung to a normal state, which are characteristic of alveolar pneumonia in cases which recover, would all be unlikely, if not impossible, in the presence of severe interstitial inflammation and lymphangitis. Further, because the alveolar septa and bronchial walls suffer no disorganization during the active stage of the inflammation, when recovery occurs the exudate is removed from the alveoli by resolution and there is no occasion for a process of reorganization. Therefore, the lung is able to recover perfectly and rapidly, without permanent change in structure which would inevitably cause disablement of function. Hence the comparative rarity of such conditions as fibrosis or bronchiectasis occurring as a sequel of alveolar pneumonia.

Atypical cases. It is clear that in typical cases it is no very difficult matter to distinguish between alveolar pneumonia and confluent broncho-pneumonia, for there are many points of difference sufficiently clearly defined. But from time to time cases are met with which are really difficult to place in either category, because of their atypical features. Among the cases which present this problem there are two groups:—(a) those which deviate in some important particular from the picture of alveolar pneumonia which has been.
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described: (b) those in which one part of the lung presents the typical picture of alveolar pneumonia, while obvious broncho-pneumonia is present in other parts.

For the purpose of classification in our series, all cases of the latter kind were excluded from the alveolar pneumonia group. With regard to the former, every case must be considered on its merits. In our series, a few cases which presented certain atypical features were classified as alveolar pneumonia, because, after due consideration, the weight of evidence was held to be in favour of that diagnosis. Atypical cases are most frequent in the earlier age periods. After the age of two years the cases tend more and more to approximate to the adult type of ‘lobar’ pneumonia.

The most important deviation is the involvement of the bronchi within the pneumonic area in active inflammation. No case in which this occurs can be regarded as typical alveolar pneumonia. But we have occasionally found it in cases which in other respects conformed strictly to the alveolar type. The bronchi may be denuded of epithelium, their walls invaded by inflammatory cells and much swollen; in one of our cases they had even suffered considerable disorganization and showed a degree of acute dilatation (Plate II, Fig. 5).

Some observers would undoubtedly class such a case as broncho-pneumonia. Yet, if in all other respects the pathological picture be typically that of alveolar pneumonia, it would appear to us to be more correctly placed in that group. Our experience has led us to believe that the inflammation of the bronchial walls in cases of this kind is probably secondary to a primary alveolar pneumonia, and is not the primary manifestation of infection as in broncho-pneumonia. In other words, it is possible that occasionally the infection, instead of remaining localized in the alveolar spaces, may spread to the bronchi and invade their walls as a secondary development. This is a serious occurrence which, it may be supposed, increases the gravity of the disease and prejudices the chances of recovery. It may be that it seldom, if ever, occurs in cases which recover: even in fatal cases it is rare.

Obviously in cases of this kind the pathological diagnosis must remain in doubt, and a matter of personal opinion. In the Glasgow series, all such cases were evidently classed as broncho-pneumonia. We have retained some of them in our alveolar pneumonia group. We would venture to express the opinion that in some of these doubtful cases it would be impossible to come to a reliable decision by a study of the limited field available in ordinary small microscopic sections, and in this respect the whole-lung sections which we have been able to use are of great importance.

ILLUSTRATIVE CASES.

CASE 1. **Double pneumonia of alveolar (lobar) type.** (Plate I, Figs. 1 and 2). Female, aged 3 years, seventh child. Mongolian imbecile. Breast-fed for 18 months. History of diphtheria, with good recovery, seven weeks before the fatal illness. Fat, flabby child. Died within 24 hours of admission after an illness of sudden onset and of six days’ duration. Physical signs of consolidation in both lungs. Large heart and marked evidence of circulatory failure.

On post-mortem examination, the right upper lobe was partially and the left lower lobe more completely consolidated. The pneumonic areas were of a deep red colour and the overlying pleura was inflamed. The remaining lobes were free of pneumonia and showed some
emphysema. No general bronchitis was present. There was marked enlargement of the heart, especially on the right side, in association with a large defect in the membranous part of the septum.

Microscopically, the pneumonia in both lungs was at much the same stage (red hepatization). There was no doubt as to its alveolar character. There was the usual exudate in and trivial inflammation of, the bronchi in the consolidated lobes. Both lungs showed evidence of previous damage—a slight fibrosis of unequal distribution, arterial changes, and lymphocytic accumulations in bronchial and other connective tissues. There was no history of a former illness, but this finding was not surprising in view of the susceptibility of mongols to respiratory infections.

Case 2. Pneumonia of alveolar type, with relapse. (Plate I, Figs. 3 and 4). Male, aged 10 months. Second child of unemployed father; home conditions bad. Breast-fed. No previous illnesses. General condition good. Five teeth. Died after a three weeks' illness, in which there were three distinct pyrexial periods in close proximity, followed by low fever in the last few days (Chart I).

CHART I.

RECURRING ALVEOLAR PNEUMONIA (CASE 2).

The child was not under observation during the first period. The second was associated with consolidation of the right lower, and the third with consolidation of the right upper lobe. During the latter there were signs of meningeal irritation. The left lung remained unaffected throughout.

Post mortem, the left lung and right middle lobe were healthy. The right lower lobe was the seat of an almost completely resolved pneumonia, with early organization of the overlying pleural exudate. The right upper lobe, with the exception of the apex and anterior border, was consolidated; the pneumonia recent; the colour and consistence fairly uniform; the margin sharp; the pleura acutely inflamed. The bronchi contained some pus. There was little to note elsewhere in the body.

On microscopic examination, the left lung showed merely superficial catarrh of the larger air-passages. In the right lower lobe, remnants of exudate in alveoli and the presence of large mononuclear cells provided ample evidence of a recent pneumonia in the final stages of resolution. The process was least advanced in the portion of the lobe adjacent to the root. There was catarrhal desquamation of the epithelium of bronchi, but no active inflammation. In the
PLATE I.

Figs. 1 and 2.—Double alveolar pneumonia in girl of 3 years (illustrative Case 1). Consolidation of right upper and left lower lobes.

Figs. 3 and 4.—Alveolar pneumonia in boy of 10 months (illustrative Case 2). Pneumonia resolving in right lower lobe. More recent consolidation of most of right upper lobe. Left lung unaffected. A=Lymphatic gland at root of right lung.

PLATE II.

Fig. 5.—Alveolar pneumonia in boy of 5 months (illustrative Case 3). Almost complete consolidation of right lung. Some dilatation of bronchi.

Fig. 6.—Alveolar pneumonia in boy of 14 months. Consolidation of half of left lower lobe.

Fig. 7.—Alveolar pneumonia in boy of 4 months. Consolidation of small area at base of right lung.

Fig. 8.—Confluent broncho-pneumonia in boy of 1 year, included for purposes of contrast with preceding illustrations of alveolar pneumonia.

PLATE III.

Fig. 9.—×120. Alveolar pneumonia in boy of 9 months showing uniform fibrino-cellular exudate in alveoli, with thickening of alveolar walls due to congestion of capillaries and swelling of endothelial and alveolar lining cells.

Fig. 10.—×300. Alveolar pneumonia in boy of 4 years and 9 months, showing fibrino-cellular exudate in alveoli. Rather later stage than above. No swelling or infiltration of alveolar walls.

Fig. 11.—×150. Alveolar pneumonia in girl of 3 years (same case as Figs. 1 and 2). Bronchus in pneumonic lobe, showing relative freedom from inflammation and intact epithelium.

Fig. 12.—×100. Alveolar pneumonia in boy of 9 months (same case as Fig. 9). Small bronchi (B) in consolidated area, with exudate in lumina but undamaged walls. Perivascular connective tissue also free from infiltration. A=Blood-vessels.

Fig. 13.—×120. Alveolar pneumonia in boy of 9 months (same case as Figs. 9 and 12). Interlobular septum broadened as result of deposit of fibrin.
right upper lobe, the pneumonia was of alveolar type. Alveoli were completely filled with fibrinous exudate containing polymorphonuclear and catarrhal cells; alveolar walls clearly distinguishable and not infiltrated with inflammatory cells; the exudate was of the same type throughout and not 'zonal' in distribution as in broncho-pneumonia. The bronchi showed up clearly owing to the presence of a cellular exudate, but the epithelium was intact and the substance of the walls not appreciably inflamed. The interlobular septa were oedematous. There was recent exudate on the pleural surface.

The diagnosis of alveolar pneumonia was clear on clinical and pathological grounds.

CASE 3. *Alveolar pneumonia involving most of one lung, with a patch in the lower lobe of the other lung.* (Plate II, Fig. 5.) Male, aged 5 months. Third child. Mother died of puerperal septicemia. Fed on cow's milk mixtures. Fatal illness lasted two weeks (see Chart II.). Onset of acute symptoms sudden but preceeded by 'cold in head.' Pale (rather thin) infant, with signs of early rickets. Consolidation noted in right lower lobe on sixth day; spread to involve most of lung posteriorly. Effusion suspected but not confirmed by exploration. Cough short and obviously painful. Breathing rapid but not embarrassed. Some accompaniments in left lung throughout illness, but no pneumonia detected.

On post-mortem examination, the whole right lung, except for the middle lobe and the apical portion of the upper lobe, was solid. The colour was a more or less uniform greyish-red. There was well-marked bronchitis, but an absence of peri-bronchial motting. A thick fibrinous deposit was present on the visceral pleura. The left lung contained an irregularly shaped but fairly well-defined patch of pneumonia in the substance of the lower lobe. It showed no other area of consolidation. The appearance of the pneumonic patch was not that of confluent broncho-pneumonia.

Microscopic examination confirmed the presence of rather severe bronchitis in the consolidated parts; some of the bronchi, in the right lung especially, were denuded of epithelium and appreciably dilated. Nevertheless, the pneumonia in its uniformity and other characters was essentially alveolar in type, not only in the extensively involved right lung but also in the partially consolidated left lower lobe, and no doubt was felt in so diagnosing the case.
ARCHIVES OF DISEASE IN CHILDHOOD.

SUMMARY.

1. An analysis of twenty-three autopsies in cases of alveolar (lobar) pneumonia in young children is given. Eighteen were under two years of age.

2. The study of this post-mortem material supports the view widely held on clinical grounds that this type of pneumonia is not uncommon in the first two years of life.

3. The morbid anatomy and histology of alveolar pneumonia in infancy and early childhood are described.

4. Atypical forms of alveolar pneumonia in children are briefly discussed.

5. Short clinical and post-mortem reports of three cases of alveolar pneumonia, two of them in infants under one year, are presented.

6. In this study, paraffin sections of entire lungs have been used. Illustrations of these are given.

The large sections illustrated in this and the succeeding papers are the work of Mr. T. D. Hamilton of the Royal College of Physicians' Laboratory, Edinburgh.

REFERENCES.

CHARLES McNEIL, AGNES R. MACGREGOR &
W. ALISTER ALEXANDER.

STUDIES OF PNEUMONIA IN CHILDHOOD.
III. BRONCHO-PNEUMONIA.
STUDIES OF PNEUMONIA IN CHILDHOOD.

III. BRONCHO-PNEUMONIA.

BY


(From the Royal Edinburgh Hospital for Sick Children, and the Laboratory of the Royal College of Physicians, Edinburgh).

Broncho-pneumonia, if we consider its frequency, its high mortality and its serious and lasting sequelae, must be regarded as the most important type of pneumonia in early childhood. The recognition of the type and of its peculiar prevalence in the first years of life, began in the years following the clinical and pathological studies of Laennec. From this time, about 1820, until about the middle of the century, there was much discussion and controversy regarding this infantile type of pneumonia, based largely on post-mortem investigation. The factors of atelectasis, collapse, and inflammation, and the parts played by them in producing consolidation in the lungs of young infants, were much debated. In 1837, Seifert introduced the term broncho-pneumonia.

About 1850 Barthez and Rilliet put the discussion on firmer ground. They adopted the term broncho-pneumonia (using other synonyms including lobular pneumonia); they declared that the essential and primary lesion in the condition was a severe inflammation of the finer bronchial tubes, the changes in the lungs being derived from this bronchitis; and they identified as being practically inseparable, capillary bronchitis and broncho-pneumonia. They considered broncho-pneumonia to be the characteristic and common type in young children; but they also pointed out that cases of croupous or lobar pneumonia were met with even at the earliest age. The final statement of their views can be read in the chapter on broncho-pneumonia in their book *Maladies des Enfants* (1884), where they also give a full account of the long controversies of the preceding sixty years. This chapter remains still the classical presentation of the subject. There have been no substantial additions to our knowledge since it was written. There is still lacking a satisfactory explanation of the prevalence of this type of pneumonia in early childhood: on the one hand, a constitutional factor is alleged; on the other, some special bacterial cause.

West in this country, and Henoch in Germany, writing in the same decade, diverge little from the teaching of Barthez and Rilliet. They both emphasize the close, indeed inextricable, relation between bronchitis and broncho-pneumonia in young children.

It may be useful to set down together the numbers of our cases of bronchitis, broncho-pneumonia, and alveolar (lobar) pneumonia, already given in the statistical survey, grouping them in age periods (Table I).
TABLE I.

Age Periods in Authors' Series of Cases.

<table>
<thead>
<tr>
<th>Age period</th>
<th>Bronchitis</th>
<th>Broncho-pneumonia</th>
<th>Alveolar pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 2 years</td>
<td>...</td>
<td>155</td>
<td>110</td>
</tr>
<tr>
<td>2-5 years</td>
<td>...</td>
<td>55</td>
<td>31</td>
</tr>
<tr>
<td>5-12 years</td>
<td>...</td>
<td>21</td>
<td>3</td>
</tr>
</tbody>
</table>

Two points should be remembered in considering these figures. First, an attempt has been made to separate bronchitis from broncho-pneumonia in infants. Secondly, the group of broncho-pneumonia includes only a small number of cases of meases and whooping-cough. Both these facts have reduced the numbers of this group in comparison with the collected figures given by many other writers; and they give a relative prominence to the numbers of alveolar (lobar) pneumonia in the first age period.

Our figures justify the following general statement as to the relative incidence of the two types of pneumonia in childhood; whereas cases of alveolar (lobar) pneumonia occur throughout the whole period of childhood with fairly steady frequency, the great majority of cases of broncho-pneumonia are concentrated in the first two or three years of the period. This statement is in accord with the view prevalent to-day and for many years past.

**Pathological Study.**

Broncho-pneumonia is the form in which pneumonia is most often seen in the post-mortem room of a children's hospital. While differences of opinion may exist as to the relative frequency of broncho-pneumonia and alveolar pneumonia in cases which recover, there can be no doubt at all as to the preponderance of the former among those which are fatal.

In the first paper of this series, it was stated that of 945 consecutive autopsies performed in the Royal Edinburgh Hospital for Sick Children, 140 (14.8%) were cases of broncho-pneumonia, and 23 (2.5%) of alveolar pneumonia. This figure (140) excludes a group of 29 cases of terminal hypostatic pneumonia which, for the purpose of the analysis, were placed in a class by themselves, although they might reasonably be regarded as a sub-group of broncho-pneumonia. Some facts of interest derived from a survey of the 140 cases may be given.

**Age.** The ages of the children ranged from 1 week to 7½ years. 70 were under one year old; 48 were between one and two years. Thus, about 84 per cent. of all the cases were in children under two years of age.

**Sex.** There were 78 boys and 62 girls, showing no significant difference in incidence between the sexes.

**Complications.** In 51 of the 140 cases the broncho-pneumonia was accompanied by some serious complication, which in some instances was the
actual cause of death. The nature and frequency of these complications were as follows:—empyema (34); suppuration in the lungs (27); pericarditis (10); peritonitis (8); meningitis (4); gangrene of lung (1); suppurative pyelonephritis (1); laryngeal diphtheria (2).

**Morbid Anatomy.**

The upper respiratory passages. There is usually an acute catarrhal inflammation of the upper air passages, which becomes more severe towards the lower end of the trachea and in the main bronchi. Often an immense amount of thick purulent secretion is found at autopsy in the main bronchi, trachea and larynx. As a rule there is a generalised acute bronchitis affecting bronchi of all sizes throughout both lungs. The walls are swollen, the mucous membrane intensely red, the lumina filled with mucus-pus. This inflammation is often much more severe in the smaller than in the larger bronchi, and there may be some dilatation of the finer tubes.

**Site and extent of pneumonic consolidation.** In 20 cases in our series the right lung only was affected; in 8 the left lung only; in 112 both lungs were involved. In almost all instances when pneumonia was confined to one lung, bronchitis was present in the other. It is quite probable that, owing to the impossibility of examining microscopically every part of every lung which appeared to be free from consolidation, minute patches may have been overlooked. The number (28) of cases classed as unilateral may therefore be larger than it ought to be. In a certain number of bilateral cases, pneumonia was much more extensive in one lung than in the other (Plate II, Fig. 7 & 8), but it was more usual to find it similar in extent and apparent duration on the two sides (Plate I, Fig. 3 & 4; Plate II, Fig. 5 & 6).

In most cases pneumonic areas were present in all lobes. The lower lobes, however, especially the posterior and basal portions, were more constantly and usually more severely affected than other parts. If any confluence of broncho-pneumonic patches were present, it was most often at the base or along the posterior border. The parts most frequently found to be free from pneumonic patches were the anterior borders of the upper lobes. We have noticed, however, that a strip of consolidation at the antero-inferior angle of the left upper lobe, along the lower margin of the cardiac notch, is of remarkably frequent occurrence.

The size of individual areas of consolidation varies greatly in different cases. When there is no confluence, the patches are often exceedingly small, although they may be present throughout the whole of both lungs, with air-containing lung substance between them (Plate I, Fig. 1). Each of these small patches forms in relation to a bronchus or bronchiolo, which occupies the centre of it. When there is copious exudation into the alveoli surrounding the central inflamed bronchiolo and neighbouring patches become confluent over large areas, the resulting consolidation may affect a whole lobe or even almost a whole lung. In these cases a diagnosis of lobar pneumonia may suggest itself and differentiation may present some difficulty. It is quite
usual to find small discrete patches occupying the anterior parts of the lungs, with confluence in large areas at the bases and posterior borders (Plate II, Fig. 6).

The appearance of the pneumonic areas. This naturally varies greatly according to their size, their duration and the amount of confluence. When there is no confluence and the pneumonic patches are very small and occur in relation to practically every bronchiole, the cut surface of the lung shows innumerable sharply defined patches of pinhead size or even smaller, each with a tiny bronchiole in its centre. These minute patches project slightly above the general level of the cut surface, and the wall of the bronchiole is conspicuous owing to inflammatory thickening. At an early stage the patches are red; later, grey; still later, definitely yellow. The intervening lung substance is congested. The gross appearance of this form of broncho-pneumonia is sometimes remarkably like that of acute miliary tuberculosis, but close inspection reveals the presence of the central bronchiole in each patch and removes the likelihood of error. On slight pressure, quantities of purulent material exude from the bronchioles.

To the touch the lungs feel 'shotty,' the pneumonic areas being readily detected by palpation. Sometimes, indeed, their presence is more easily discerned by the fingers than by the eyes. In some cases, although the minute bronchioles are acutely inflamed, it is impossible to detect any consolidation by macroscopic examination, and a diagnosis of capillary bronchitis is apt to be made. But we have yet to find a case of this kind in which the microscope failed to reveal consolidation of tiny groups of alveoli surrounding the inflamed bronchioles.

When there is confluence so widespread that consolidation is almost or quite of lobar extent, certain features peculiar to broncho-pneumonia usually serve to distinguish it from alveolar pneumonia. The consolidated area is rarely as massively and completely consolidated as in alveolar pneumonia. There is almost always a certain amount of collapse associated with the consolidation. Because of this collapse, an area of confluent broncho-pneumonia is less voluminous than a corresponding area of alveolar pneumonia; sometimes indeed it is even less voluminous than adjacent aerated lung substance (Plate III, Fig. 9). It has a rubber-like resilience, unlike the somewhat brittle firmness of alveolar pneumonia; and an unequal or nodular consistence, readily appreciated on handling the organ. Where the area of confluent broncho-pneumonia abuts upon aerated lung substance, the margin is usually indefinite and irregular, and small pneumonic patches are present beyond it (Plate I, Fig. 3). The cut surface differs from that of an area of alveolar pneumonia. It is usually moist and shiny instead of dry, dull and granular, and there is conspicuous mottling corresponding to the distribution of small bronchi and bronchioles. Usually each bronchiole is surrounded by a small zone which is yellow or greyish yellow in colour and, being more completely consolidated, stands out slightly above the level of the adjacent lung substance. The walls of the bronchioles are swollen and stand out prominently; the lumen is often a little dilated and contains pus. The intervening lung substance is
red or greyish red, and is in a condition of partial collapse and partial consolidation which renders it completely airless. This conspicuous peribronchial mottling is exceedingly characteristic of confluent broncho-pneumonia and points unmistakably to that diagnosis.

Suppuration and necrosis. In nearly 29 per cent. of the cases of broncho-pneumonia in our post-mortem series (27 out of 140) suppuration had occurred in some part of the lungs, associated in numerous instances with areas of necrosis, which had the characters of septic infarcts and were caused by thrombosis of blood vessels. These necrotic areas occurred in consolidated parts, and were sometimes red, but more often pale in colour. They had a great tendency to septic softening, and invariably showed suppuration at the edges, if not more extensively. Apart from these septic infarcts, when abscesses were present in the lungs they almost always originated in bronchi and were usually multiple and of small size.

Emphysema. Acute emphysema is often a very conspicuous feature in broncho-pneumonic lungs. It affects those regions of the lungs where pneumatic patches are either absent or small and discrete, usually the anterior portions of the upper lobes. It may be merely of the vesicular variety, but interstitial emphysema also is often present and sometimes produces a most remarkable appearance (Plate II, Fig. 5 and 6). The air, escaping from ruptured alveoli into the stroma of the lungs, tracks along interlobular septa, distending them and separating their fibrous bundles, and forms bullae under the pleura which may reach a large size, up to an inch or more in diameter. Rupture of these bullae may occur and produce pneumothorax, but considering the frequency of their presence and the stretching of the pleura which they cause, it is perhaps surprising that that accident does not happen more often that it appears to do. Sometimes the air finds its way along the septa to the root and so to the mediastinum. It may then spread further and produce subcutaneous emphysema of the neck and chest wall.

This severe emphysema, which is characteristic of broncho-pneumonia and unusual in the alveolar type, may be explained as being in part 'complementary' in nature, intensified doubtless by the laboured respiration and severe cough usual in these cases. But it is probable that a more important factor in its production in this exaggerated form, is partial obstruction of the bronchi in emphysematous parts by the inflammatory exudate resulting from acute bronchitis, or the minute patches of pneumonia which are so often present (Plate IV, Fig. 17).

The pleura. Pleurisy is not constant as it is in alveolar pneumonia. It is indeed usually absent, unless consolidated areas of some size are present immediately beneath the pleura. Extensive confluent broncho-pneumonia usually shows fibrous pleurisy, often with a very scanty exudate, affecting the pleura over the consolidated parts. As in alveolar pneumonia, it would seem that cases which have a copious pleural exudate tend to develop empyema. Subpleural petechiae, sometimes very numerous and widespread, are extremely common in broncho-pneumonia.
Lymphatic glands. Intense congestion and very great swelling of the broncho-pulmonary and tracheo-bronchial glands are characteristic of broncho-pneumonia (Plate I, Fig. 1; Plate II, Fig. 6). The degree of enlargement is, indeed, sometimes very remarkable. Although these glands show evidence of intense acute inflammation, we have rarely found suppuration in them, even when it had occurred in the lungs.

Other internal organs. Toxic changes in the organs vary greatly in different cases of broncho-pneumonia. Sometimes they are remarkably slight in proportion to the severity of the local condition in the lungs. When they are really severe, as they are in a certain number of cases, the existence of septicæmia can usually be proved by bacteriological examination of the blood. Dilatation of the right side of the heart, with a pale soft myocardium, is usual.

**Morbid Histology.**

Broncho-pneumonia is an inflammatory condition affecting primarily the walls of bronchi and bronchioles and spreading to the alveoli immediately related to them. In the area of an early lesion (Plate III, Fig. 11) is a bronchiole with catarrhal contents in its lumen and inflammatory infiltration in its walls, polymorphonuclear leucocytes being numerous among the infiltrating cells. The condition affecting the bronchiole is much more than a superficial catarrh; it is an intense inflammation of the substance of the wall throughout its whole thickness, indicating that the infection is not located merely in the lumen but penetrates the wall and invades the lymphatics (Plate III, Fig. 12; Plate IV., Fig. 13). This severe acute interstitial inflammation of the wall may affect bronchi of any size but is most severe in the smaller tubes. It may cause serious damage. Complete destruction of the epithelium is usual, and the infiltration of the wall by polymorphonuclears may be so dense that its structure becomes indistinguishable. Some dilatation of the smaller bronchi is of common occurrence, and a copious cellular exudate, usually devoid of fibrin, is present within them.

Around the central bronchiole is a group of consolidated alveoli, the walls of which are thickly infiltrated with inflammatory cells, so that they may be much obscured and difficult to distinguish. Often the infiltration of the walls seems to precede consolidation of the lumen and extends beyond the edge of the consolidation patch (Plate III, Fig. 11; Plate IV, Fig. 17).

In severe cases every branch of every bronchus down to its finest ramifications forms the centre of a pneumonic patch (Plate I, Fig. 1 and 2). The consolidated alveoli around a bronchus are not always those which are directly connected with it by continuity of lumen. Even tubes of some size, cut at a considerable distance from their termination, may be surrounded by a ring of consolidated alveoli. We are unable to accept the view that these alveoli are always the expansions of minute branches of the central bronchus. Their arrangement as a collar, often not more than one or two alveoli deep, around the whole circumference and along a considerable length of the bronchus, points to the conclusion that infection reaches these alveoli through the bronchial wall and the alveolar septa, and not along the lumen. Acute interstitial inflammation is an essential part of the process.
PLATE I.

Fig. 1. (Male, aged 3 years and 9 months. Case I.) Acute broncho-pneumonia following measles. Wide dissemination of small discrete pneumonic patches; little confluence. Enlarged bronchial glands.

Fig. 2. (Female, aged 1 year. Case II.) Acute broncho-pneumonia, of 12 days' duration. Wide dissemination of minute pneumonic patches; confluence in middle lobe and medial border of upper lobe.

Figs. 3 & 4. (Male, aged 1 year. Case III.) Acute broncho-pneumonia, of 4 weeks' duration. Extensive confluence, especially in right lung (Fig. 3.) Enlarged bronchial glands.

PLATE II.

Figs. 5 & 6. (Female, aged 7 months. Case IV.) Acute broncho-pneumonia, of 8 days' duration. Extensive confluence at bases of lower lobes. Discrete patches and bronchitis elsewhere. Marked interstitial emphysema, best seen at apices. Enlarged bronchial glands.

Figs. 7 & 8. (Male, aged 2 years and 6 months. Case V.) Acute pneumonia of mixed type, of 11 days' duration. Massive consolidation of whole lower lobe of right lung (Fig. 7), mainly of alveolar type. Irregular patches of broncho-pneumonia in upper and middle lobes of same lung. Very small early broncho-pneumonic areas in both lobes of left lung (Fig. 8).

PLATE III.

Fig. 9. (Female, aged 2 years. Case VI.) Broncho-pneumonia following measles 6 weeks before death. Widespread consolidation of small patches with collapse of intervening lung tissue, rendering large areas airless. Severe purulent bronchitis. Dilatation of smaller bronchi.

Fig. 10. (Male, aged 1 year and 3 months. Case VII.) Pneumonia of mixed type. Massive uniform consolidation of entire upper lobe, with characters of alveolar pneumonia. Capillary bronchitis and small broncho-pneumonic areas in lower lobe; slight confluence at periphery.

Fig. 11. (Same case as Fig. 1.) Early broncho-pneumonic patch. Central bronchiole (B) with walls obscured by inflammatory cells; cellular exudate in adjacent alveoli; infiltration of alveolar septa.

Fig. 12. (Same case as Figs. 5 & 6.) Small bronchus showing cellular exudate in lumen; destruction of epithelial lining; dense inflammatory infiltration of walls; spread of inflammation to adjacent alveoli.

PLATE IV.

Fig. 13. Higher magnification of part of wall of bronchus shown in Fig. 12. A = bronchial wall infiltrated with cells, most of which are polymorphs; B = layer of muscle; C = remains of lining epithelium; D = exudate in lumen.

Fig. 14. (Same case as Fig. 2.) Blood vessel (A) at bifurcation in broncho-pneumonic lung, showing dense infiltration of perivascular stroma by inflammatory cells. B = bronchiole with inflamed walls.

Fig. 15. (Same case as Figs. 2 & 14.) Group of alveoli in area of confluent broncho-pneumonia, showing exudate of predominantly fibrinous nature.

Fig. 16. Large lymphatic vessels (L) at root of lung from case of broncho-pneumonia, showing great dilatation, purulent content, and spread of inflammation to surrounding tissues. A = blood vessel.

Fig. 17. (Same case as Figs. 5, 6, 12 & 13.) Acute vesicular emphysema in lung tissue surrounding a patch of early broncho-pneumonia. Central bronchiole (B) inflamed; bronchial and alveolar walls infiltrated; contiguous alveoli consolidated.

Fig. 18. (Same case as Fig. 9.) Illustrating collapse of lung in broncho-pneumonia. Parts of two inflamed and dilated bronchioles (B) are shown, with exudate in alveoli immediately adjacent and collapse of intervening lung substance. An interlobular septum is seen passing obliquely across the middle of the field.
PLATE I.

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.
PLATE III.

Fig. 9.

Fig. 10.

Fig. 11

Fig. 12.
STUDIES OF PNEUMONIA IN CHILDHOOD

There may be, in addition, consolidation in the terminal alveolar expansions of the central bronchiole. Where there is confluence this is always present and extensive, but the interstitial inflammation persists in the peribronchial zone.

In the acute interstitial inflammation, lymphangitis plays an important part. Beginning in the peribronchial lymphatics it soon spreads to the perivascular and septal lymphatics also. The perivascular connective tissue may be infiltrated almost as thickly as the bronchial walls (Plate IV, Fig. 14); the larger lymphatic vessels in the septa, under the pleura and at the root, are often greatly dilated and filled with contents of almost purulent character, the tissue in their neighbourhood participating in an acute inflammatory change (Plate IV, Fig. 16). The severe involvement of the lymphatic system of the lungs explains the inflammatory enlargement of the root glands which has already been mentioned.

This progressive lymphangitis, with associated acute interstitial inflammation, is an important feature of broncho-pneumonia. Its severity varies in different cases, but we have found no case in a large series examined with the aid of whole-lung sections, in which it was not present. Sometimes the interstitial inflammation is more conspicuous than the alveolar consolidation, of which there may be very little. Such cases have been described by some authors as a separate group under the name of 'acute interstitial broncho-pneumonia.' Influenzal and post-measles pneumonias are stated to be often of this type. But our studies have led us to believe that a progressive lymphangitis with acute interstitial inflammation of the bronchial walls, alveolar septa and stroma, is a constant feature of all forms of true broncho-pneumonia, and is indeed of the very essence of the pathological process.

Further, it is this feature of the disease that accounts for the fact that broncho-pneumonia is much more apt than alveolar pneumonia to be followed by undesirable results, such as suppuration, necrosis, bronchiectasis and fibrosis. That suppuration and necrosis in the lungs are not uncommon in fatal broncho-pneumonia has already been indicated. Both are to be attributed directly to interstitial inflammation and lymphangitis. When suppuration originates in the bronchial walls, which is often the case, it is merely a further development of the usual severe inflammation of those structures. The thrombosis of blood vessels which leads to the formation of areas of infarction is caused by involvement of the vessel walls in an acute inflammation spreading to them from the perivascular lymphatics. The association between acute broncho-pneumonia and development of bronchiectasis and fibrosis of the lungs will be dealt with in another paper.

The alveolar exudate. In very small and early broncho-pneumonic lesions the exudate in the tiny group of alveoli surrounding the central bronchiole is often composed entirely of polymorphonuclear leucocytes (Plate III, Fig. 11; Plate IV, Fig. 17). When the patch is somewhat larger, a greater amount of exudation into the alveoli having taken place, it usually contains fibrin, which may be in large amount. Often a patch of this kind shows a series of zones in which the composition of the exudate varies. In the lumen and
walls of the central bronchiole and the alveoli nearest to it, polymorphonuclear cells are present to the exclusion of everything else. Outside this purely cellular zone the alveoli contain fibrin and cells in varying proportions, and their walls show less infiltration than those of the alveoli nearer the bronchiole. At the periphery of the patch there may be a ring of alveoli whose contents almost consist entirely of catarrhal cells shed from the walls, together with a varying amount of oedematous fluid. Beyond this again is a ring of collapsed alveoli which contain little or no exudate. When the pneumonic patches are numerous, they may be separated from each other only by a narrow strip of collapsed alveoli, and the affected part may be completely airless, simulating a confluent broncho-pneumonia (Plate IV, Fig. 18).

Even in massively confluent broncho-pneumonia this ‘zonal’ character of the exudate is usually preserved. The peripheral alveoli of each area of pneumonia are rarely completely filled with exudate, but are partially collapsed, so that the fact that the consolidation is essentially patchy and peribronchial in distribution is evident. This, in conjunction with the presence of acute interstitial inflammation, excludes the diagnosis of alveolar pneumonia. The peribronchial mottling which is so distinctive a macroscopic character of confluent broncho-pneumonia is, of course, due to this feature of the process.

Fibrin is usually most plentiful when alveolar exudation is most abundant, and is therefore found chiefly in areas of massively confluent broncho-pneumonia. In such cases certain fields may present an appearance indistinguishable from alveolar (croupous) pneumonia, the exudate being as rich in fibrin as it ever is in that disease. The photograph shown in Plate IV, Fig. 15 (taken from one of the confluent areas in the lung shown in Plate I, Fig. 2) illustrates this point. The case was a typical broncho-pneumonia, about which there could be no doubt, but the field shown might pass for one of alveolar pneumonia with a richly fibrinous exudate. It is not possible to distinguish between the two types of pneumonia by the characters of the alveolar contents in a limited field.

Atypical or mixed cases.

In any large series of cases of pneumonia there are likely to be some in which the pneumonic process appears to be of alveolar type in one part and broncho-pneumonic in another. This combination of the types in a single case is considered by some observers to occur fairly often. It has been indicated above that the presence of small areas which resemble alveolar pneumonia is not uncommon in confluent broncho-pneumonia, but we do not consider that all cases which show these ought to be classed as ‘mixed’ cases. Our series included only five to which this term seemed properly applicable. Three of them have been examined with whole lung sections. Two are illustrated (Plate II, Fig. 7 and 8; Plate III, Fig. 10). In these cases unmistakable broncho-pneumonic lesions were present in parts of one or both lungs. But each presented in addition a large area, usually extending to one whole lobe at least, the characters of which were, in most particulars, those of alveolar pneumonia rather than confluent broncho-pneumonia. Microscopic examination revealed that the appearances throughout the consolidated lobe were
in the main those of alveolar pneumonia, and parts might be perfectly typical, but in certain portions some interstitial inflammation was present in the bronchial walls. Although our first inclination was to regard these as examples of unusually massive confluent broncho-pneumonia, detailed study did not confirm that opinion. Both types of pneumonia were certainly present. The sequence of events in such cases is a difficult matter to determine. Either alveolar pneumonia must be superimposed upon an initial bronchitis, or the primary condition is alveolar pneumonia and broncho-pneumonia arises as a secondary development. We are of opinion that the latter event may occasionally occur.

Broncho-pneumonia usually develops from bronchitis. When the infection, originally located in the bronchial lumen, penetrates the wall and invades the peribronchial lymphatics, broncho-pneumonia results. If this view be correct, the critical step in the development of broncho-pneumonia is the invasion of the bronchial wall and lymphatics by the infecting agent. Should a similar invasion occur during the course of a primary alveolar pneumonia, the subsequent development of the case would be after the manner of broncho-pneumonia. In ordinary cases of alveolar pneumonia this does not occur. In our previous paper* we emphasized the fact that in typical alveolar pneumonia the bronchial walls and the whole framework of the lungs are remarkably free from inflammatory infiltration. But in that paper we described certain cases which were atypical in that the bronchial walls in the consolidated parts did show inflammatory infiltration, that is to say, the beginnings of interstitial inflammation and peribronchial lymphangitis. Had those patients survived a little longer, we believe that the infection might have spread to other parts of the lungs, and that the lesions resulting from that spread would have taken the form of broncho-pneumonia. We suggest, therefore, that broncho-pneumonia may develop either from bronchitis or, as a rare event, from a patch of primary alveolar pneumonia in which a progressive lymphangitis takes origin.

**DISCUSSION.**

The conception of broncho-pneumonia set forth in the foregoing pathological study raises certain questions bearing upon the general problem of that disease, and offers an explanation of some of its clinical features. The greater severity of broncho-pneumonia compared with alveolar pneumonia is manifested clinically in the prolonged course, the tendency for undesirable consequences to follow, and the high mortality. It is manifested pathologically by the widespread distribution of the lesions in the lungs, and more particularly by the progressive involvement of the lung substance and lymphatics in the inflammatory process. An inflammation in which the infection invades the tissues in this way is obviously one which is likely to spread widely, almost certain to persist for a long time—if it be not quickly fatal—and liable to resolve imperfectly and to leave permanent effects. In view of the nature of the pathological change, it seems unlikely that true broncho-pneumonia
can ever end by crisis and rapid resolution, and it is not surprising that the usual course in cases which recover is a slow and irregular lysis, subject to many interruptions.

The course of a pneumonic infection in a child would seem to depend upon whether or not this persistent involvement of the lymphatics by the infection occurs. If it does not, the result is alveolar pneumonia, a disease which is attended by a relatively trivial mortality and usually ends in a perfect recovery. If, on the contrary, the infection does thus invade the lymphatics, the result is broncho-pneumonia, with its intimidating mortality and tendency to cause permanent disability in a proportion of the survivors. The important problem to be explained is why the broncho-pneumonic infection should result in this massive and progressive invasion of the lung substance and lymphatics.

It was pointed out in our previous paper that in alveolar pneumonia the infection is located chiefly in the alveoli, whose walls possess no lymphatics. Therefore, the development of lymphangitis is unlikely. In broncho-pneumonia the infection is primarily and chiefly in the bronchi, whose walls possess a rich supply of lymphatic vessels. Conditions are therefore more favourable for the development of lymphangitis. Yet in both diseases, it is generally agreed, the infection reaches the lungs by the air passages; in both it must pass through the bronchi. According to Blake and Cecil lobar (alveolar) pneumonia experimentally produced begins with lymphangitis in the bronchial walls. This, however, soon passes off with the onset of consolidation, when the infection passes out into the alveolar spaces. If this view be correct, it would seem that broncho-pneumonia results from the persistence and spread of this primary lymphangitis. Probably, then, the explanation of this important difference between the two types must be sought, not in any different mode of infection, but either in a special quality of the virus or in a condition of predisposition of the patient.

The association between broncho-pneumonia and other acute infective fevers, such as measles, whooping-cough and influenza, is well known. In these cases the antecedent fever acts in some way as a preparation for the subsequent in-road of the pneumonic infection. As already stated, it is when some definite predisposing condition of this kind has been present that the interstitial inflammation is commonly found in its most extreme form.

But broncho-pneumonia in children is often primary, without an antecedent infective fever. Some cases of apparently primary broncho-pneumonia may be instances of influenzal pneumonia, in which the nature of the initial illness is not recognised. But it can hardly be supposed that this explains all cases in which there is no obvious sequence of another infection. Nor do we think it likely that the explanation of these primary cases will be found in the constant presence of a virus of special quality or special virulence. Rather is it to be sought in some condition of the patient, non-infective, yet predisposing in its effect.

Among predisposing conditions of this kind are age (under two years), bottle feeding, unhygienic surroundings, lack of fresh air and sunshine, rickets. That these conditions predispose a child to broncho-pneumonia is well known.
The comparative rarity of broncho-pneumonia, either primary or secondary, among better-class children, emphasizes the importance of home environment in preventing or promoting predisposition in a child.

It would follow from this, as a general conclusion, that the prevention of broncho-pneumonia in children depends to a corresponding extent upon the control of predisposing conditions.

**Abstracts of Cases Illustrated.**

*Case I.* (Plate I, Fig. 1, and Plate III, Fig. 11.) *Acute disseminated broncho-pneumonia following measles.* Male, aged 3 years and 7 months. Breast-fed for 1 year. Scarlet fever at 1 year. Pneumonia at 2 years. Fatal illness started with measles 3 weeks before admission. Admitted moribund and died almost at once.

Post-mortem, development and nutrition fairly good. Much thin mucous pus in upper respiratory passages. Scanty fibrinous pleural exudate on both sides. Lungs voluminous, and extensively and almost equally affected with small patches of pneumonia showing as tiny yellow spots round bronchi and bronchioles. Little tendency to confluence. Lung substance very moist, large amounts of frothy fluid exuding on pressure. Mediastinal glands swollen and of a deep red colour. Heart grossly dilated in all chambers and muscle pale and flabby. Moderate degree of toxic change in solid abdominal organs.

*Case II.* (Plate I, Fig. 2, and Plate IV, Fig. 14 and 15.) *Acute disseminated broncho-pneumonia with confluence in parts, of 12 days' duration.* Female, aged 1 year. Fourth child. One died at 3 months. Two bedroom rooms; gas burning all day. Breast-fed for 3 weeks. Thereafter on condensed milk. First tooth at 9 months. Chicken-pox at 7 months, with middle ear inflammation. At 9 months, in hospital for 2 weeks with sharp respiratory illness. Continued to cough. Readmitted 4 days before death. Had been acutely ill for 8 days, with severe cough and noisy breathing. Big pale flabby child. Four teeth. Temp. 102. Pulse 160. Respirations 52. Dyspnæic and cyanosed. Lower chest drawn in on inspiration. Generalized bronchitis, with doubtful consolidation on both sides. Severe suffocative symptoms before death.

Post-mortem, both pleural sacs partially obliterated by loose organized adherences. Both lungs widely involved. Broncho-pneumonia mostly discrete, but in right lung (Fig. 2) confluence in middle lobe, posterior-medial part of upper lobe, and posterior-inferior portion of lower. Microscopic evidence of chronic process in two areas in right lung, one in upper lobe near root and other in middle lobe (this chronic interstitial process, as well as organized pleural adherences regarded as legacy of respiratory illness 3 months before death). Mediastinal glands large and inflamed. Heart dilated on right side. Early acute peritonitis in upper abdomen. Marked toxic changes in spleen, liver and kidneys. No evidence of rickets or lymphoid hyperplasia.

B. Pfeiffer grown in pure culture from heart blood and in mixed culture from lung substance.

*Case III.* (Chart A, Plate I, Fig. 3 and 4.) *Acute broncho-pneumonia, with widespread confluence, of 4 weeks' duration.* Male, aged 1 year. Father unemployed. Three other children. Bad home. Artificially fed from birth on boiled cow's milk. Severe digestive disturbance at 3 months. Hernia operation at 4 months. At 10 months, in hospital for 3 weeks with dyspepsia. Subsequent progress unsatisfactory. Readmitted 3½ weeks before death, having been acutely ill for 3 days. Symptoms at outset mainly gastro-intestinal, but illness obviously respiratory. General state of nutrition poor. Acute bronchitis passed into typial broncho-pneumonia. Mouth and nasopharynx became septic and double otitis developed. Went steadily downhill. For temperature, etc., see chart.

Post-mortem, body extremely emaciated. Bilateral fibrinous pleural exudate. Very extensive broncho-pneumonia in both lungs (Figs. 3 and 4), especially right (Fig. 3). Posterior part of each base solid, and throughout rest of lungs large pneumatic patches of irregular shape and size, with intervening crepitant areas. Yellow mottling characteristic of confluent broncho-pneumonia prominent in solid areas. Smaller bronchi dilated. Mediastinal glands enlarged and red, and mediastinal tissues oedematous. No gross dilatation of heart. Very slight toxic changes in liver and kidneys. Spleen small.
Case IV. (Plate II, Fig. 5 and 6; Plate III, Fig. 12; Plate IV, Fig. 13 and 17.) Acute broncho-pneumonia, with confluence at bases, of 8 days’ duration. Female, aged 7 months. Illegitimate child, adopted by deaf and dumb woman. Fed on cow’s milk and oatflour. No previous illness. Admitted to hospital with 4 days’ history of fever, cough and heavy breathing. Temp. 105. Pulse 176. Respirations 50. Indifferently nourished. Flushed and distressed, with indrawing of lower chest. Crepitations most numerous at bases. Cyanosis a conspicuous feature. Steam, oxygen and bleeding of no avail. Died 4 days after admission.

Post-mortem, much mucous-pus in large air passages. Pleural surfaces sticky but without definite exudate. Numerous subpleural petechial hemorrhages over pneumonic patches. Extensive pneumonia in lower lobes of both lungs (Fig. 5 and 6). Large areas in each lung relatively free from pneumonia, but no doubt as to broncho-pneumonic nature of consolidation. Presence of air in connective tissue framework of lung (interstitial emphysema) a conspicuous feature at autopsy (shown very well in large sections). Heart muscle pale and soft, and chambers greatly dilated. Relatively slight toxic changes in organs.

Chart A.

Temperature and Weight Chart of Case III.


Post-mortem, slight icteric tinge in skin and conjunctive. Brain and meninges normal except for hyperemia. Very thick mucous-pus in upper air passages. Fibrinous pleurisy on right side, with 1 ounce of thick pus (pneumococal) at base posteriorly. Left pleural sac normal. Lungs afforded striking contrast. Left (Fig. 8) relatively healthy; some bronchitis and very early broncho-pneumonia. Right (Fig. 7) extensively consolidated. Lower lobe totally solid. Greyish red on section. Colour and consistence less uniform than in typical alveolar pneumonia. Right upper lobe more irregularly consolidated. One small area of pneumonia in middle lobe. Much thick pus in bronchi throughout lung. Condition
in lower lobe like lobar pneumonia, with atypical features of severe bronchitis and inflammatory infiltration of alveolar septa in certain areas. Condition in upper lobe more suggestive of broncho-pneumonia. Mediastinal glands moderately enlarged and pinkish-grey. Some pallor of myocardium but no dilatation of heart. Fairly well-marked toxic changes in organs.

It is suggested that in this case the first development was a perfectly typical alveolar (lobar) pneumonia, that the inflammatory process obtained a more than usually severe hold on the bronchial walls, and that the disease developed thereafter along the lines of broncho-pneumonia.

Case VI. (Plate III, Fig. 9, and Plate IV, Fig. 18.) Broncho-pneumonia of several weeks' duration, following measles. Female, aged 2 years. Father a hawker. Three other children alive, one suffering from abdominal tuberculosis. Another had died of tuberculosis. Breast-fed for 1 year. Very late in cutting teeth (16 months). Always delicate and subject to cough. Treated for rickets. Measles 5 weeks before admission. Details of subsequent progress uncertain, but evidently had severe cough and lost much weight. On admission, very ill and emaciated, with cyanosis, laboured breathing, and troublesome cough. Consolidation obvious in both lungs, especially right. Condition thought to be tuberculous, but no bacilli in sputum or feces. Died 4 days after admission. Very little pyrexia while under observation.

Post-mortem, much very thick purulent secretion in air passages. Right pleural sac obliterated by recently organised adhesions. Left pleural sac healthy. Both lungs extensively involved. Right lung (Fig. 9) the more completely consolidated. On section, innumerable small sharply defined yellow patches of broncho-pneumonia, with much pus in, and usually dilatation of, the central bronchi. Intervening lung tissue collapsed. Features referred to well shown in large section (Fig. 9) and in detail in Fig. 18. Left lung very similar, but pneumatic patches more discrete, superficially resembling miliary tubercles. Mediastinal glands greatly swollen, especially on right side. Toxic changes in organs remarkably slight. No tuberculosis in body.

Case VII. (Plate III, Fig. 10.) Pneumonia of mixed type. Male, aged 1 year and 3 months. Artificially fed on cow's milk. First tooth at 6 months. At 2 months, had bronchitis, and at 8 months a rather severe respiratory illness which was probably broncho-pneumonia and from which recovery was incomplete. Fatal illness started suddenly 4 weeks before death and was regarded as severe bronchitis with the gradual superimposition of pneumonia late in the illness.

Post-mortem, marked emaciation. Acute fibrinous pleurisy on right side. Massive consolidation of whole upper lobe of right lung (Fig. 10), which had naked-eye and microscopic characters of alveolar (lobar) pneumonia in an early stage. Degree of infiltration of bronchial walls in this lobe unusual in alveolar pneumonia, however. In middle and lower lobes, acute capillary bronchitis and typical broncho-pneumonia. Left lung much less affected, but the seat of bronchitis and a number of patches of combined collapse, edema and pneumonia. Mediastinal glands very large. Heart greatly dilated. Toxic changes in organs not extreme. Pneumococci in culture from right upper lobe.

The clinical record indicates that pneumonia did not become obvious until the patient had been ill for some considerable time and the pathological findings are in keeping with this observation. It has been very difficult to determine the precise sequence of events in this case, but it looks as if a pneumonia of alveolar type had been superimposed on an initial bronchitis.

**SUMMARY.**

1. An analysis of 140 fatal cases of broncho-pneumonia in children is presented. The age incidence was:—In the first year, 70; in the second year, 48; from two to twelve years, 22 cases. Thus 84 per cent. of the total occurred in the first two years.

2. A description of the morbid anatomy and histology of broncho-pneumonia in children is given, based on the appearances of the lungs at autopsy and on microscopic study of large sections.
3. Of the total (140), 5 cases were atypical or mixed, showing the characters of alveolar (lobar) pneumonia in one part and of broncho-pneumonia in other parts of the lungs.

4. The essential pathological process in broncho-pneumonia, and its bearing on the clinical features and etiology, are briefly discussed.

REFERENCES.

STUDIES OF PNEUMONIA IN CHILDHOOD.

IV. BRONCHIECTASIS AND FIBROSIS OF THE LUNG.

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It is stated that Laennec was the first to describe the condition of bronchiectasis, although fibroid conditions of the lung were described by earlier morbid anatomists.

In "De L'Auscultation Mediate" (1826) Laennec has a short chapter entitled 'Dilatation of Bronchi,' in which he gives the history, the clinical condition and the morbid anatomy of four cases. In three of these the origin of the condition was apparently in childhood. One was a child of three years who died three months after whooping cough. Another was a man in middle life, who from infancy was subject to a cough attended by an expectoration of yellowish or greyish colour: this had not in any way prevented him from following his occupation. The third was an old piano teacher, aged seventy-two years, affected upwards of fifty years with habitual cough, expectoration of opaque yellow sputa, and short oppressed breathing. However, she was always able to attend to her affairs, and indeed never considered herself as sick. Laennec goes on to describe minutely the bronchial dilatations, and the dense contracted condition of the lung substance which he refers to as 'a cartilaginous production extending from the bronchial walls into the substance of the lungs.' His account of the subject is not only important historically: it is still useful, sound and accurate. Later reports of bronchiectasis confirm his findings of a condition dating back to childhood in a majority of cases; compatible not only with long life but even with moderate health and capacity for work; and dependent on bronchial dilatation associated with pulmonary fibrosis. His theory of etiology is also worth quoting: it is 'a temporary dilatation produced by a voluminous sputum, and is rendered permanent by the constantly successive secretion of similar ones'.

Corrigan's paper on 'Cirrhosis of the Lung' in 1838 is the next important contribution to the subject. He reported four cases. As his title indicates, Corrigan regarded the fibrous change in the lung as the primary condition, which produces by traction the dilatation of the bronchial passages. This explanation of bronchiectasis obtained and still obtains much support.

For a long period, there was confusion between cases of true bronchiectasis and of tuberculous cavitation; and until the demonstration of tubercle bacilli in sputum was possible, the separation of the two conditions was difficult. But in 1891 Clark, Hadley and Chaplin reported 45 cases of bronchiectasis under the descriptive term 'fibroid lung': and in all these a tuberculous condition was excluded by repeated examination of the sputum. In contrast to the small series of Laennec and Corrigan, the majority of these 45 patients were alive and 'in the enjoyment of excellent health'. Another important feature of the series was that, although only eight of the cases were under ten years of age, in the great majority the originating illness had occurred before the age of five years. In 33 the condition had followed measles or whooping cough or both.

In 1905 Clive Riviere published an analysis of 33 cases, all in children, with 3 autopsies. In 23, the original illness occurred under 5 years of age: in nearly all it was of the nature of bronchitis or broncho-pneumonia, and was especially associated with measles and whooping

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in either physical broncho-pneumonia. In a degree bronchial subsequent although the introduction of pneumonia and indefinite group where physical definite of the. Findlay and Graham as first discovered and described bronchiectasis 1900. This brief historical survey brings out several interesting points. Bronchiectasis was first discovered and described in the post-mortem room, many years after the process had begun: it was next studied during life, but still at an advanced stage. Also the great majority of the reported cases indicated as the original cause an acute respiratory illness in early childhood. Since 1900 careful studies of cases in children have been made, but it is uncommon to find reports of cases where the condition had been observed from its beginning, although Findlay and Graham were able to observe three ‘almost from the beginning’, following respectively double pleurisy, broncho-pneumonia and lobar pneumonia. Lastly, bronchiectasis was so commonly associated with fibrosis of the lung that the latter condition received an important place in the terminology, as shown by the terms ‘cirrhosis of the lung’, ‘fibroid lung’, and ‘pulmonary fibrosis’. 

In the first paper of these ‘Studies of Pneumonia ’* we referred to a group of 33 cases of ‘bronchiectasis’ following pneumonia and bronchitis, which have been under our observation. This group was a composite one, including definite cases of bronchiectasis with or without fibrosis of the lung, and an indefinite group where physical and X-ray examination was inconclusive of either bronchiectasis or fibrosis. Yet in this indefinite group, the chronic and special character of the bronchitis and the history of an originating pneumonia or bronchitis seem to justify the diagnosis of some fibrous change in the bronchi and the interstitial stroma of the lung. Some years ago, before the introduction of lipiodol, one of us (C. McN.) reported 18 cases of ‘fibrosis of the lungs and bronchi, following broncho-pneumonia’, of which only 6 were of definite or massive fibrosis; while in the remainder the fibrosis was indefinite, although the clinical character of the cases in both groups was similar. The subsequent use of lipiodol in some cases of the indefinite group has demonstrated in them bronchial dilatation, and it is possible that this method may reveal some degree of bronchiectasis in many cases of chronic cough and spit following broncho-pneumonia. Certainly the use of lipiodol has shown beyond doubt that definite bronchiectasis may exist without producing either the classical physical signs or evidence in an ordinary radiograph.

From all these data, it would seem that the majority (probably the great majority) of cases of bronchiectasis date back to early childhood and originate in broncho-pneumonia or bronchitis. It might be hoped, therefore, that microscopic study of the bronchial changes in acute and chronic cases of broncho-pneumonia would throw light on the origin of bronchiectasis. The main
purpose of the present paper is to present such a microscopic study of a series of cases of broncho-pneumonia, and of early and advanced bronchiectasis.

As an introduction to this study, it may be of interest to give a short clinical record, with lipiodol X-ray photographs, of two cases of bronchiectasis, in both of which the condition is definite, has existed for some years and has permitted fairly good general health.

Clinical Case A. John M., present age 7 years. Admitted to hospital in the fifth week of double broncho-pneumonia following measles, at the age of 2½ years. The boy was wasted very weak and pale, and in an extremely grave condition. His lips, tongue and mouth were covered with numerous dirty ulcers; these involved the larynx also, as shown by his complete aphony. There was irregular and patchy consolidation of both lower lobes; radiographs confirmed the pneumonic condition of the lungs. He slowly improved, and remained in hospital for twenty weeks. His recovery was marked by persistent and paroxysmal cough, which had not entirely left him on his discharge. His general health was then excellent. His cough became worse again in the following winter, and was of the typical paroxysmal "morning cough" type, with the expectoration of a moderate amount of purulent but not offensive spit. It remained, with exacerbations and improvement, until his re-admission at the age of 5½ years. His general health had kept fairly good; he was never in bed, and he had gone to school. On re-admission, his colour was good, his nutrition fairly good; there was very slight clubbing of the fingers. His lungs showed no percussion dulness; but there were numerous hollow-cracking rales at both bases, with broncho-vesicular breathing at these areas. The ordinary radiograph of the lungs showed luminous fields; but the cardiac shadow was overlaid with an indistinct tracery which suggested thickened bronchi. The lipiodol-radiograph showed a definite bronchiectasis

![Fig. 1.](image-url)
at both bases close to the spinal column: and on the left side one or two slightly widened bronchial tubes could be seen passing across to the periphery above the dome of the diaphragm. (Fig. 1.) He is again under observation, æt. 7 years, four and a half years after his original pneumonia: the condition of bronchiectasis has not apparently progressed: cough and spit remain as before: the general condition is fairly good: the boy is able to attend school, and to play.

Commentary. A case of limited bilateral bronchiectasis, without massive fibrosis of the lungs, following measles and broncho-pneumonia. General health fairly good. Duration, 4½ years.

Clinical Case B. Jessie W., present age 14 years. She had measles and pneumonia at the age of 3 years, and was said to be seriously, but not dangerously, ill for several weeks. She was not under our observation during this illness. Since this time, she has never been free from cough: she has bouts of cough every morning on waking: and brings up some thick greenish spit. Her general health has been good, although she has always been a little thin: but she is full of energy and high spirits, and takes her full share in games. Came under observation, aged 8 years, and has been watched closely until now. The general and local condition has not appreciably changed since then. Obvious physical signs of extensive fibroid change and catarrh in the lower half of the left lung, with flattening and deficient movement on this side: outward displacement of the heart, the apex beat being in mid-axilla in the 5th interspace. Slight cyanosis of the lips, cheeks and fingers, but little or no clubbing of the fingers. Lipiodol-radiograph (Fig 2) confirms the massive fibrosis in the left lower lobe, and shows extensive bronchiectasis of the terminal air tubes on this side, and widening of the main bronchi, displacement of the trachea and heart to the left side. The bronchial tree of the right lung shows normal tapering of its twigs, some of which can be seen passing across the middle line to the left side, indicating that part of the right lung has passed across the mediastinum.

Commentary. A case of extensive unilateral bronchiectasis, with massive fibrosis of the left lung, and displacement of mediastinal structures: following measles and pneumonitis. General health fairly good. Duration, 11 years.
In our last paper particular stress was laid upon one feature of the pathological process in acute broncho-pneumonia. That feature was the presence, and often great severity, of acute interstitial inflammation of the bronchial walls, alveolar septa and general stroma of the lungs. It was pointed out that this condition favours a prolonged persistence of the inflammation, hinders rapid and perfect resolution, and in a proportion of cases brings about chronic pathological changes in the lungs. Two of the most important of these chronic changes, bronchiectasis and fibrosis of the lungs, are the subject of the present study. These two conditions are intimately bound up one with the other and cannot be considered entirely apart.

**Bronchiectasis.**

*Acute bronchiectasis.* A very common post-mortem finding in the lungs of children who die of acute broncho-pneumonia is widening of the lumina of small bronchi, especially those in the centres of consolidated patches. The term acute bronchiectasis or bronchiolectasis is frequently used to designate this. But there are two entirely distinct types of change which may produce this widening of the tubes. In severe cases of broncho-pneumonia it is sometimes due to a destructive change in the walls of the bronchi (ulcerative bronchitis) which is described in detail below, and which, in the event of the patient’s survival, necessarily leads to permanent changes in the lungs. In many cases, however, the widening of the bronchial lumen is due to pure dilatation, with acute overstretching of the wall, unaccompanied by any important structural change. This latter condition, very common in acute broncho-pneumonia, affects small bronchi in the consolidated areas and also those in unconsolidated parts. It is analogous to acute emphysema of the alveoli, which often accompanies it; it is probably due to the same causes, and is doubtless capable of complete recovery without permanent damage. It is probably this condition which Rilliet and Barthez described as ‘acute bronchial dilatation’ occurring occasionally in acute broncho-pneumonia.

In descriptions of acute bronchiectasis it is not always clear which of these two entirely different conditions is intended; and indeed, without microscopic examination, it may not be possible to distinguish them. In order to avoid confusion it seems advisable to restrict the application of the term acute bronchiectasis or bronchiolectasis (for it is almost exclusively the small tubes which show the change) to the condition of true dilatation.

It is not, however, with acute bronchiectasis that the present study is principally concerned, but with the sequence of changes which, originating in acute respiratory disease, especially broncho-pneumonia, may lead to the development of chronic bronchiectasis.

*Chronic bronchiectasis.* The mode of development of chronic bronchiectasis is a problem which cannot be said to have been satisfactorily solved. Modern standard text-books of pathology advance various suggestions, none of which seems entirely adequate.
According to Muir,'bronchiectasis may be ascribed to certain mechanical factors acting on a weakened bronchial wall, and . . . fibrosis of the lungs plays a very important part. . . . The chief mechanical factor is forced inspiration, especially that which follows the act of coughing . . . This will be specially effective when the lung beyond is not free to expand . . . as in permanent collapse or in interstitial pneumonia . . . 'The actual contraction of the connective tissue also may play a part, as was maintained by Corrigan.' The association of bronchiectasis with acute respiratory disease in childhood is referred to by Muir, who states that 'it is likely that in many cases of cylindrical bronchiectasis the lesion is started in early life by whooping-cough, the bronchitis of measles or of other diseases . . . In these (cases) the supporting muscular tissue of the bronchi has apparently been destroyed, though we cannot say why this should be brought about.'

Karsner states that 'the more acute forms of bronchiectasis are due to destructive disease of the wall . . . Such dilatations are due almost entirely to the disease of the wall and not contributed to in any large measure by increased intrabronchial air pressure'. He appears, however, to regard the chronic form as having a different explanation and mentions the factors of weakening of the wall by chronic inflammation, and the dilating effects of cough, accumulation of secretion, and fibrosis of the lung substance between the bronchi.

Kaufmann, who recapitulates the same views, suggests that 'there is a possibility of congenital weakness of the bronchial walls in the bronchiectases of childhood'.

MacCallum favours the view that a partial obstruction of a bronchus, such as can be overcome by the active inspiratory effort, but prevents the egress of air during expiration, leads to 'continuous distension of the obstructed bronchus, which finally widens it and is a prominent cause of the condition known as bronchiectasis'. He admits that 'there are many (cases) where obstruction is not . . . obvious, and these offer difficulties'; and quotes Dr. Crowe as stating 'that in dogs in which he has produced strictures of a bronchus, easily seen through the bronchoscope as an extreme narrowing of the lumen, there is no dilatation of the distal part as long as the bronchus remains uninfected'. He affirms that the only point on which there is agreement is 'that the infection and inflammation which weakens the bronchial wall and destroys its elasticity is a necessary factor.'

It is therefore abundantly clear that agreement has not been reached on the problem of how the cavities are produced, and that, as MacCallum truly states, the question needs further study.

During the course of our study of broncho-pneumonia we met with a series of seven cases in which a succession of changes was traceable which seems to us to throw some light on this problem. The observations recorded in this paper, on which certain conclusions are based, were made during the course of a very full examination of these seven cases, with the help of whole-lung sections. Details of some of the cases are given at the end of the paper.

The first stage of the process which leads to the formation of bronchiectatic cavities was found in a case of prolonged broncho-pneumonia, in which a very severe purulent bronchitis was an outstanding feature and acute interstitial inflammation of the bronchial walls was of more than usually intense degree. At the stage represented by this case the condition of the affected bronchi is as follows:—

The lumen is enlarged and filled with pus; the epithelial lining is completely destroyed; all trace of muscle in the wall has vanished; in some instances every vestige of the original wall, including the cartilage, has disappeared and the bronchus is represented by a space bounded directly by consolidated alveoli (Fig. 9). Bronchi may be found whose walls are in process of being destroyed. Sometimes only a part of the wall is affected (Fig. 10). At one side of the bronchus it may be intact while at the
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FIG. 3.

FIG. 4.
(For Description of Figures, see page 189).
other it is necrotic or has disappeared. The process of necrosis and suppuration which destroys the bronchus wall may involve adjacent alveolar tissue to a variable extent, or may be confined to the bronchus. In some instances the great enlargement of the lumen at the part where the wall is destroyed makes it obvious that a certain amount of alveolar tissue also has perished. In this way there are formed cylindrical or saccular expansions of the bronchi, which are clearly not due to dilatation properly so called, but to a process of excavation, with loss of tissue from the bronchus wall and sometimes also from the surrounding lung substance, as a result of necrosis accompanying suppuration (Fig. 5 or 6). The cavities are often very sharply defined. This is the destructive change in the wall to which Karsner ascribes 'the more acute forms of bronchietasis'. We suggest that, at least in certain cases, it is responsible for the development of the chronic form also, and is the fundamental change underlying that condition.

At a slightly later stage (represented by Case II) the early beginnings of repair are apparent. The cavities heal by granulation. From the wall of the cavity (usually formed at first by consolidated alveoli) there springs a growth of young fibroblasts and capillaries which forms a granulation-tissue membrane around the space. Fig. 12 and 13 show the earliest stage of this healing process at one side of a bronchus whose wall has been completely destroyed.

The growth of this granulation tissue continues until a definite fibrous layer, at first extremely vascular, bounds the cavity. After a time epithelium, surviving in neighbouring parts of the bronchus which have not suffered destruction, grows over the surface of the new granulation-tissue wall and gives the cavity an epithelial lining continuous with that of the bronchus. This relining process begins even while there is ample evidence of the persistence of active inflammation. Healing of the cavities in this way is represented at various stages, in Cases III, IV and V in our series. It is illustrated in Fig. 11, 14 and 15. The bronchus wall shown in Fig. 14 has remained intact at one side, while destruction at the other side has produced a saccular expansion of the lumen. The destroyed part has been replaced by a new wall composed of young and very vascular fibrous tissue, among which no trace of muscle or cartilage is to be found (Fig. 15). Over a part of this new wall a layer of epithelial cells has spread, the covering being not yet quite complete. The epithelium is of a cubical type and not ciliated.

The beginning of fibrosis of the lung substance between the ectatic bronchi may be found at this stage, but is only of slight degree. In our cases it was confined to alveoli immediately related to affected bronchi, and took the form of proliferation of fibroblasts in the alveolar walls which caused considerable thickening, and in two cases an exudate in the alveolar spaces was in process of organization by means of leashes of young fibroblasts and capillaries which sprang from adjacent alveolar septa (Fig. 18). Nowhere, at this stage, was dense contracting fibrous tissue found; nor were fibrous pleural adhesions present.
Later on the granulation-tissue wall of the cavity becomes thicker and more definitely fibrous. There is no regeneration of muscle or cartilage, and little or no new elastic tissue appears to be formed. The new wall may be as thick as, or thicker than, the original one, and may have a complete epithelial lining, but it is a purely fibrous structure, lacking in all those elements which endow the normal bronchial wall with strength and elasticity (Fig. 16).

The absence of muscle, cartilage and elastic tissue, and loss of characteristic structure in the walls of ectatic bronchi have been repeatedly described. This change is usually ascribed to 'atrophy' of these essential elements as a result of chronic inflammation or strain. To our mind, the fibrous membrane which lines these cavities is often not the original wall at all, but a new structure formed from granulation tissue around a space produced by an active process of destruction.

The true chronic stage of bronchiectasis is represented in our series by Cases VI and VII. In Case VI (Fig. 4) the amount of bronchial dilatation was not very great. In the lower lobe some of the bronchi showed a cylindrical expansion of the lumen but there were no large cavities. The walls of these bronchi presented exactly the changes which have been described. One is illustrated in Fig. 16. This wall is composed of a considerable thickness of vascular fibrous tissue covered with epithelium; muscle and cartilage are absent. Case VII (Fig. 3) was one of typical, very severe chronic bronchiectasis. The whole left lung was occupied by cavities of various sizes, mostly large. In the walls of the cavities there was no muscle, no cartilage, virtually no elastic tissue. Most of them had an epithelial lining, the cells being of a small debased cubical type.

At this stage the lung substance between the cavities shows advanced chronic interstitial pneumonia, being occupied by dense fibrous tissue, among which may be detected the remains of obliterated alveoli and small bronchi. This was the state of affairs in both of our chronic cases. In Case VII, dense fibrous pleural adhesions were present. The condition of the lung substance in the lower lobe of Case VI is shown in Fig. 19. The part illustrated is typical of practically the whole lobe. Yet there was no evidence that the contraction of this very dense fibrous tissue had stretched the bronchial walls. On the contrary, it seemed rather to have had the opposite effect, for in places the walls of the dilated bronchi were thrown into folds, showing that they were certainly not expanded to their full capacity. This is illustrated in Fig. 16.

In Case VII (Fig. 3), the cavities were so numerous and of such a size that the lung substance between them was represented by little more than broad fibrous septa, in some of which remains of alveoli, more or less completely obliterated, were demonstrable. The smaller bronchi in communication with those from which the cavities were formed, had also suffered obliteration.

From the observations which have been recorded the following conclusions have been drawn, offering an explanation of those cases of chronic bronchiectasis
which follow acute respiratory diseases in children, especially broncho-
pneumonia. The initial change which underlies the whole process occurs during
the acute phase of the disease, and takes the form of severe acute interstitial
inflammation of the bronchial wall, going on to necrosis and suppuration. This
causes the formation of a cavity by loss of tissue from the bronchus wall, and
evacuation of a certain amount of adjacent alveolar substance in most instances.
The cavity may be cylindrical or saccular in shape according to the extent of
the evacuation and whether it affects the whole circumference of the bronchus
equally or is more extensive at one side. Subsequently the cavity is lined
by granulation tissue, becoming fibrous, and finally may be covered by bronchial
epithelium, usually of a modified type. Thus a new wall is constituted round
a bronchial lumen which has been enlarged to a greater or less degree according
to the extent of the initial destructive process.

According to this view, a bronchiectatic cavity is not a dilated bronchus,
but an excavation in the lung substance, starting in a bronchus, and is strictly
analogous to a tuberculous abscess. It is not necessary, in order to explain
the existence of the cavities, to postulate the operation of any of the factors
usually credited with dilating effects. Destruction of tissue, and not dilatation,
is the essence of the process. Nevertheless those factors may be instrumental
in enlarging the cavities after they are formed. It may readily be assumed
that anything which might tend to dilate a bronchus would be doubly effective
in stretching the relatively weak fibrous walls of the cavities. Secretion and
inflammatory products are bound to accumulate in the cavities, especially
as the absence of muscle and ciliated epithelium deprives the altered bronchi
of the principal means by which a healthy bronchus rids itself of secretion.
This accumulation makes probable the occurrence of that partial obstruction
to which MacCallum attaches importance as a dilating factor. Infection
flourishes in the stagnant contents and causes enlargement of the cavities by
further ulceration and excavation. Fibrosis of the lung substance, especially
close to bronchi, accompanies the process of healing of the cavities and is
probably constant in chronic cases. It may, in some instances, by contraction
tend to dilate the cavities further, as Corrigan believed, but this can be only
after the bronchiectasis is well established, and we have found no direct evidence
that it has this effect.

In putting forward this view of the mode of formation of bronchiectatic
cavities, we do not claim that it explains all cases. Our studies have been
confined to cases in children, in whom the disease could be clearly traced to
its origin in broncho-pneumonia. Certain cases which develop without any
evidence of antecedent acute respiratory disease may demand some other
explanation. We are, however, of opinion that very many cases of chronic
bronchiectasis (many even of those which manifest themselves only in adult
life) owe their origin to broncho-pneumonia or bronchitis in childhood; and
there is a considerable body of evidence to support this view. Where bronchiect-
asis is due to foreign bodies in the lungs, the presence of infection is probably
an essential factor, and the process by which the cavities are formed may well
be similar to that which we have described. We have not, however, any
observations of our own to record with regard to this.
PATHOLOGY OF FIBROSIS OF THE LUNGS.

Non-tuberculous chronic fibrosis of the lungs is usually associated either with gross fibrous thickening of the pleura such as results from long-standing empyema, or with chronic changes in the bronchial walls, with or without definite bronchiectasis. It is with the latter type that the present study is concerned.

It may be stated that the chronic form of bronchiectasis is always accompanied by some degree of fibrosis of the lungs, but that fibrosis may occur without gross enlargement of bronchial lumen such as could be detected clinically as bronchiectasis. As has been described in the foregoing study, in cases of bronchiectasis where cavities are formed by active destruction, fibrosis of the adjacent lung substance accompanies the process of reconstruction of the wall of the cavities. It begins in the immediate vicinity of the damaged bronchi, but may ultimately lead to an almost complete fibrous replacement of the alveolar tissue throughout the affected portion of the lung. The fibrosis is brought about in various ways.

(a) There may be proliferation of fibroblasts, with laying down of new fibrous tissue in the inflamed walls of alveoli adjacent to the damaged bronchi. This leads to great thickening of the alveolar septa and a corresponding reduction in the size of the spaces. Accompanying this change in the wall, there is usually an alteration in the character of the lining epithelium of the alveoli, which becomes cubical instead of flattened, and very much more conspicuous than it ought to be. Fibrous tissue proliferation may affect also the coarse stroma of the lungs, increasing the width of the interlobular septa and the amount of perivascular and peribronchial fibrous tissue. It may be regarded as the result of long continued interstitial inflammation of the lung framework, which in its acute form is so constant a feature of broncho-pneumonia.

(b) In certain cases organization of an exudate in the alveolar spaces takes place. The alveoli come to be occupied by strands or leashes of young fibroblasts and their fibres, which pass from alveolus to alveolus, and the origin of which from the alveolar wall at some point may be demonstrable. This remarkable appearance is illustrated in Fig. 18, which shows the process at an early stage. Its end result, if the patient survive, must be obliteration of the alveolar spaces by fibrous tissue and massive fibrosis of the affected part. This is what is known as 'organizing pneumonia.' Sometimes it occurs throughout a large area of lung as a direct result of pneumonia in which the exudate does not resolve, but becomes organized. During the course of our present investigation, we have seen two cases of this kind, in neither of which was any bronchial dilatation present. The same process, but limited to alveoli adjacent to the damaged bronchi, was observed in Cases III and V of our bronchiectasis series, in which it contributed materially to the early fibrosis of the lungs noted in those cases. At a later stage, when many alveolar spaces have been obliterated and the new fibrous tissue has become dense, it would be difficult, if not impossible, to distinguish fibrosis due to this process from that produced in other ways.
(c) In bronchiectatic lungs, many small bronchi communicating with those from which the cavities are formed become obliterated. We were able to observe the process of obliteration at various stages in our series of cases. During the initial stage of ulcerative bronchitis, the smaller bronchi may suffer in exactly the same way as the larger, and have their walls completely destroyed. The healing process which follows, with growth of granulation tissue forming a new wall around the cavities may, in the case of small bronchi, lead to obliteration, the whole lumen being filled with proliferating fibroblasts and new capillaries. An example of this obliterative bronchiolitis, taken from Case II, is shown in Fig. 17. In this way many small bronchi may be completely obliterated. In some instances the new granulation tissue does not occupy quite the whole lumen; spaces are left which may ultimately be lined with bronchial epithelium. This produces the curious effect of a bronchus divided into a number of minute epithelial-lined spaces separated by masses of fibrous tissue. This obliterative bronchiolitis contributes to fibrosis of the lungs not only by the formation of fibrous tissue in the small bronchi themselves, but also by producing in the alveoli communicating with them a permanent condition of collapse, which must result in further fibrosis.

In conclusion it may be stated that the pathological processes underlying bronchiectasis and pulmonary fibrosis are intimately connected. Destructive changes in the bronchial walls, the processes of healing which follow these, and the persistence of infection in and around the damaged bronchi, are together responsible for the fibrosis which accompanies bronchiectasis. Apart from those cases where fibrosis is of pleural origin, and occasional rare cases of organizing pneumonia, it would seem doubtful whether massive fibrosis of the lungs takes place in the absence of severe bronchial damage, although it is evident that the degree of bronchial damage need not be such as to produce bronchiectasis clinically obvious. Case VI of our series (Fig. 4) is an instructive example of this, where, with massive fibrosis of a lobe, only very slight bronchial dilatation was present. Yet the bronchial walls were profoundly altered, and the pathological changes which they showed were precisely the same as those in Case VII (Fig. 3) except in respect of the size of the cavities. For this reason cases of frank bronchiectasis, and cases of fibrosis of the lungs without obvious bronchiectasis (if not of pleural origin), may be reasonably regarded as belonging to the same pathological group; and the extended use of lipiodol in radiography of the chest will probably reveal bronchial enlargement in many cases of 'fibroid lung' previously believed to be free from bronchiectasis.

**Abstracts of Fatal Cases.**

(The case numbers are those used in the "Pathological Study").

**Case I.** Broncho-pneumonia of seven weeks' duration, with ulcerative bronchitis. (Fig. 5, 9 and 10).

Male, aged 6 months. Eighth child. Four others had died in infancy, 2 shortly after birth and 2 of broncho-pneumonia following measles and whooping-cough. House of 2 small rooms, with leaking roof. Breast-fed for 2 months and thereafter on cow's milk under direction of child welfare clinic. Turned ill 2 days before admission in February, 1926, with fever, heavy
breathing and cough. Died 7 weeks after admission. While under observation, there was a
remittent temperature, a steady loss of flesh, a troublesome cough, considerable dyspnea,
generalized bronchitis, and, after about a week, evidence of consolidation in the right upper lobe,
followed by consolidation in both lower lobes.

*Post-mortem* examination. Body very emaciated. Much purulent secretion in main air-
passages. Pleural sacs healthy. Right lung—anterior portions of upper and lower lobes and
most of middle lobe very emphysematous (vesicular and interstitial); posterior part of upper
lobe, most of lower lobe, and middle lobe near root consolidated as a result of patchy pneumonia
and collapse; bronchi greatly inflamed, filled with pus, and slightly dilated. Left lung—whole
upper lobe and anterior part of lower lobe emphysematous; posterior portion of lower con-
solidated; bronchi as above but not so severely affected. Mediastinal glands much enlarged.
Heart and other organs atrophied. Little or no obvious toxic change.

*Microscopic* examination. In general the condition is one of purulent bronchitis with
both discrete patches and extensive areas of confluent broncho-pneumonia. Changes are most
advanced in the right upper lobe, where clinically consolidation was first noted. Here the
bronchitis has been intense and the walls have undergone complete disintegration, with very
considerable erosion and excavation. In this case the process of destruction was still active
at the time of death, unchecked by any effort at repair.

**Case II.** Broncho-pneumonia of several weeks' duration, following measles, with severe
bronchial damage. (Fig. 6, 12, 13 and 17.)

Female, aged 2 years. This case was reported (Case VI, p. 123) and illustrated
(Fig. 11) in the third paper of this series², but it is thought desirable to amplify the description
of the bronchial changes. These are widespread and are most advanced in the smaller bronchi.
All the latter are plugged with thick pus, and show some degree of distension or excavation;
in some, no vestige of the original wall remains and the lumen is surrounded merely by con-
solidated alveolar tissue. While the inflammatory process was thus intensely active at the time
of death, in a few instances there has been an attempt at repair. Here and there in the walls of
the cavities, very young granulation tissue is visible and a beginning has been made of the
reconstitution of the wall. Efforts at repair are also seen in several of the capillary bronchioles,
and here the effect has been different; organization is leading to obliteration. These bron-
chioles are represented by small circular patches of fibro blasts and delicate connective tissue
fibres surrounding a clump of degenerated polymorphonuclear cells. There is therefore an
oblitative bronchiolitis in progress.

**Case IV.** Broncho-pneumonia of nine weeks' duration, with early bronchiectasis
(Fig. 7 and 11.)

Female, aged 15 months. Four other children, one in hospital with tuberculosis. Breast-
fed for 11 months. First tooth at 7 months. No previous illness, but for 2 weeks before admi-
ission had a cough. Admitted in September, 1926, at age of 12 months, having been acutely ill
with fever, cough and grunting breathing for 24 hours. Diagnosed as severe acute bronchitis,
possibly broncho-pneumonia. Marked constitutional disturbance but no definite consolidation.
After a week, improvement occurred and temperature came down by lysis. On 14th day, tem-
perature rose to 101.4° and a rash developed. Scarlet fever suspected but not confirmed at
the fever hospital, child being sent home after 3 days. Progress at home unsatisfactory; con-
tinued to cough; appetite poor; no energy or inclination to move about; weight lost. Re-
admitted in November, 8 weeks after the onset of the acute respiratory illness. No rise of
temperature, but child pale and listless. Weight 12½ lb. "Chesty" cough. Moist sounds in
both lungs, with a suspicion of dulness at the left base. Four days after admission, temperature
rose for first time to 101°; pulse uncountable; respiration 56. Unpleasant odour noticed in
neighbourhood of patient at this date. Fifteen c.c. of thick foul-smelling pus removed through
9th left interspace. Death occurred 5 days after admission. Whole illness lasted therefore
for about 9 weeks.

*Post-mortem* examination. Body that of a small and poorly nourished child. About 1 oz.
of thick yellow pus with a very foul odour in left pleural sac, with much fibrino-purulent exudate
in relation to it. Right pleura healthy. Left lung—mixture of collapse and patchy pneumonia;
numerous bronchiectatic cavities with a smooth greenish lining in lower lobe. Right lung—more
extensively consolidated, again in a patchy fashion; innumerable small bronchiectatic cavities with a yellowish lining membrane in pneumonic areas. Mediastinal glands much enlarged. Heart atrophied. No toxic changes in spleen, but liver fatty.

**Microscopic examination.** There is some discrete broncho-pneumonia in the upper and more extensive consolidation in the other lobes. The bronchi are all pathological, but those in the apical regions show overstretching rather than serious destructive change. Bronchiectatic cavities are most numerous in the lower lobes and some are of considerable size. There the bronchial inflammation has been of great severity. In many cases, the original wall has completely disappeared; in others, part of the circumference is more or less intact, while the remainder is destroyed. The process is still active, but in all there has been some attempt at repair and reconstitution of the wall by granulation tissue. There is early fibrosis of the lung in the affected parts; alveolar walls are thickened and very cellular; in places the lining alveolar cells tend to be cubical; there is broadening of the septa.

**Case V.** Early chronic bronchiectasis, with terminal acute broncho-pneumonia. (Fig. 8, 14 and 15.)

Female, aged 16 months. Indefinite history of epilepsy on the mother's side. One other child, aged 12, healthy. Artificially fed from birth. Cut first tooth just before admission. Mentally defective. Had had one severe and numerous minor fits. Several indefinite illnesses, some of which were evidently respiratory. Admitted in February, 1926, having been ill for 4 days with gastro-intestinal symptoms, cough and grunting respiration. Ill-nourished but not obviously rachitic. All the signs of early broncho-pneumonia on admission. Died 11 days later, consolidation having become progressively more marked in both lungs.

**Post-mortem examination.** Right pleural sac moist. Some loose fibrous adhesions over left lung. Extensive consolidation along posterior borders of both lungs. Consolidated parts dark red on section, with yellow mottling round bronchi. Mediastinal glands greatly swollen. Heart not greatly altered. Little toxic change in organs.

**Microscopic examination.** Chief interest centres in the condition of the bronchi in the right lung. They are all acutely inflamed but many show in addition changes of a more chronic nature. In general, there is quite considerable dilatation. In the more dilated of the larger bronchi, in which the chronic changes can be studied best, there is profound alteration of the walls. The epithelium may be entirely absent or modified to a low cubical type. The sub-epithelial tissue is greatly increased in amount, and appears as very vascular granulation tissue thickly infiltrated with polymorpho-nuclear cells. In some instances practically the whole thickness of the wall is composed of tissue of this type, muscular structure being unrecognizable. Some of the large bronchi near the root show these changes only in certain parts of their walls, while other parts appear almost healthy. The picture is one of recent acute inflammation arising in bronchi which were previously the seat of chronic changes associated with bronchiectasis. In the lung substance itself, there is no general fibrosis, but there are areas, closely related to diseased bronchi, where there is diffuse overgrowth of connective tissue varying from slight increase in the thickness of the alveolar walls to the production of a structure resembling granulation rather than lung tissue. Careful examination reveals that the fibrosis is in large part the result of organization of an exudate in the alveolar spaces.

**Case VI.** Chronic fibrosis of the lung, with slight bronchiectasis; terminal acute broncho-pneumonia. (Fig. 4, 16 and 19.)

Female, aged 6 years. Mother died in childbirth 6 months before patient's fatal illness. Five other children alive; 2 died in infancy. Home conditions bad. Past history unreliable. Said to have been always delicate and subject to bronchitis, and about a year before admission to have suffered from a respiratory illness, the details of which were not known. Was "always coughing." Admitted in March, 1926, having been taken suddenly ill about 30 hours previously. Was fevered and had vomited repeatedly. On admission, temperature 104.8°; pulse 160; respiration 32. Semi-comatose and toxic. Throat inflamed; swab negative for diphtheria. Cerebro-spinal fluid normal. Blood culture sterile. Leucocytes 6,200. Death occurred 7 days after admission. Two days before death, the lungs "showed signs of broncho-pneumonia."

**Post-mortem examination.** Large quantity of turbid fluid in left pleura, with masses of thick loosely-attached fibrin on aero-surface. Right pleural sac healthy. Left lung—acute broncho-pneumonia in upper lobe; slight dilatation of bronchi and fibrosis, in addition to pneumonia.
with areas of suppuration, in lower lobe. Right lung—commencing broncho-pneumonia, with purulent bronchitis and some bronchial dilatation. Marked enlargement of mediastinal glands. Early fatty change in liver and kidneys.

**Microscopic examination of left lung.** The lymphatic vessels at the root are greatly dilated and full of pus. The upper lobe is in great part air-containing, but shows bronchitis and small patches of broncho-pneumonia. The lower lobe similarly shows evidence of acute inflammation, with suppuration in several places, but there are also very striking chronic changes. The size of the lobe is below normal, owing partly to collapse consequent on pleural effusion and partly to fibrosis. The larger bronchi are dilated, but there are no big bronchiectatic cavities. Their walls are much altered. In most an epithelial lining is present, but seldom of normal character. Muscle fibres are hardly discernible; the walls are composed of very vascular granulation tissue, densely infiltrated with lymphoid and other mononuclear cells. In some instances, the appearance of reduced alveolar spaces lined with cuboidal cells among this tissue shows that most of the original bronchus wall has been destroyed. A striking feature is the lymphocytic infiltration of peribronchial tissue.

The smaller bronchi are not dilated; merely indeed are reduced in size. Each is surrounded by a dense collection of small mononuclear cells. In some places no true lumen can be distinguished, but, in the midst of vascular connective tissue and lymphocytes, merely a few small spaces lined by low columnar epithelium. In addition to these widespread chronic bronchial changes there is very extensive fibrosis in this lobe, which would appear to have resulted both from the obliteration of bronchi and from proliferative changes in alveolar walls; organization of exudate in alveolar spaces is not demonstrable. What little lung tissue in this lobe is not affected by interstitial pneumonia is collapsed.

**Case VII.** Advanced unilateral bronchiectasis, with terminal acute broncho-pneumonia. (Fig. 3).

Male, aged 6 years. Fairly healthy in infancy, though rather late in cutting teeth and walking. Subject to "eczema" from an early age. Measles at 2 years: no complication. Admitted to Royal Infirmary, Edinburgh, in October, 1927, at age of 4½ years for treatment of infantile dermatitis. Ten days later developed pneumonia, which dragged on for many months and passed directly into a condition of bronchiectasis. Was in hospital for more than 8 months on end and was treated latterly by repeated bronchoscopic lavage. First admitted to the R.H.S.C. in July, 1928, i.e., 10 months after the onset of the respiratory illness. At that date, was coughing up two or three cupsfuls of thick offensive sputum each day. General development quite good, but nutrition poor. Fingers clubbed. Physical signs confined to left lung. Mediastinal structures slightly drawn over to left side. Remained in hospital till January, 1929, i.e. for 6 months. On discharge, was coughing up ½ to 3 ozs. of pus each morning. Re-admitted in February, 1929, having been fairly well in interval and having gained 2 lb. Began to have a slight evening rise of temperature and on tenth day to have all the signs of acute broncho-pneumonia. Died 14 days after re-admission, i.e. about 18 months after the onset of the original pneumonia.

**Post-mortem examination.** Left pleural sac completely obliterated by dense fibrous adhesions. Right pleura acutely inflamed. Left lung smaller than right and occupied throughout by a large number of bronchiectatic cavities, the walls of which were fairly smooth and of a deep red colour, and the contents of which consisted of very foul pus. Cavities separated by septa of completely fibrosed lung substance. Right lung voluminous and the seat of widespread acute broncho-pneumonia. No chronic changes. Tracheo-bronchial and broncho-pulmonary glands enormously enlarged. Heart dilated and right ventricle possibly slightly hypertrophied.

**Microscopic examination of left lung.** Most of the cavities have an incomplete lining of small epithelial cells, beneath which is a layer of vascular connective tissue thickly infiltrated with lymphocytes. This layer varies greatly in thickness and in places its free edge is necrotic. It merges into denser fibrous tissue, amongst which are to be found alveolar spaces lined by altered epithelium and small bronchi more or less completely obliterated. The whole of the septa between the cavities is composed of this fibrosed and obliterated lung substance. The medial part of the lower lobe shows extensive fibrosis without cavities. The absence of bronchi of any size in this area, and the presence (where bronchi apparently ought to be) of small spaces lined
by cubical epithelium, surrounded by aggregations of lymphocytes, suggests that obliteratorive bronchitis was a marked feature of the process in this part of the lung. Cartilage is present only in the main bronchus. Elastic tissue can be demonstrated by special staining in the walls of the blood vessels, in the main bronchus, and in the walls of such alveoli as remain, but is completely absent in the walls of the cavities.

**Summary.**

1. A brief historical survey of bronchiectasis and fibrosis of the lung in childhood is given, followed by clinical records of two cases.

2. The genesis of these two conditions is traced in a series of seven fatal cases.

3. The conclusion is reached that many cases have an origin in an acute respiratory illness.

4. Bronchiectasis ensues when inflammation is of such severity as to disorganize the bronchial wall. The cavities so formed are subsequently lined by a new wall of granulation tissue.

5. Fibrosis of the lung necessarily accompanies established bronchiectasis.

**References.**


STUDIES OF PNEUMONIA IN CHILDHOOD

DESCRIPTIONS OF FIGURES.

Fig. 1. Lipiodol-radiogram of Clinical Case A.
Fig. 2. Lipiodol-radiogram of Clinical Case B.
Fig. 3. (Case VII. Male, aged 6 years). Advanced unilateral bronchiectasis in left lung. Acute broncho-pneumonia in right lung. Great enlargement of root glands.
Fig. 4. (Case VI. Female, aged 6 years). Chronic fibrosis, with slight bronchiectasis, in lower lobe of left lung. Marked glandular enlargement.
Fig. 5 ((x2.)) (Case I. Male, aged 6 months.) Ulcerative bronchitis and confluent broncho-pneumonia in right upper lobe. Bronchi distinctly enlarged; majority filled with pus. B = bronchus illustrated in Fig. 9.
Fig. 6 ((x21.)) (Case II. Female, aged 2 years.) Ulcerative bronchitis and acute broncho-pneumonia in left upper lobe. Plugs of pus in excaved bronchi. Considerable collapse between pneumonic patches.
Fig. 7 ((x24.)) (Case IV. Female, aged 15 months.) Early bronchiectasis in right lung. One cavity of considerable size towards pleural surface. Several other bronchi enlarged. Confluent broncho-pneumonia in relation to affected bronchi. Obliteration of interlobular fissure. B = portion of bronchiectatic cavity illustrated in Fig. 11.
Fig. 8 ((x2.)) (Case V. Female, aged 16 months.) Early chronic bronchiectasis with terminal acute pneumonia in left lung. B = bronchus illustrated in Figs. 14 and 15.
Fig. 9 ((x60.)) (Same case as Fig. 5.) Ulcerative bronchitis. Bronchial wall completely destroyed and margin of cavity formed by consolidated alveoli. Plug of pus in lumen.
Fig. 10 ((x60.)) (Same case as Figs. 5 and 9.) Ulcerative bronchitis. Bronchial wall completely destroyed at one side (A) and relatively healthy at the other.
Fig. 11 ((x110.)) (Same case as Fig. 7.) Early bronchiectasis. Diverticulum of large cavity. Reconstitution of wall by granulation tissue.
Fig. 12 ((x110.)) (Case II.) Ulcerative bronchitis with beginning of healing. A = young granulation tissue.
Fig. 13 ((x300.)) Magnification of area A in previous photograph. Young fibroblasts sprouting out and replacing acute inflammatory products. Clump of polymorphonuclear cells to left of field.
Fig. 14 ((x60.)) (Same case as Fig. 8.) Bronchus in which disintegration and erosion of half of the circumference had occurred and in which repair was in process. Intact wall on the left; denuded and excavated wall on the right of the field. A = portion of wall shown in Fig. 15.
Fig. 15 ((x120.)) Magnification of above. Vascular granulation tissue in wall, in which a few modified alveolar spaces (A) are visible. Extension of epithelium to form a new lining for eroded portion. New epithelial cells, seen on right, of a lower grade than original epithelium. Purulent exudate in lumen.
Fig. 16 ((x120.)) (Same case as Fig. 4.) Wall of damaged, slightly dilated, bronchus. Whole thickness of wall composed of very vascular fibrous tissue, infiltrated with inflammatory cells; muscle absent. Epithelial lining formed of several layers of small cuboidal cells.
Fig. 17 ((x300.)) (Same case as Fig. 6.) Obliterative bronchiolitis. Original wall of bronchus destroyed. Organization of exudate in lumen by young fibroblasts in process and leading to obliteration. Small amount of pus still present in centre.
Fig. 18 ((x300.)) (Same case as Figs. 8, 14 and 15.) Organizing pneumonia. Alveolar space seen, partly occupied by a mass of proliferating fibroblasts and young connective tissue fibres attached to the wall at one point. A few inflammatory cells, remnants of exudate, present.
Fig. 19 ((x120.)) (Same case as Figs. 4 and 16.) Chronic fibrosis of lung, with obliteration of alveoli. A few remnants of alveoli represented by small epithelial lined spaces. Dense aggregation of lymphocytes marks site of obliterated bronchus.
CHARLES McNEIL, AGNES R. MACGREGOR & W. ALISTER ALEXANDER.

STUDIES OF PNEUMONIA IN CHILDHOOD.

V. EMPYEMA.
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BY


(From the Royal Edinburgh Hospital for Sick Children, and the Laboratory of the Royal College of Physicians, Edinburgh.)

CLINICAL CONSIDERATIONS.

Incidence. In our clinical series of 648 cases of pneumonia in children from birth to twelve years, analysed in the first of these studies, empyema occurred in 89, giving a frequency of 1 in 7. This approximates closely to the incidence of 1 in 8 in Spence's series of 204 cases of empyema from the Babies' Hospital, New York, and of 1 in 9 of Dunlop's 98 cases. Our definition of empyema was the existence of pus or sero-purulent fluid in the pleura, even in small amount, determined either during life or after death: the same standard was adopted by Spence. In our cases, the incidence was lower in the earlier age periods and was appreciably higher in later childhood. Thus, in the periods from birth to two years and from two to five years, it was almost equal—1 in 10; while from five to twelve years, it was 1 in 5. There were 3 examples of well-marked pyo-pneumo-thorax in the series.

Mortality. For the total, the mortality was 40.5 per cent. For the age periods already given, it was as shown in Table 1.

<table>
<thead>
<tr>
<th>Age period</th>
<th>Death rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 2 years</td>
<td>75 per cent.</td>
</tr>
<tr>
<td>2 to 5 years</td>
<td>31.5 per cent.</td>
</tr>
<tr>
<td>5 to 12 years</td>
<td>8.5 per cent.</td>
</tr>
</tbody>
</table>

Sex. There were 53 boys and 36 girls in the group, figures which correspond closely to the 124 boys and 80 girls in Spence's series, and also to the general preponderance of boys over girls in our inclusive group of all types of pneumonia.

Site. The right pleura was involved in 35 and the left in 47 cases. The percentage of deaths was higher in the right-sided (16 deaths) than in the left-sided group (16 deaths). Of 7 bilateral cases, 3 recovered. In the great majority of cases, the empyema was basal. In 4 it was localized about the
middle of the parietal pleura; all these recovered, 3 after single or repeated aspiration without further drainage. A brief record of one of these cases follows:—

**CASE I.** Male, aged 8 years. Pneumonia 3 weeks before admission. Crisis after 2 weeks' acute illness, followed by relapse. On admission, percussion dullness limited to a considerable area in right axilla. X-ray photograph (Fig. 1) showed a large circular shadow on the right side, with luminous lung above and below. The first two explorations were negative; a third in the 3rd interspace aspirated 5 ounces of thick pneumococcal pus. Steady uninterrupted convalescence followed. It is possible that this empyema was interlobar; if so, it is the only example of an interlobar collection in the clinical series.

**Type of pneumonia.** The antecedent pneumonic illness was alveolar (lobar) in type in 45 cases, with 6 deaths: broncho-pneumonic in 13 cases, with 13 deaths; and undetermined in 31 cases, with 17 deaths.

**Syn-pneumonic and meta-pneumonic empyema.** In a study of 52 cases of empyema in children under 2 years of age, Cameron introduced this classification. The prognosis depends to a large extent on the presence or absence of active pneumonia at the time of development of the empyema, the high death-rate in syn-pneumonic empyema being due to the extent and severity of the underlying pneumonia. This difference in prognosis is most evident in the first two years, but in later years the death-rate in syn-pneumonic empyema is still appreciably higher than in the meta-pneumonic or residual type. It has been found possible to classify 86 of our 89 cases on this basis, and the results (Table II) generally confirm the value of the classification as a guide to prognosis.

**TABLE II. (CLINICAL.)**

<table>
<thead>
<tr>
<th>Age period</th>
<th>Syn-pneumonic</th>
<th>Meta-pneumonic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Deaths</td>
</tr>
<tr>
<td>Birth to 2 years</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>2 to 5 years</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5 to 12 years</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>30</td>
</tr>
</tbody>
</table>

**Bacteriology.** This was recorded in 70 of the 89 cases (Table III).

**TABLE III. (CLINICAL.)**

<table>
<thead>
<tr>
<th>Micro-organism</th>
<th>Total</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcus</td>
<td>53</td>
<td>18</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mixed</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>
Among the total of 244 post-mortem cases of pneumonia in children analysed in our first study, there were 69 of empyema, giving a frequency of almost 27 per cent.

*Site and extent of empyema cavities.* The right side only was affected in 25 cases; the left in 25; 19 were bilateral. In 27 empyemata, organized adhesions were absent and the whole sac was involved. In 33 instances, organized adhesions obliterated part of the pleural cavity and the pus was shut off in circumscribed pockets of varying size. In the remainder the empyema occupied the greater part of the pleural sac, but limited adhesions were present.
Where organized adhesions are present, the pus may collect in several separate pockets in one pleural cavity. In 8 of our 33 cases two such independent collections were found; in one case there were three pockets separated from each other by firm fibrous adhesions.

The sites of the localized collections of pus may be of some interest. The most usual position was at the base (19 cases, of which 6 involved the diaphragmatic surface, most of the rest being posterior). In only one case was the pus entirely confined to the space between the inferior surface of the lung and the diaphragm. In 8 cases collections of pus were found in the region of the apex, 3 of them being situated on the medial aspect. In 3 cases the
pockets were on the mediastinal surface near the root; in 7, on the anterior surface; and in 6 on the posterior. In 2 cases interlobar collections were found, but in only one of these was the pus entirely imprisoned between the lobes.

**Character of the empyema fluid.** In the localized empyemata with fibrous adhesions, the fluid was usually of the nature of thick pus. Where adhesions were absent and the whole sac was involved, it was more usual to find thin pus or sero-purulent fluid, with masses of thick fibrin floating in it or adhering to the pleural surfaces. The amount of this thick fibrinous exudate was often very great.

**Types of associated pneumonia.** In 58 of the 69 cases, pneumonia of some kind was present in the lungs at the time of death; in 11 no pneumonia could be detected at autopsy. In 45 cases it was possible to determine the type of the pneumonia; in 13 this was not possible, because only remnants of pneumonia were present, and these cases were placed in a group termed 'unclassified.' Table IV shows the types of pneumonia in which empyema occurred, the number of cases of empyema associated with each type, and, for comparison, the total number of cases of each of these types in our whole series.

It will be noted that the incidence of empyema was somewhat higher relatively in alveolar than in broncho-pneumonia. But at the same time it is important to remark that almost exactly one-half of the empyemata in this series occurred in cases of broncho-pneumonia. We find it, therefore, impossible to agree with the view which has been expressed, that empyema seldom occurs in broncho-pneumonia. Our experience is that the great majority of fatal cases of empyema in children under two years of age complicate broncho-pneumonia (see Fig. 3, 4, 5 and 6).

**TABLE IV. (Post-mortem)**

<table>
<thead>
<tr>
<th>Type of pneumonia</th>
<th>Total</th>
<th>Emphyema</th>
<th>Per cent. Emphyema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broncho-pneumonia</td>
<td>140</td>
<td>34</td>
<td>24</td>
</tr>
<tr>
<td>Alveolar (lobar) pneumonia</td>
<td>23</td>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td>Septic (pyemic) pneumonia</td>
<td>4</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Chronic pneumonia (bronchiectasis)</td>
<td>5</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>Unclassified</td>
<td>17</td>
<td>13</td>
<td>70</td>
</tr>
<tr>
<td>No pneumonia</td>
<td></td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

**Age incidence.** All the children were under 8 years of age; 47 were under two years. The largest number (31 cases) was found between the sixth and eighteenth months. The high incidence of fatal cases in the first two years is explained, as has already been stated, by the deadly character of the accompanying pneumonia during that age period.
Fig. 3. Same as Fig. 4. Right lung. Capillary bronchitis and acute broncho-pneumonia throughout, with confluence along medial border.

Fig. 4. Girl aged 1 year and 9 months (Case II). Left lung. Empyema of 3 weeks' duration. Organizing exudate over entire pleural surface; sub-pleural abscess (A) on diaphragmatic surface; broncho-pneumonia and collapse throughout lung.

Fig. 5. Girl aged 9 months (Case III). Right lung. Empyema of 5½ weeks' duration. Fibrous thickening of pleura on lateral surface; large sub-pleural abscess (A) about to rupture at base; deep-seated abscess (B) in lower lobe; almost complete collapse of lung.

Fig. 6. Same case as Fig. 5. Left lung. Acute broncho-pneumonia, especially in lower lobe. Well-marked acute vesicular emphysema. (The tri-lobed appearance of this lung is an artefact.)
Sex. There were 42 boys and 27 girls in this series.

Complications accompanying empyema. A fairly large proportion of the empyema cases showed other grave complications of pneumonia. The chief of these were pericarditis, peritonitis and meningitis. In 21 of the 69 cases of empyema, one or more of these three conditions occurred. Their frequency was:—Pericarditis, 16; peritonitis, 7; meningitis, 2. For comparison, the frequency of these complications in the 175 cases of pneumonia without empyema in our series was:—pericarditis, 2; peritonitis, 3; meningitis, 4. These figures show that in this series both pericarditis and peritonitis occurred much more frequently in cases of empyema than in pneumonia without empyema, but that this was not the case with meningitis. Pericarditis was present in 23.2 per cent. of the cases of empyema, compared with 1.1 per cent. of the cases of pneumonia without empyema; the corresponding figures for peritonitis were 10.1 per cent. compared with 1.7 per cent.; while for meningitis they were 3 per cent. compared with 2.2 per cent.

These facts may have some bearing on the question of the channel by which the infection spreads to these various secondary sites. In the case of meningitis there can be little doubt that the usual route by which the infection reaches the meninges is the blood stream. In the case of pericarditis and peritonitis there is a possibility of a more local spread, probably by lymphatics; but the view that these also are results of a blood-spread infection is widely favoured. The figures just presented would seem to support the view that pericarditis and peritonitis may be often—perhaps most often—the result of spread of infection by the more direct route, and not of a blood infection. It is always dangerous to draw conclusions from small numbers of cases, and it must be admitted that there is a greater probability of blood infection in cases of pneumonia complicated by empyema, because they are on the average more severe and prolonged, and run a greater risk of the development of a secondary septicemia. Yet if all these three conditions were alike caused by blood infection, it might be expected that the incidence of all three would be similarly affected by the occurrence of empyema.

Suppuration in the lungs. Suppuration or necrosis in the lungs was found in 26 of the 69 cases of empyema (37.7 per cent.). Seventeen of these were cases of broncho-pneumonia, while only one was alveolar (lobar) pneumonia. Exactly one-half of the cases of broncho-pneumonia with empyema showed suppuration or septic necrosis in the lungs. In a few instances where suppuration was present, it could be shown at autopsy that an abscess or abscesses in the lung had burst into the pleural sac, and had thus, in all likelihood, caused the empyema. In several other instances abscesses, as yet unruptured, projected immediately beneath a stretched, infected and sometimes necrotic pleural membrane (Figs. 4 and 5). Sometimes the abscesses were deep-seated, and had no apparent connection with the empyema.

In the 175 cases of pneumonia without empyema, suppuration or necrosis was found in 21 (12 per cent.). From this it would appear that these changes in the lungs are distinctly more common in cases of empyema than in pneumonia without that complication. While in some instances it is fairly obvious that
the suppuration in the lung is the direct cause of the empyema, in others it is no easy task to determine which of the two conditions arose first. For while it is evident that suppuration in the lung renders empyema more likely, it is probable that the converse is true also, that the presence of an empyema increases the risk of suppuration in the lung. The reason for this is as follows. Suppuration in the lungs in cases of the kind being considered is usually in the form either of bronchial abscesses or of septic infarcts (Fig. 9). Brief mention of this was made in the third of these studies, when it was pointed out that bronchial abscesses are the result of suppuration starting in the bronchial walls and peribronchial lymphatics; and septic infarcts the result of thrombosis of blood vessels due to involvement of their walls in a suppurative inflammation spreading along the perivascular lymphatics (Fig. 7). It is probable that the impairment of circulation of blood and lymph, and the restricted movement of the lung in the presence of an empyema, favour the development and spread of this suppurative lymphangitis, with its grave effects upon the lung.

**Fibrosis of the pleura and lung.** A certain amount of fibrous thickening of the pleura is probably inevitable in most cases of empyema which survive long enough to allow it to occur. Even when the pus has been successfully evacuated, a quantity of thick fibrino-purulent exudate often remains adhering to the pleural surfaces. Organization of this is bound to lead to the formation of new fibrous tissue, and probably to the production of adhesions (Fig. 10).
It is remarkable with what rapidity a fairly thick layer of new fibrous tissue may form beneath an inflammatory exudate. Even after two or three weeks its amount may be quite considerable (Fig. 8).

In cases of longer standing, especially when the lung has remained for some time in a partly collapsed condition, there may be extensive fibrosis of the lung itself. The beginning of this may be found a few weeks after the onset of empyema, in the form of fibrous tissue proliferation in the interlobular septa, commencing at their junction with the pleura and spreading inward (Fig. 11); and also in the walls of alveoli immediately beneath the pleura or adjacent to thickened septa. In more advanced cases this chronic interstitial pneumonia may lead to an almost complete obliteration of the air-containing lung tissue. Interlobular septa, enormously broadened by the growth of new fibrous tissue in them, pass in from a greatly thickened pleura and divide the lung substance into widely separated lobules, in which the alveoli are more or less completely collapsed and show a variable amount of fibrous thickening of their walls. Fibrosis of the alveolar walls is, however, sometimes less striking than might be expected. The constant outstanding feature of pleurogenic fibrosis of the lung would appear to be the immense thickening of the septa which, together with the thickened pleura, effectively prevents the normal expansion of the lung.
CASE II (Fig. 3, 4 and 8). Left-sided empyema, complicating acute broncho-pneumonia. Female, aged 1 year and 9 months. Died 3 weeks after onset of illness, and 3 days after admission to hospital. Pus (pneumococcal) removed by syringe from left pleura on day before and day after admission. On post-mortem examination, large quantity of thick yellow pus in left pleural sac; whole pleura covered with thick fibrino-purulent exudate with exception of medial surface where loose adhesions were present. Left lung collapsed and airless; several small abscesses in lower lobe, one immediately under pleura and in relation to empyema cavity. Right pleura healthy. Right lung emphysematous, with recent acute broncho-pneumonia; strip of consolidation along medial border. Tracheo-bronchial glands swollen and soft. Microscopically, degree of organization and formation of young fibrous tissue in left visceral pleura surprisingly advanced for an inflammation of 3 weeks' duration; marked bronchitis in left lung, suppurative in lower lobe; several small abscesses of bronchial origin in infero-medial portion; combination of collapse and consolidation in lung substance.

CASE III, (Fig. 2, 5 and 6). Right-sided empyema, complicating broncho-pneumonia. Female, aged 9 months. Died some 5½ weeks after onset of illness and 10 days after admission to hospital. Pus (pneumococcal) removed by syringe on two occasions while in hospital. X-ray photograph (Fig. 2), taken on day before death, of considerable interest because of displacement of heart to affected side. On post-mortem examination, more than half a pint of greenish-yellow pus in large pocket on lateral aspect of right lung; remainder of pleural sac obliterated by recently organized adhesions. Right lung collapsed and compressed against mediastinal tissues; projecting sub-pleural abscess on infero-medial aspect; smaller abscess in substance of lower lobe. Left pleura healthy. Left lung very markedly emphysematous, almost completely overlapping...
heart : bronchitis and small areas of broncho-pneumonia present, especially in lower lobe. 
Microscopically, great thickening of right pleura in relation to empyema cavity seen to be due 
mainly to well-advanced organization. Bronchi throughout right lung inflamed, with thick 
cellular walls denuded of lining epithelium; abscess in substance of lower lobe, referred to 
above, obviously of bronchial origin; solid condition of right lung due largely to collapse, but 
very definite broncho-pneumonic element also evident.

The displacement of the heart to the affected side in this case, illustrated in the X-ray 
photograph, must be ascribed, in part at any rate, to the push of the markedly emphysematous 
functioning left lung. There is no question of its being the result of traction by a fibrosed right 
lung, as the illness was too short to allow of the necessary degree of fibrosis, and, in any case, 
microscopic examination effectually rules out the possibility. It is of interest in connection with 
the recent observations of Tallermann and Jape.

Case IV, (Fig. 7). Fulminating pneumonia, of septic type, with early empyema. Boy, 
aged one month; twin; breast-fed. Illness said to have been of only 36 hours' 
duration; convulsions the most prominent feature. On post-mortem examination, about 
an ounce of turbid blood-stained fluid in right pleura. Right lower lobe solid and of a deep red 
colour, with certain areas in process of undergoing softening. Left pleura inflamed in patches 
but without any fluid content. Left lower lobe less completely consolidated than right, but 
also haemorrhage and the site of breaking-down pneumonic areas. Microscopically, essential 
condition seen to be broncho-pneumonia of a very acute septic type, but consolidation contributed 
to by haemorrhage and necrosis; suppurative lymphangitis a prominent feature.

Case V, (Fig. 9). Right-sided empyema, complicating pneumonia with septic infection. 
Male, aged 1 year and 2 months. Died 3½ weeks after onset of illness and 12 days after admission 
to hospital. Clinically, regarded as case of lobar pneumonia, at first of right upper and later 
of left lower lobe. Cerebral symptoms prominent. Emphyema (pneumococcal) detected on 
right side 6 days after admission, i.e., 2½ weeks after beginning of illness; treated by repeated 
aspiration. On post-mortem examination, not much pus, but very thick fibrino-purulent exudate 
in lower part of right pleural sac. Right upper lobe extensively consolidated, as a result partly 
of pneumonia and partly of necrosis; several independent areas of latter, some of them becoming 
purulent. Small abscesses also present in middle lobe. Mixture of pneumonia and collapse 
in infero-lateral part of right lower lobe. Left pleura acutely inflamed over lower lobe: no 
free fluid. Large patch of pneumonia of alveolar type in left lower lobe. Microscopically, 
commencing organization of copious pleural exudate on right side; type of pneumonia in right 
upper lobe difficult of definition, as septic infection so widespread. Necrosis regarded as having 
developed in pneumonic lung as a result of infection of vessel walls from perivascular tissues, 
and consequent thrombosis.

Case VI, (Fig. 10). Long-standing left-sided empyema. Female, aged 1 year and a half. 
Illness of about 11 weeks' duration. Main incidence of pneumonia said to be at first in right 
lung, later in left. Admitted 3 weeks after onset of symptoms, with left-sided empyema 
(pneumococcal). Treated by repeated aspiration and then by drainage through cannula inserted 
between ribs. Progress fairly satisfactory for some weeks. Severe constitutional symptoms 
and jaundice before death. On post-mortem examination, left pleural sac largely obliterated 
by dense organized adhesions; drainage opening communicating with relatively small 
unobliterated pocket; abscess in chest wall in relation to drainage opening. Left lung much 
collapsed; remnants of broncho-pneumonic process in substance; bronchi slightly dilated 
and filled with pus. Recent acute pleurisy with effusion on right side. Small scattered patches 
of consolidation and softening in right lung, more suggestive of blood-borne than air-passage 
infection. Profound toxic changes in organs, especially liver. Death regarded as result of 
terminal septicaemia.

Case VII (Fig. 11). Left-sided empyema: original pneumonia probably broncho-pneumonia. 
Male, aged 1 year and 8 months. Died after an illness which, so far as could be ascertained, 
lasted about 6 weeks. Admitted 3 weeks after onset. Emphyema suspected but not discovered 
till a week later; aspirated on two occasions and then drained by rib-resection. Cavity not 
large and drainage apparently complete. Constitutional disturbance continued, however, 
and death occurred about a week after operation. On post-mortem examination, left pleural 
sac obliterated by dense fibrous adhesions except at point of drainage, where small empty cavity
remained. Left lung partially collapsed, but not pneumonic. Right pleura acutely inflamed. No pneumonia obvious in right lung. Early acute pericarditis and peritonitis. Pronounced toxic changes in organs. Microscopically, right pleura greatly thickened by well-organized fibrous tissue; interlobular septa in relation to pleura also markedly thickened. Intervening lung substance collapsed. Surprising degree of fibrosis in pleura and stroma of lung, for inflammation of 6 weeks' duration. Death, as in last case, due to septicemia.

SUMMARY.

A short survey of 89 clinical and 69 post-mortem cases of empyema in children is presented. Figures are given showing age incidence, mortality, associated types of pneumonia, and frequency and situation of localised collections of pus. The association of empyema with lung abscess, pulmonary fibrosis, and certain other complications is briefly discussed.

REFERENCES.


ACKNOWLEDGMENTS.

In connection with this series of studies of pneumonia and its complications in childhood, we wish to express our indebtedness to:—The Committee of the Laboratory of the Royal College of Physicians, Edinburgh; Lieut.-Col. A. G. McKendrick, superintendent of the Laboratory; the late Dr. J. W. Dawson and Lieut.-Col. W. F. Harvey, in whose department most of the technical work was carried out; Mr. T. D. Hamilton, who prepared the very beautiful large sections with which we worked, and who was also responsible for the photographs; Dr. Norman Carmichael and Dr. Lewis Thatcher, for permission to refer to and illustrate certain of their cases; Professor J. Lorrain Smith, for his sympathetic interest and helpful and suggestive criticisms; the Carnegie Trust for a grant to one of us; and the very kind friend, who prefers to remain anonymous, whose generosity has defrayed the expenses of this research.
Tuberculosis in Children

BY

AGNES R. MACGREGOR, M.B., F.R.C.P.E.

(From the Royal Edinburgh Hospital for Sick Children)

Reprinted from the Edinburgh Medical Journal, December 1930
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</tr>
</tbody>
</table>

Introduction.

The presentation from time to time of facts derived from carefully performed and accurately recorded post-mortem examinations has, in the case of so important a disease as tuberculosis, a certain practical interest and value. It may serve to show any significant changes in the incidence or type of the disease, and to indicate directions in which progress has been, or has failed to be, made.
In 1909, Shennan\(^1\) collected from the post-mortem records of this hospital, and published an analysis of, 413 cases of tuberculosis examined during the period 1883 to 1904. In 1914 and 1916 the same author\(^2\) published further studies including cases examined during the period 1910 to 1913. In 1925 the present writer\(^4\) reviewed in detail 48 cases examined during the years 1922 to 1924, which are included in the series now under consideration.

The present study covers the period from July 1922 to November 1929, during which tuberculous lesions were found in 250 cases. In 204 of these, tuberculosis was the cause of death. In 46 death was due to other causes, the tuberculosis being incidental and in some instances quiescent. All the children examined were patients in the Royal Edinburgh Hospital for Sick Children, and all were under twelve years of age. With few exceptions, the autopsies were performed and recorded by the writer.

This study represents work done in the course of the routine duties of the writer as pathologist to the hospital. Certain unavoidable defects must be admitted. No attempt has been made to carry out a complete microscopic investigation of the cases. The data presented are for the most part those obtained by careful macroscopic examination, although the microscope has been used whenever reasonable doubt existed as to the presence or the nature of possible tuberculous lesions. The possibility of small foci having been overlooked must be recognised. Perhaps especially in three types of case this possibility must be taken into account. Firstly, in cases of death from causes other than tuberculosis, small tuberculous foci might be missed, although they have been looked for throughout this series with great care. The risk of missing any focus other than an extremely inconspicuous one is very slight; much less in the body of a child than in that of an adult. Secondly, where there is caseous tuberculosis of the thoracic glands and no primary lung focus is found, the existence of the latter cannot be categorically denied unless the examination of the lungs has been extraordinarily minute and painstaking. This matter is referred to again in a later section of this paper. Thirdly, the presence of tuberculosis in the tonsils can often be determined only by complete microscopic examination. As in many cases this has not been carried out, full justice cannot be done to this lesion in the figures presented.

---

\(^{1}\) Shennan, W. (1909).

\(^{2}\) Shennan, W. (1914).


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Another important defect in the pathological material is a scarcity of surgical tuberculosis, especially bone and joint and genito-urinary cases. This is unavoidable when the material under consideration is drawn entirely from the post-mortem room, as these forms of the disease have a relatively low mortality.

Statistical Analysis.

Incidence of tuberculosis in relation to other causes of death. During the period covered by the 250 tuberculous cases (July 1922 to November 1929), 1127 autopsies were performed in the hospital. Tuberculosis in some form was, therefore, found in 22 per cent. of all autopsies, and in 18 per cent. was the cause of death. The corresponding figure in Shennan's series was 36 per cent. showing tuberculous lesions. If a just comparison can be drawn between the two series, a remarkable reduction in the incidence of tuberculosis is indicated in the later period.

Site of the primary or principal lesions.—In most cases it is a matter of no great difficulty to arrive at an opinion as to the site of the oldest progressive lesions. Examination of the lymphatic system provides helpful information, for infection of the glands plays an important and conspicuous part in tuberculosis of childhood, and in a vast majority of cases caseous enlargement is to be found in one or more of the three principal groups (cervical, thoracic, abdominal). These caseous glands may be themselves the site of the primary infection or, being the regional glands of the area first affected, they may be a guide to its position.

Table I shows the number of cases in this series in which lymph glands in the various groups showed tuberculous foci visible to the unaided eye, exclusive of purely acute miliary tubercles. For the purpose of the percentages, only 247 of the
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250 cases have been considered, because in the other three the examination was incomplete owing to restrictions imposed by the relatives of the children.

It is evident from the facts shown in Table I. that in most cases disease was found in more than one of the three principal groups of glands. But usually the degree of enlargement and the apparent duration of the disease were much greater in one group than in the others. The glands which showed the most advanced lesions being taken as a guide, the position of the probable primary focus could usually be located with reasonable certainty.

According to the site of the principal lesions the cases may be grouped as shown in Table II.

<table>
<thead>
<tr>
<th>TABLE II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of Principal Lesions.</td>
</tr>
<tr>
<td>Principal lesions cervical in .</td>
</tr>
<tr>
<td>&quot; thoracic in .</td>
</tr>
<tr>
<td>&quot; abdominal in .</td>
</tr>
<tr>
<td>Meningitis only in .</td>
</tr>
<tr>
<td>Incompletely examined .</td>
</tr>
</tbody>
</table>

These figures show an almost equal incidence of thoracic and abdominal cases in the whole series, the cervical group being very small. But it will be shown later that among those cases in which tuberculosis was the cause of death, there was an important preponderance of primary thoracic tuberculosis.

Incidental and Latent Tuberculosis.

Much interest attaches to the question of latent tuberculosis in children, as the disease in adult life is frequently ascribed to infection acquired during childhood. Those cases in which tuberculosis was "incidental" have therefore been studied in detail. They numbered 46 out of the 250 cases, representing 18.4 per cent. This is a notably higher proportion than the 4 per cent. in Shennan's series characterised as "latent."

In considering this group it is advisable to draw a distinction between the terms "incidental" and "latent" or "quiescent." For the purpose of this paper all those cases are termed "incidental" in which the tuberculous lesions found were not regarded as the cause of death; but by the use of this term no indication is intended to be given of the state of activity
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exhibited by the lesions or of their extent. The terms "quiescent" and "latent" may be legitimately employed only when the lesions show no evidence of a progressive character.

Of the 46 cases, 12 showed active and progressive visceral, in addition to glandular, lesions, and were therefore by no means "latent" cases. One showed old healed (calcified) foci in lungs and thoracic glands. The other 33 had lesions in lymph glands only, and were "latent" cases in the sense that there was no evidence of progressive spread to other sites, although in many the glandular lesions were of a moderately active character and their potentialities for evil probably considerable. On this liberal (if perhaps dubious) interpretation of the term "latent," it might be said that 34 cases showed latent tuberculous lesions. This represents 14 per cent. of all tuberculous cases and 3 per cent. of all autopsies. It would seem from this that the prevalence of latent tuberculosis in children under twelve years of age is small, at least in this part of the country.

Age incidence.—Table III. shows the ages of the "incidental" and of the "latent" cases, arranged in yearly periods; the percentage of all tuberculous cases and of all autopsies to show "incidental" or "latent" lesions; and, for comparison, the total number of tuberculous cases and of all autopsies in each age-group.

TABLE III.

Age Incidence ("Incidental" Group).

<table>
<thead>
<tr>
<th></th>
<th>0-1</th>
<th>1-2</th>
<th>2-3</th>
<th>3-4</th>
<th>4-5</th>
<th>5-6</th>
<th>6-7</th>
<th>7-8</th>
<th>8-9</th>
<th>9-10</th>
<th>10-11</th>
<th>11-12</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Incidental.&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>4</td>
<td>7</td>
<td>6</td>
<td>11</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td></td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Per cent. of all tuberculosis</td>
<td>7</td>
<td>10</td>
<td>18</td>
<td>38</td>
<td>28</td>
<td>12</td>
<td>12</td>
<td>37</td>
<td>22</td>
<td>37</td>
<td>28</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Per cent. of all autopsies</td>
<td>0.7</td>
<td>5.6</td>
<td>20</td>
<td>14</td>
<td>3</td>
<td>7</td>
<td>14</td>
<td>25</td>
<td>33</td>
<td>33</td>
<td>25</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>&quot;Latent.&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>...</td>
<td>5</td>
<td>3</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>4</td>
<td>34</td>
</tr>
<tr>
<td>Per cent. of all tuberculosis</td>
<td>...</td>
<td>7</td>
<td>9</td>
<td>35</td>
<td>28</td>
<td>12</td>
<td>12</td>
<td>37</td>
<td>22</td>
<td>37</td>
<td>28</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Per cent. of all autopsies</td>
<td>...</td>
<td>2</td>
<td>3</td>
<td>19</td>
<td>14</td>
<td>3</td>
<td>4</td>
<td>14</td>
<td>25</td>
<td>33</td>
<td>25</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Total tuberculosis</td>
<td>54</td>
<td>73</td>
<td>33</td>
<td>29</td>
<td>18</td>
<td>8</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>7</td>
<td>3</td>
<td>7</td>
<td>250</td>
</tr>
<tr>
<td>Total autopsies</td>
<td>568</td>
<td>236</td>
<td>93</td>
<td>54</td>
<td>37</td>
<td>31</td>
<td>29</td>
<td>22</td>
<td>5</td>
<td>12</td>
<td>9</td>
<td>12</td>
<td>1127</td>
</tr>
</tbody>
</table>

Note.—Age unknown in 19 non-tuberculous cases.

Table IV. presents the same information as Table III., but with the cases arranged in longer age periods. The separate figures for the first four half-years are also given.
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TABLE IV.
Age Incidence ("Incidental" Group).

<table>
<thead>
<tr>
<th></th>
<th>0-1/2</th>
<th>1-1½</th>
<th>1½-2</th>
<th>2-5</th>
<th>5-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Incidental.&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>...</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Per cent. of all tuberculosis</td>
<td>...</td>
<td>13</td>
<td>9</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Per cent. of all autopsies</td>
<td>...</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>&quot;Latent.&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>...</td>
<td>...</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Per cent. of all tuberculosis</td>
<td>...</td>
<td>...</td>
<td>4</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Per cent. of all autopsies</td>
<td>...</td>
<td>...</td>
<td>1</td>
<td>4</td>
<td>0-6</td>
</tr>
<tr>
<td>Total tuberculosis</td>
<td>22</td>
<td>32</td>
<td>46</td>
<td>27</td>
<td>127</td>
</tr>
<tr>
<td>Total autopsies</td>
<td>379</td>
<td>189</td>
<td>163</td>
<td>73</td>
<td>804</td>
</tr>
</tbody>
</table>

The figures presented in Tables III. and IV. emphasise the rarity of latent tuberculosis in the earlier years of life. It is surely very significant that in 568 autopsies on children under one year old, among whom there were 54 having tuberculous lesions, not one was found in which tuberculous infection, being present, had failed to progress to such extent that active secondary visceral lesions had formed. It would seem that when an infant under one year becomes infected and a lesion is established, the chance of the disease being arrested is very small. Moreover, among 236 autopsies on children between one and two years, with 73 tuberculous cases, only 5 showed latent infection. Apparently, then, the childhood infection to which adult tuberculosis is so often ascribed must usually be acquired after the age of two years; otherwise it would probably become progressive and prove fatal during childhood.

Site of the primary focus in the "incidental" cases. Lymph glands were affected in every one of the 46 cases. In 33 no foci were found elsewhere than in lymph glands, and in only one of these was more than one group of glands affected (mesenteric and cervical). There were visceral lesions in 13 cases, situated as follows:—Lungs, 6 cases, all with caseous thoracic glands and all but one active and progressive; intestinal ulcers, 3 cases; bone, 1 case; early miliary tuberculosis, 5 cases.

Table V. shows the site of the primary foci in the "incidental" and "latent" cases.

"Incidental" tuberculosis was found much more often in the mesenteric glands than anywhere else in the body. Over 82 per cent. of the "latent" foci were in that situation. It
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would seem that foci in the thorax, even when discovered incidentally, are frequently progressive and not confined to the site of the primary focus. It is perhaps noteworthy that in babies under two years incidental lesions were found in the thorax more often than in the abdomen (6 cases thoracic against 4 abdominal); but in 4 of these the disease was of an active and progressive character.

**TABLE V.**

*Site of Primary Focus (“Incidental” Group)*.

<table>
<thead>
<tr>
<th>Site</th>
<th>Incidental</th>
<th>Latent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Thoracic (lungs or glands)</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal</td>
<td>33</td>
<td>28</td>
</tr>
</tbody>
</table>

Evidence of healing in latent foci.—As previously stated, even in those cases which, for the purpose of this study, have been admitted to the “latent” group, the foci were not always truly quiescent lesions in which infection had definitely been overcome. Evidence of healing, in the form of calcification or complete fibrous scarring, was found in only 15 cases (12 in mesenteric glands, 3 in thoracic glands and/or lungs). The earliest age at which calcification was found was 22 months, in 1 case. The other 14 were all over 3 years 9 months, and 10 of them were over 5 years.

**Progressive and Fatal Tuberculosis.**

In 204 of the 250 cases of this series, tuberculosis was the direct cause of death. This represents 81.6 per cent. of all the tuberculous cases and 18 per cent. of all autopsies during the period under consideration.

**Site of principal lesions.**—Table VI. shows the position of the principal lesions in the 204 “fatal” cases.

**TABLE VI.**

*Site of Principal Lesions (“Fatal” Group).*

<table>
<thead>
<tr>
<th>Principal lesions cervical in</th>
<th>11 cases (5.4 per cent.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>thoracic in</td>
<td>107 cases (52.4 per cent.)</td>
</tr>
<tr>
<td>abdominal in</td>
<td>80 cases (39.2 per cent.)</td>
</tr>
<tr>
<td>Meningitis only in</td>
<td>3 cases (1.5 per cent.)</td>
</tr>
<tr>
<td>Incompletely examined</td>
<td>671 cases A 3</td>
</tr>
</tbody>
</table>

(Cont.)
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It will be noted that whereas in the whole series the incidence of thoracic and of abdominal cases was almost equal (see Table II.), among those cases in which tuberculosis was the cause of death primary thoracic tuberculosis was much more prevalent than abdominal.

*Age incidence.*—Tables VII. and VIII. show the age distribution of the 204 “fatal” cases. The cases are divided into groups (cervical, thoracic, etc.) according to the site of the principal lesions. The incidence of fatal tuberculosis in relation to other causes of death is also shown. In Table VII. the age distribution is shown in yearly periods; in Table VIII. the cases are grouped in longer age periods, and in addition the separate figures for the first four half-years are given.

**Table VII.**

*Age Incidence ("Fatal" Group).*

<table>
<thead>
<tr>
<th></th>
<th>0-1</th>
<th>1-2</th>
<th>2-3</th>
<th>3-4</th>
<th>4-5</th>
<th>5-6</th>
<th>6-7</th>
<th>7-8</th>
<th>8-9</th>
<th>9-10</th>
<th>10-11</th>
<th>11-12</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>6</td>
<td>3</td>
<td>...</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1</td>
<td>...</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>34</td>
<td>30</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>9</td>
<td>15</td>
<td>1</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>...</td>
<td>1</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis only</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>65</td>
<td>27</td>
<td>18</td>
<td>13</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>204</td>
<td></td>
</tr>
<tr>
<td>Total autopsies</td>
<td>568</td>
<td>236</td>
<td>93</td>
<td>54</td>
<td>37</td>
<td>29</td>
<td>22</td>
<td>5</td>
<td>12</td>
<td>9</td>
<td>12</td>
<td>1127</td>
<td></td>
</tr>
<tr>
<td>Per cent. fatal tuberculosis</td>
<td>9</td>
<td>28</td>
<td>33</td>
<td>35</td>
<td>23</td>
<td>24</td>
<td>20</td>
<td>33</td>
<td>33</td>
<td>25</td>
<td>18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note.—Age unknown in 19 non-tuberculous cases.

**Table VIII.**

*Age Incidence ("Fatal" Group).*

<table>
<thead>
<tr>
<th></th>
<th>0-4</th>
<th>1-5</th>
<th>2-6</th>
<th>3-7</th>
<th>4-8</th>
<th>5-10</th>
<th>5-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Thoracic</td>
<td>14</td>
<td>20</td>
<td>18</td>
<td>12</td>
<td>64</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Abdominal</td>
<td>3</td>
<td>6</td>
<td>21</td>
<td>11</td>
<td>41</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>Meningitis only</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>28</td>
<td>42</td>
<td>24</td>
<td>116</td>
<td>58</td>
<td>30</td>
</tr>
<tr>
<td>Total autopsies</td>
<td>379</td>
<td>189</td>
<td>163</td>
<td>73</td>
<td>184</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>Per cent. fatal tuberculosis</td>
<td>6</td>
<td>15</td>
<td>26</td>
<td>33</td>
<td>13</td>
<td>32</td>
<td>25</td>
</tr>
</tbody>
</table>

Chart I. presents in graphic form some of the facts given in Table VII. It shows, in yearly periods, the age distribution...
of the whole "fatal" group and separate curves for the thoracic and abdominal cases.

The highest incidence is in the second year (29 per cent. of total), and especially in the first half of that year (18 per cent. of total). In relation to other causes of death, however,

tuberculosis takes a higher place during the period 2 to 5 years than in the younger age-group. This is obviously due to the high mortality from diseases such as pneumonia and enteritis among children under 2 years.

The youngest child in this series was aged 2 months, the eldest 11 years and 11 months.
Agnes R. Macgregor

It is noteworthy that the high mortality during the first year is mainly due to the prevalence of thoracic tuberculosis; while in the second year and during the period 2 to 5 years abdominal cases are in excess of thoracic; and in the later years thoracic again become the more numerous. Further, the thoracic cases reach their highest point in the first year, whereas the abdominal are more than three times as many in the second as in the first year. There is a remarkably high prevalence of abdominal cases in the first half of the second year. Only one abdominal case was over 8 years of age.

Seasonal incidence.—For the purpose of studying the seasonal incidence of fatal cases of tuberculosis, the seven complete years from 1st January 1923 to 31st December 1929 have been considered. During that period 1128 post-mortem examinations were carried out, and death was caused by tuberculosis in 206 of these.

Chart II. shows the monthly incidence during the seven years' period, giving curves for the whole tuberculous group,
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for the thoracic and abdominal groups separately, and, for comparison, the total autopsies.

The curve representing the whole tuberculous group shows that, apart from a fall during August, September and October the incidence is fairly constant throughout the year. The proportion of tuberculous to total autopsies is, however, considerably higher during the first seven months than during the later part of the year. When the thoracic and abdominal cases are considered separately, it is evident that the former

are distinctly more numerous during the first half of the year, while the latter show no such definite seasonal variation. During the whole period from January to June thoracic cases exceed abdominal; but in five of the six later months abdominal equal or exceed thoracic.

In view of a statement which is sometimes made, to the effect that there is a higher incidence of tuberculous meningitis during the spring months than during the rest of the year, the 138 cases of meningitis which occurred during the seven years' period were separately considered. Chart III. represents the results.
Agnes R. Macgregor

It is evident that the incidence of tuberculous meningitis has been higher in the earlier part of the year, especially during the first four months. But this applies only to those cases of meningitis in which the primary focus was thoracic. Cases of abdominal origin were actually more numerous in summer and early winter.

Table IX, which shows quarterly incidence, presents the various facts already mentioned in a different form.

### Table IX.

**Quarterly Incidence.**

<table>
<thead>
<tr>
<th></th>
<th>1st Quarter</th>
<th>2nd Quarter</th>
<th>3rd Quarter</th>
<th>4th Quarter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All &quot;fatal&quot; Tuberculosis.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary thoracic</td>
<td>35</td>
<td>36</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Primary abdominal</td>
<td>18</td>
<td>20</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>57</td>
<td>40</td>
<td>49</td>
</tr>
<tr>
<td><strong>Tuberculous Meningitis.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary thoracic</td>
<td>29</td>
<td>27</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Primary abdominal</td>
<td>8</td>
<td>13</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>41</td>
<td>30</td>
<td>26</td>
</tr>
</tbody>
</table>

**Yearly incidence.**—The number of tuberculous cases varied considerably from year to year, as shown in Chart IV.

A large increase in 1925 was followed by a gradual fall during the three years following, but 1929 again showed a slight increase. The proportion of tuberculous to total autopsies varied from 14 per cent. in 1923 to 24 per cent. in 1925. It may be noted that in no year did the percentage of tuberculous cases rise nearly as high as the figures given by Shennan for his two series in the periods 1883-88 (41.2 per cent.) and 1889-1904 (36.8 per cent.).

When the thoracic and abdominal groups are considered separately, no steady increase or decrease during the seven years' period is noticeable in either group. Thoracic cases vary from 24 per cent. of all tuberculosis in 1924 to 64 per cent. in 1928, and abdominal cases vary from 26 per cent. in 1923 to 57 per cent. in 1924.

**Sex incidence.**—In the whole "fatal" tuberculous group, 57 per cent. of the children were boys and 43 per cent. girls, compared with 59 per cent. boys and 41 per cent. girls among all autopsies.
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When the thoracic and abdominal groups are considered separately, a more striking difference in sex incidence becomes evident. In the thoracic group, 48.5 per cent. were boys and 51.5 per cent. girls; while in the abdominal group, 67.5 per cent. were boys and 32.5 per cent. girls.

The Thoracic Group.—The cases in which the principal and presumably primary, lesions were in the thorax form the largest group among the "fatal" cases, numbering 107 or 52.4 per cent. Included in this group are those in which the apparent primary focus was in the lungs and those in which it was in the thoracic lymph glands. In every case there was caseation, more or less extensive, in the tracheobronchial and/or root glands on one or both sides.

The question of the "primary lung focus."—Many authorities are of opinion that when the tracheobronchial or root glands are caseous, a primary focus is always present in one of the lungs, and can be found if search be made with sufficient care.
Agnes R. Macgregor

It is certainly true that careful search will, in a great majority of cases, reveal some focus in the lungs which may be regarded as probably of equal standing with, or older than, the disease in the thoracic glands. In the present series, however, such a focus was not demonstrated in all cases, although it was always diligently sought.

Type and extent of tuberculous lesions in the lungs.—Table X. shows the character of the disease in the lungs in the 107 cases in which the principal lesions were in the thorax.

TABLE X.

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated caseous nodules</td>
<td>32</td>
</tr>
<tr>
<td>Lymphatic (proliferative) tuberculosis</td>
<td>28</td>
</tr>
<tr>
<td>Pneumonic (exudative) tuberculosis</td>
<td>31</td>
</tr>
<tr>
<td>Single cavity and miliary tubercles</td>
<td>2</td>
</tr>
<tr>
<td>Acute miliary tubercles only</td>
<td>13</td>
</tr>
<tr>
<td>No lesion discovered</td>
<td>1</td>
</tr>
</tbody>
</table>

It will be seen from the figures presented in Table X. that in 93 out of 107 cases (87 per cent.) tuberculous disease of some standing—probably representing the primary infection—was present in the lungs; while in 14 (13 per cent.) no focus was discovered which could be considered to have been antecedent to, or contemporary with, the disease in the glands.

Isolated caseous nodules.—These, when present, may reasonably be regarded as primary foci of infection. They were found in 32 cases. They were usually single and seldom large, although often they were of fairly long standing, showing encapsulation with a thick layer of fibrous tissue. Frequently they were surrounded by a group of satellite tubercles, and sometimes the path by which infection spread from the lung focus to the regional glands was marked out by clusters of these little tubercles along the lines of lymphatic vessels.

The caseous nodules were multiple in only four cases. The frequency of their occurrence in the various lobes of the lungs was as follows:—

Right upper lobe 14 cases.
middle lobe 3
lower lobe 7
Left upper lobe 5
lower lobe 7

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The much greater frequency of these nodules in the right upper lobe than in any other is remarkable. They were not often situated at the apex. Often they were near the pleural surface, but sometimes were deeply placed.

As an aid to the detection of the nodules, which are sometimes very small, a careful examination of the tracheobronchial and root glands is valuable, as their condition often provides a reliable guide to the probable site of the primary lung focus. The greatest degree of caseous enlargement is usually found in the regional glands of the particular lobe which contains the nodule—e.g., when the right superior tracheobronchial gland is the largest of the group, the primary lung focus, if present, will probably be found in the right upper or middle lobe; while if the inferior tracheobronchial gland show the greatest enlargement, the focus should be sought in the lower lobe on the corresponding side. The detection of deep-seated nodules of small size is greatly facilitated by attention to this point.

Lymphatic-spread (proliferative) tuberculosis.—Under this heading are included two types of tuberculous disease which may be combined. In one, tubercles of varying chronicity form in rows and clusters along lymphatic paths in the lungs, showing the “staphyloid” arrangement often described as typical of lymphatic-spread pulmonary tuberculosis. The tubercles have the characteristic structure of “proliferative” foci, with central caseation, giant cells, endothelioid cell and lymphocyte zones, and fibrosis varying with the degree of chronicity. They are sharply circumscribed, and the adjacent alveoli are aerated and free from exudate. In children this type is often apparently a rather acute process, spreading rapidly and widely throughout the lungs.

The other form is often a more chronic, slow-going process, usually localised to one lobe and sometimes to a relatively small area, and producing therein a diffuse proliferation of granulomatous tissue which renders the part solid by reason of what is really an interstitial pneumonia. The chief path of spread appears to be the peribronchial lymphatics, from which the process extends to adjacent alveolar tissue, producing extreme thickening of alveolar walls and obliteration of the lumina. Caseation is seldom extensive and may be absent. A form frequently assumed by this type is the so-called “root-spread” tuberculosis, where, with caseous glands in the
hilum, an area of lung is involved adjacent to the root and spreading out therefrom towards the periphery.

Not infrequently these two forms of disease are combined, one lobe showing the massive proliferative process just described while the rest may be involved in a more recent spread with formation of "staphyloid" tubercles.

Lymphatic-spread tuberculosis, in one or both of these two forms, was present in 28 cases.

Pneumonic (exudative) tuberculosis.—In this type of lesion the process is one of exudation into the alveolar spaces followed by caseation, rather than one of local cell proliferation leading to the formation of typical tubercle follicles. It is the most severe and rapid of all forms of pulmonary tuberculosis and frequently involves the greater part of one or both lungs. It is particularly apt to lead to cavity formation, and the cavities are often multiple and large. This type was present in 31 cases.

Cavity formation.—Cavities were present in the lungs in 36 cases. Of these, 29 had cavities in only one lobe; 5 in two lobes; 2 in more than two lobes. The position of the cavities in the lungs was as follows:

<table>
<thead>
<tr>
<th>Location</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper lobe</td>
<td>19</td>
</tr>
<tr>
<td>&quot; middle lobe</td>
<td>4</td>
</tr>
<tr>
<td>&quot; lower lobe</td>
<td>7</td>
</tr>
<tr>
<td>Left upper lobe</td>
<td>11</td>
</tr>
<tr>
<td>&quot; lower lobe</td>
<td>6</td>
</tr>
</tbody>
</table>

The type of tuberculous disease present in the lungs in which cavities had formed was as follows:

<table>
<thead>
<tr>
<th>Type</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonic (exudative)</td>
<td>21</td>
</tr>
<tr>
<td>Lymphatic (proliferative)</td>
<td>13</td>
</tr>
<tr>
<td>Localised cavity and miliary foci</td>
<td>2</td>
</tr>
</tbody>
</table>

The most severe cases of cavitation were those of the pneumonic type, in which the cavities were often extensive and of a very acute character. The cavities associated with lymphatic-spread tuberculosis were often relatively small and of a more chronic type.

Associated tuberculous lesions outside the thorax.—Table XI. shows the position and frequency of the more important secondary lesions outside the thorax in the 107 primary thoracic cases.
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TABLE XI.
Secondary Lesions outside Thorax (Thoracic Group, 107 Cases).

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical lymphadenitis</td>
<td>35</td>
</tr>
<tr>
<td>Abdominal lymphadenitis</td>
<td>68</td>
</tr>
<tr>
<td>Intestinal ulcers</td>
<td>33</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>15</td>
</tr>
<tr>
<td>Foci in bones</td>
<td>2</td>
</tr>
<tr>
<td>Meningitis</td>
<td>84</td>
</tr>
<tr>
<td>Acute miliary tuberculosis</td>
<td>85</td>
</tr>
<tr>
<td>Subacute visceral foci</td>
<td>17</td>
</tr>
</tbody>
</table>

Cervical lymphadenitis associated with thoracic tuberculosis. The relation between cervical glandular and pulmonary tuberculosis is a matter of considerable interest, and one on which much difference of opinion exists, especially with regard to the frequency with which pulmonary tuberculosis is preceded by infection of the cervical glands. One prevalent view on this question is expressed by Fishberg, who states: "It appears that children suffering from glandular tuberculosis very rarely develop pulmonary tuberculosis in later life; and when a lung lesion does occur, it runs a very mild course and tends to cicatrization." A different view is taken by Melville Dunlop, who expresses the opinion that "the whole natural history of the disease . . . would suggest that persons suffering from pulmonary tuberculosis had previously suffered from some infection of the lymphatic glands, frequently of the cervical glands."

In view of the interest and importance of this question, the state of the cervical glands was carefully investigated in the 107 thoracic cases, with the following results.

Tuberculous lesions, exclusive of acute miliary tubercles, were found in 35 cases (32.7 per cent.). In fully one-half of this number the involvement was relatively slight and enlargement was not such as was likely to be recognised during life, the glands showing merely small discrete foci in their interior. In 14 of the 35 cases the supraclavicular glands alone of the cervical group were affected, and they were in close relation to, and were probably infected from, grossly enlarged caseous glands within the thorax. In most of these 14 cases the enlargement was sufficiently great to be obvious on clinical examination. In the other 21 cases the upper cervical glands were affected alone or in combination with the inferior group; in several, the tonsillar gland on one or both sides alone showed
evidence of infection. In only 2 of these 21 cases was there advanced caseation with considerable enlargement; in the other 19 enlargement was very slight and only small foci were present, which, to judge by appearances, were of much more recent origin than the disease in the thorax. In none of these 35 cases did the disease in the cervical glands appear to be older than that in the lungs or thoracic glands.

From a study of these cases, therefore, no direct evidence could be obtained in support of the view that pulmonary tuberculosis frequently results from a previous infection of the cervical glands. It was shown, however, that secondary involvement of the cervical glands is not uncommon, and that infection may be present without any considerable enlargement.

Study of the distribution of disease in the cervical glands, and of the associated thoracic lesions, served to indicate the probable paths of infection. In the 14 cases in which only the supraclavicular glands were affected, the tracheobronchial and superior mediastinal glands on the same side showed advanced caseous enlargement, and it was obvious that infection had spread from them to the adjacent glands at the root of the neck. Of the 21 cases in which the upper cervical glands were affected, 18 had severe open pulmonary tuberculosis; while in the remaining 3, although obviously open lesions were not demonstrated in the lungs, secondary involvement of the mesenteric glands suggested the probability that tubercle bacilli may have been swallowed. These facts seem to justify the conclusion that secondary infection of the cervical glands occurs not infrequently in cases of pulmonary tuberculosis by way of the tonsils, as a result of infected sputum lodging in that region.

_Abdominal lymphadenitis_ associated with thoracic tuberculosis. Tuberculous lesions, other than acute miliary tubercles, were present in abdominal glands in 68 of the 107 thoracic cases. The glands affected were the mesenteric and those in the upper abdomen, especially the upper part of the para-aortic chain and the celiac group.

Table XII shows the frequency of involvement of these groups, and also the frequency of associated ulcers in the intestine.

The mesenteric glands were affected in 66 of the 68 cases and the upper abdominal glands in 19 cases, in 8 of which the disease in the latter was more advanced than in the mesenteric group.
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TABLE XII.

Abdominal Lymphadenitis (Thoracic Group).

<table>
<thead>
<tr>
<th>Glands</th>
<th>With Ulcers</th>
<th>Without Ulcers</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenteric only</td>
<td>20</td>
<td>29</td>
<td>49</td>
</tr>
<tr>
<td>Upper abdominal only</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Both combined</td>
<td>10</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>38</td>
<td>68</td>
</tr>
</tbody>
</table>

The route by which infection travels to the mesenteric glands in cases of thoracic tuberculosis is doubtless most often by the lumen of the bowel, when open pulmonary lesions are present. Infection via the bowel may be assumed when ulcers are present in the intestine, but, as will be seen from the figures quoted in Table XII., there were ulcers in less than half of the cases in the present series. When there are no ulcers the possibilities are as follows:—

1. Infection from the lungs may travel by the lumen of the bowel and pass to the mesenteric glands without giving rise to intestinal ulceration. This is well known to occur in the case of primary alimentary infections, and there would seem to be no reason why it should not occur also in secondary infections from the thorax.

2. A descending lymphatic infection may occur from the thoracic to the upper abdominal and so to the mesenteric glands. In the present series this seemed probable in 8 cases, and possible in 17.

3. Spread of infection by the blood, long enough before death to allow relatively chronic lesions to form, is a possibility, but its occurrence is not easily proved.

Intestinal ulcers were present in 33 of the 107 thoracic cases. The most extensive ulceration was found associated with pneumatic tuberculosis with cavities in the lungs. In some cases of this kind ulcers were extraordinarily numerous and were present throughout the intestine from the duodeno-jejunal flexure to the anus. In one case an ulcer was present in the second part of the duodenum, below the papilla. In 15 of the 33 cases with ulcers there were cavities in the lungs; in 18 there were no cavities. Five of the cases without excavation in the lungs had pneumatic (exudative) pulmonary...
Agnes R. Macgregor

tuberculosis; 5 had subacute or chronic lymphatic-spread tuberculosis; 6 had isolated caseous nodules in the lungs; and in 2 none but acute miliary tubercles were found in the lungs.

Tuberculous ulcers in the bowel, secondary to pulmonary tuberculosis, are believed to be usually due to the swallowing of infective material from the lungs. Children who do not expectorate must, when cavities are present, swallow large quantities of infected sputum, so that the severe intestinal ulceration so often found in cases of phthisis is only to be expected. But if the lumen of the bowel is to be regarded as the probable route of infection in all cases of secondary intestinal ulceration, it is evident that bacilli from the lungs may be swallowed even when there are no cavities, as in 18 cases in this series no cavities were found. In the cases of pneumatic tuberculosis without cavities (5 cases), swallowing of bacilli was probable, as there was, despite the absence of excavation, a heavy infection of the air passages in the lungs. It must be admitted as possible in the cases of lymphatic-spread tuberculosis also, and in those with isolated caseous nodules (some of which had lymphatic-spread tubercles as well), because in these there might well have been somewhere in the lungs an eroded bronchus which escaped detection or was not macroscopically detectable (11 cases). It is difficult to believe that it could have occurred in the purely miliary cases (2), in both of which the ulcers were extremely early ones and might have resulted from blood-spread miliary foci in the mucous membrane of the bowel.

Peritonitis, in most of the 15 cases in which it was present, was more or less localised to the upper abdomen, being most severe on the diaphragm and about the liver and spleen, and apparently resulting from a spread of infection from the thorax through the lymphatics of the diaphragm.

Full details of the cases of meningitis are given in a later section of this paper.

The Abdominal Group.—The cases in which the principal, and presumably primary, lesions were in the abdomen numbered 80 among the "fatal" group (39.2 per cent.). The mesenteric glands were caseous and to some extent enlarged in all these cases. Table XIII. indicates the nature of the principal abdominal lesions.

Of the 19 cases under the heading "mesenteric glands only," all showed acute miliary tuberculosis and all but two
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meningitis. Of the 17 cases under the heading "mesenteric glands and intestinal ulcers," all showed acute miliary tuberculosis and 14 ended with meningitis. All these were simply examples of generalised blood spread from a localised primary infection.

TABLE XIII.

Principal Abdominal Lesions (Abdominal Group).

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenteric glands only</td>
<td>19</td>
</tr>
<tr>
<td>Mesenteric glands and intestinal ulcers</td>
<td>17</td>
</tr>
<tr>
<td>Tuberculous peritonitis</td>
<td>42</td>
</tr>
<tr>
<td>Genito-urinary tuberculosis</td>
<td>2</td>
</tr>
</tbody>
</table>

Tuberculous peritonitis.—The cases of tuberculous peritonitis formed an important group, 42 in number. In 33 the peritonitis was general, affecting the whole peritoneal cavity; in the other 9 it was more or less limited in extent, but cases in which the only peritoneal involvement took the form of tubercles in the serous coat of the intestine at the site of ulcers, are not included in this group.

Plastic and ascitic types of peritonitis.—The plastic type, with universal adhesions, thickening of the serous membrane with tuberculous granulation tissue, and an absence of free fluid, was present in 36 of the 42 cases. The ascitic type, with much free fluid and serous membrane studded with tubercles but free from adhesions, was found in its pure form in only one case. Five cases were of mixed type.

The abdominal glands, principally the mesenteric, were affected and showed caseation in all the 42 cases. The degree of enlargement varied greatly, being enormous in some and slight in others.

Intestinal ulcers were demonstrated in 19 of the 42 cases, but were probably present in others. Complete examination of the bowel was frequently rendered impracticable by inseparable adhesions.

Cause of death in tuberculous peritonitis. Perforation of the intestine at the site of a tuberculous ulcer caused death in 11 cases; acute intestinal obstruction in 1; tuberculous meningitis in 9; multiple cerebral tuberculomata in 1 case. In the remaining 20 cases death was attributed to exhaustion and cachexia; in 14 of these there was extreme emaciation with severe degenerative changes in the liver and other organs.
Intestinal tuberculosis in the abdominal group.—Intestinal ulcers were demonstrated in 36 of the 80 primary abdominal cases (19 with peritonitis and 17 without peritonitis). In none of these were there any detectable “open” tuberculous lesions in the lungs, and in the few in which any pulmonary tubercles were present their character was such that the possibility of infection of the bowel from that source could be confidently ruled out.

Site of the ulcers.—While the terminal foot of the ileum was undoubtedly the commonest position, no part was immune, and there were cases in which the upper part of the small intestine, or some part of the colon, was the site of a single ulcer in relation to a caseous gland in the mesentery.

The mesenteric glands showed caseous tuberculosis in every case. It was not possible to draw any accurate conclusions on the question of whether the glands or the ulcers usually represented the primary focus of infection.

Perforation of ulcers was found to have occurred in 11 cases, all associated with tuberculous peritonitis. There would seem to be little tendency to perforation in the absence of peritonitis.

Associated tuberculous lesions outside the abdomen.—Table XIV. shows the position and frequency of the more important secondary lesions outside the abdomen in the 80 primary abdominal cases.

<table>
<thead>
<tr>
<th>Table XIV.</th>
<th>Secondary Lesions outside Abdomen (Abdominal Group, 80 Cases).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion</td>
<td>Number of Cases</td>
</tr>
<tr>
<td>Cervical lymphadenitis</td>
<td>8</td>
</tr>
<tr>
<td>Thoracic lymphadenitis</td>
<td>19</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>11</td>
</tr>
<tr>
<td>Pleurisy</td>
<td>11</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1</td>
</tr>
<tr>
<td>Foci in bones</td>
<td>2</td>
</tr>
<tr>
<td>Meningitis</td>
<td>40</td>
</tr>
<tr>
<td>Acute miliary tuberculosis</td>
<td>38</td>
</tr>
<tr>
<td>Subacute visceral foci</td>
<td>12</td>
</tr>
</tbody>
</table>

Cervical lymphadenitis was associated with primary abdominal tuberculosis much less frequently than with primary thoracic. In several instances in which the cervical glands showed advanced caseation it was difficult to decide whether the cervical or the abdominal lesions were the older. As a rule it was not possible to trace any path of spread between
Tuberculosis in Children

the abdomen and the neck, and it seemed probable that the cervical lymphadenitis may have resulted from a separate or coincident infection via the tonsils.

Thoracic lymphadenitis.—In 19 of the 80 cases, tuberculous lesions, other than acute miliary tubercles, were present in glands within the thorax. In 10 the tracheobronchial glands were affected. The lesions were always less advanced than those in the abdominal glands, and usually took the form of caseous foci without great enlargement. In only 2 of the 10 cases were there tuberculous lesions in the lungs (scattered subacute foci, probably blood-spread), so that the possibility of the glands having been infected from the lungs was, in a majority of instances, definitely ruled out. The route of spread would appear to be usually by lymphatics from the upper abdomen.

In the remaining 9 cases, all of which had tuberculous peritonitis, the glands affected were the sternal or internal mammary glands, the diaphragmatic glands which lie along the anterior border of the diaphragm on its upper surface, and the anterior mediastinal glands. In cases of peritonitis these glands were affected much more often than the tracheobronchial group.

Pulmonary lesions, other than acute miliary tubercles, were present in 11 cases and were of a comparatively unimportant character. The usual form which they assumed was that of discrete foci of subacute or chronic type, most often quite small and showing the scattered distribution suggestive of blood-spread as the mode of infection.

Pleurisy, present in 11 cases, was usually a direct extension through the lymphatics of the diaphragm from tuberculous peritonitis.

The Cervical Group.—The cases in which the principal, and apparently primary, lesions were in the cervical glands, or in regions drained by them, numbered only 11 among the “fatal” group (5.4 per cent.). In all these the cervical glands showed advanced caseous enlargement. In 4 the tonsils were proved to be tuberculous, but, as already indicated in the introduction, this figure probably does not represent the true frequency of tonsillar foci. In 3 cases (all babies under 6 months) there was tuberculous disease of the middle ear and mastoid antrum, to which the lymphadenitis was doubtless secondary.
Table XV. shows the distribution and frequency of associated lesions in the cervical group.

TABLE XV.
Associated Lesions (Cervical Group, 11 Cases).

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foci in tonsils</td>
<td>4</td>
</tr>
<tr>
<td>Otitis media and mastoiditis</td>
<td>3</td>
</tr>
<tr>
<td>Foci in lungs</td>
<td>1</td>
</tr>
<tr>
<td>Foci in thyroid gland</td>
<td>1</td>
</tr>
<tr>
<td>Nodule in myocardium</td>
<td>1</td>
</tr>
<tr>
<td>Mesenteric lymphadenitis</td>
<td>5</td>
</tr>
<tr>
<td>Intestinal ulcers</td>
<td>1</td>
</tr>
<tr>
<td>Meningitis</td>
<td>6</td>
</tr>
<tr>
<td>Acute miliary tuberculosis</td>
<td>9</td>
</tr>
</tbody>
</table>

The infrequency of secondary lesions in the thorax in this group is noteworthy. In the one case of pulmonary involvement the lesions in the lungs were merely small scattered subacute foci and the thoracic glands were not affected.

Tuberculous Meningitis.—The cases which died of meningitis formed so large and important a group that separate consideration of them may be of interest. They numbered 136, or 66 per cent. of all "fatal" cases. In Shennan's two series the corresponding figures were 39 per cent. and 46 per cent., so it would seem that there has been a rather startling relative increase of this peculiarly deadly form of tuberculosis.

Meningitis almost always represents merely the terminal phase of a tuberculous infection which has its primary site elsewhere. In 130 cases of the present series the primary focus was found. In 3 of the remaining 6 it was not found because the examination was incomplete. In the other 3 it was not found in spite of complete and careful examination. These three cases were remarkable and very unusual, in that not only was no focus of older standing than the meningitis discovered during a thorough examination of the body, but actually no tuberculous focus of any kind could be found anywhere in the body except in the meninges; and this, in two of the cases, despite exhaustive microscopic examination. In each of these cases the diagnosis of tuberculous meningitis was confirmed by microscopic sections of the meninges.

In the 130 cases in which the primary foci were found, they were situated as follows:—

<table>
<thead>
<tr>
<th>Location</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic</td>
<td>84 cases (63 per cent.)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>40 &quot; (30 &quot; )</td>
</tr>
<tr>
<td>Cervical</td>
<td>6 &quot; (4·5 &quot; )</td>
</tr>
</tbody>
</table>
Tuberculosis in Children

Meningitis occurred in 78 per cent. of the "fatal" thoracic cases; in 50 per cent. of the abdominal; in 54 per cent. of the cervical. There would thus seem to be a greater risk of infection spreading by the blood-stream and involving the meninges, when the principal lesions are in the thorax, than in other cases.

Associated visceral lesions in meningitis cases.—From the clinical stand-point cases of tuberculous meningitis fall into two categories: (1) those in which meningitis is the terminal phase of an illness in which the presence of tuberculosis elsewhere in the body is obvious before the onset of meningitis; (2) those in which there is no illness prior to the onset of meningitis, in which the existence of tuberculosis is not previously suspected, and in which it may be impossible to detect the primary focus during life. In a study based purely upon post-mortem material, no such distinction can be made between the cases; but some useful purpose may be served by considering the nature of the associated lesions in the present series.

Primary thoracic cases.—The tracheobronchial glands showed caseous tuberculosis and some degree of enlargement in all the 84 cases. In only 1 was no lesion found in the lungs. In 12 the lung lesions were merely acute miliary tubercles and no older pulmonary focus was discovered. In 13 cases, therefore, the lungs revealed no lesions of materially longer duration than the meningitis. In 28 cases there were isolated caseous nodules in the lungs, which were regarded as probable primary lesions. They were usually small, and probably seldom gave rise to physical signs by which their presence could have been detected during life. In 10 cases the lungs were more or less extensively involved in disseminated lymphatic-spread tuberculosis, or by the diffuse proliferative tuberculous process already described, by which some considerable part of one or both lungs was infiltrated and rendered solid. Seven cases showed pneumatic (exudative) tuberculosis without cavities. Cavities were present in 26 cases.

Primary abdominal cases.—The mesenteric glands were affected with caseous tuberculosis and some degree of enlargement in all the 40 cases. In 19, lesions antecedent to the meningitis were found only in these glands. In 15 there were also ulcers in the intestine, without peritonitis. A general tuberculous peritonitis was present in 3 cases; peritonitis of
limited extent in 6 others. Two cases had chronic tuberculosis of the genito-urinary system.

**Primary cervical cases.**—The cervical glands showed caseous enlargement in all 6 cases. None showed visceral lesions other than acute miliary tubercles. There were foci in the mesenteric glands in 2 cases.

**Age incidence.**—Tables XVI. and XVII. show the age distribution of the 136 cases of meningitis, divided into groups according to the site of the primary lesions. The percentage of all "fatal" tuberculous cases dying from meningitis is also given. In Table XVI. yearly age-periods are given; in Table XVII. longer periods are used, and the separate figures for the first four half-years are shown.

**TABLE XVI.**

*Age Incidence (Meningitis).*

<table>
<thead>
<tr>
<th></th>
<th>0-1</th>
<th>1-2</th>
<th>2-3</th>
<th>3-4</th>
<th>4-5</th>
<th>5-6</th>
<th>6-7</th>
<th>7-8</th>
<th>8-9</th>
<th>9-10</th>
<th>10-11</th>
<th>11-12</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Thoracic</td>
<td>29</td>
<td>22</td>
<td>8</td>
<td>3</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td>Abdominal</td>
<td>2</td>
<td>14</td>
<td>9</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Meningitis only</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Total meningitis</td>
<td>33</td>
<td>40</td>
<td>18</td>
<td>10</td>
<td>12</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
<td>136</td>
</tr>
<tr>
<td>Total &quot;fatal&quot; tuberculosis</td>
<td>50</td>
<td>66</td>
<td>27</td>
<td>18</td>
<td>13</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>204</td>
</tr>
<tr>
<td>Per cent. meningitis</td>
<td>66</td>
<td>61</td>
<td>67</td>
<td>56</td>
<td>92</td>
<td>71</td>
<td>86</td>
<td>40</td>
<td>100</td>
<td>75</td>
<td>100</td>
<td>100</td>
<td>66</td>
</tr>
</tbody>
</table>

**TABLE XVII.**

*Age Incidence (Meningitis).*

<table>
<thead>
<tr>
<th></th>
<th>0-4</th>
<th>4-1</th>
<th>1-14</th>
<th>14-2</th>
<th>2-6</th>
<th>5-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal</td>
<td>12</td>
<td>17</td>
<td>15</td>
<td>7</td>
<td>51</td>
<td>18</td>
</tr>
<tr>
<td>Meningitis only</td>
<td>0</td>
<td>2</td>
<td>7</td>
<td>7</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Total meningitis</td>
<td>13</td>
<td>20</td>
<td>25</td>
<td>15</td>
<td>73</td>
<td>40</td>
</tr>
<tr>
<td>Total &quot;fatal&quot; tuberculosis</td>
<td>22</td>
<td>28</td>
<td>42</td>
<td>24</td>
<td>116</td>
<td>58</td>
</tr>
<tr>
<td>Per cent. meningitis</td>
<td>59</td>
<td>71</td>
<td>60</td>
<td>63</td>
<td>63</td>
<td>69</td>
</tr>
</tbody>
</table>

Chart V. presents in graphic form some of the facts shown in Table XVI.
Tuberculosis in Children

In the first year the contrast between the thoracic and abdominal groups is remarkable—29 cases of meningitis with primary focus in the thorax and only 2 with primary focus in the abdomen. In the third and fourth years, on the contrary, primary abdominal cases were the more frequent. The largest number of cases of meningitis occurred during the second year of life, and especially during the first half of that year.

The youngest child was 3 months, the eldest 11 years and 3 months.

Tuberculoma of the brain.—Tuberculous masses were found in the brain substance in 21 cases (19 with meningitis). In 12 the tuberculomata were multiple; as many as six separate nodules were found in one case. The size varied from pinhead dimensions to about 1 inch in diameter. Sometimes they were deeply placed in the brain; more often they were near the surface and frequently visible from the exterior. In some instances there was reason to believe that a superficially placed tuberculoma had been the starting-point of meningitis.

The sites of the tuberculomata were as follows:—cerebellum, 17 cases; frontal lobes, 4; insula, 3; parietal lobes, temporal lobes, occipital lobes, each 2; pons, 1.
Secondary Blood-spread Tuberculosis.—Secondary dissemination of infection by the blood-stream is a very common occurrence in tuberculosis of children. Two distinct types of blood-spread infection were recognised in the cases, not infrequently combined.

1. Acute miliary tuberculosis.—This familiar type of tuberculosis, recognised as the "infantile" form of the disease, represents a dissemination of infection by the blood-stream shortly before death, and is characterised by the appearance of very early "grey" tubercles in the various organs. It was present in 131 of the 201 "fatal" cases which were fully examined (65 per cent.), but its extent and severity greatly varied. In 38 of the 131 cases the miliary foci were extremely few and were sometimes confined to one or two organs. In the other 93 the miliary foci were moderately or extremely numerous and widely distributed throughout the body. The organs most constantly, and usually most heavily, infected were lungs, spleen and liver. The kidneys were as a rule comparatively slightly affected, for although it was usual to find some foci in them when miliary tubercles were at all numerous elsewhere, there were often very few and sometimes none. Meningitis was present in 107 of the 131 cases with acute miliary tuberculosis.

2. Subacute visceral foci.—These lesions are scattered foci of relatively chronic type, usually showing caseation and sometimes fibrosis, distributed in the organs after the manner of a blood-borne infection but obviously of much longer standing than acute miliary tubercles. They may occur in any situation and are common in liver (where they are often bile-stained), spleen and lungs. It is quite usual to find foci of this kind associated with acute miliary tuberculosis. In 28 cases (11 with meningitis) they were found without miliary tubercles in the organs. They can be interpreted only as representing an invasion of the blood-stream by the infection at some considerable time before death; and often the variation in the size and apparent age of these foci in any one case indicates periodical invasions during the course of the disease. This type of blood-spread infection, limited in distribution and giving rise to relatively chronic foci, may assume major importance in a case of tuberculosis if the secondary lesions so produced become progressive in a situation where they may do grave mischief. Most tuberculomata in the brain, most bone lesions and
Tuberculosis in Children

many examples of chronic renal tuberculosis probably originate in this way.

Summary and Conclusions.

An analysis of 250 post-mortem cases of tuberculosis in children under 12 years of age is presented.

The cases are divided into two groups: those in which tuberculosis was the cause of death (204) and those in which it was "incidental" and not the cause of death (45).

The following general conclusions are presented:—

(1) Latent or quiescent tuberculous lesions are relatively rare in childhood, very rare under 2 years of age, almost non-existent under 1 year.
(2) Calcified foci are exceedingly rare under the age of 3 years.
(3) Tuberculous infection acquired in infancy is usually rapidly progressive and fatal.
(4) The mesenteric glands are the commonest site for latent foci.
(5) Fatal tuberculosis is much more prevalent during the first two years of life than during later childhood.
(6) A great majority of tuberculous deaths under one year are due to primary thoracic infections, usually from a human source.
(7) Primary abdominal cases are as numerous as thoracic in the second year, and exceed them in the third and fourth years.
(8) Deaths from primary thoracic tuberculosis show seasonal variation, with an increase in spring and early summer. Abdominal tuberculosis is not subject to this seasonal variation.
(9) Lymph glands show important lesions in almost all cases.
(10) Most cases with caseous thoracic glands have associated pulmonary lesions, which probably represent the primary infection.
(11) Infection of the lungs or thoracic glands from the cervical glands is rare.
(12) Infection of the cervical glands (via the tonsils probably) by sputum from open lung lesions is common.
(13) Primary thoracic tuberculosis becomes generalised and ends with meningitis in a larger proportion of cases than does abdominal or cervical tuberculosis.
In primary thoracic tuberculosis, intestinal ulceration is often present without demonstrable open lesions in the lungs.

Fatal tuberculous peritonitis is much more often of "plastic" than of "ascitic" type.

Meningitis is comparatively rare in cases of generalised tuberculous peritonitis.

Infection spreading to the thorax from tuberculous peritonitis frequently involves the internal mammary and anterior mediastinal glands.

Primary cervical lymphadenitis comparatively seldom gives rise to generalised and fatal infection or to progressive lesions within the thorax.

Sixty-six per cent. of all the "fatal" cases in this series ended with meningitis. There has been a relative increase in meningitis during the past twenty-five years.

Meningitis may occur as the only detectable tuberculous lesion in the body, but this is very rare.

Dissemination of infection by the blood is very common in children, and tends to be widespread and fatal, but may be of limited extent and may occur periodically during the course of any case.

AN EPIDEMIC OF ACUTE ENCEPHALITIS IN YOUNG CHILDREN.
AN EPIDEMIC OF ACUTE ENCEPHALITIS IN YOUNG CHILDREN

BY

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AND

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This paper is concerned with a small outbreak of illness of an unusual nature occurring in the Children's Unit of the Western General Hospital, Edinburgh. In addition to the clinical interest of the cases, there are features of considerable pathological and epidemiological importance connected with the outbreak.

Clinical Records.

Case 1. I.M.S., female, aged 1 year 7 months, was admitted to the Western General Hospital in March, 1933, at the age of 1 year 3 months. At this time she was noted as being slightly undersized but well nourished and the liver showed moderate enlargement. Prior to admission she had been treated elsewhere for gonococcal vaginitis: during the three succeeding months her health was good and progress uninterrupted, but a positive Wassermann reaction, present on admission, persisted. On the evening of July 22, 1933, the patient was noticed to be less active than usual and generally 'out of sorts': her condition remained unchanged throughout the rest of the day, and on the 23rd she was still quieter and less responsive to all forms of attention and refused food. By the afternoon of the 24th she was definitely dull and apathetic. She lay awake for long periods in her cot but without changing her position or showing response to external stimuli. The expression was heavy and drowsy, the face flushed, the conjunctivae suffused and the eyes dark-ringed and sunken. The tongue was furred and the fauces were injected. Temperature and pulse rate were normal; there was no rash, and examination of the child resulted in only negative findings. At this stage the patient was isolated with three other children (C.B., M.M., E.M.W.) from the same ward who were showing similar but less marked signs in keeping with the prodromal stage of some common infective disease.

At 10.30 p.m. of the same day (July 24) the child's condition became suddenly worse and she looked extremely ill: left undisturbed she lay motionless, staring in front of her without interest, but when examined was excessively fretful. No evidence of organic nervous disease was found. Temperature was still normal. About this time vomiting took place and recurred several times during the night. The motions were loose, but neither foetid nor frequent. There was never any improvement in the child's condition, and at 1.30 a.m. on the morning of July 25
the temperature rose to 103.2° F. This was accompanied by an acceleration of pulse which became increasingly rapid until it was imperceptible. Repeated cerebral cries were noted before the child became comatose and died at 5.30 a.m., sixty hours from the time of onset of the illness.

POST-MORTEM EXAMINATION (12 hours after death).

BRAIN. There was hyperaemia of the meninges at the base, but not elsewhere; no thrombosis of meningeal vessels, nor haemorrhage. The brain substance, both grey and white matter, was markedly congested, especially in the pons. No areas of softening were observed.

FAUCIAL TONSILS were enlarged but not obviously inflamed.

THE LUNGS were congested and there was atelectasis of the left upper lobe.

THE LIVER was slightly enlarged, firm, pale, tough, and showed fine fibrosis.

THE KIDNEYS were healthy.

MICROSCOPIC EXAMINATION. Sections were examined from cerebral cortex, optic thalamus, mid-brain, pons and medulla oblongata. All the parts examined showed considerable hyperaemia, which was accentuated in certain areas and was generally more severe in the grey matter than in the white. This was particularly noticeable in mid-brain, pons and medulla where the congestion was greatest in the grey matter beneath the floor of the fourth ventricle and around the Sylvian aqueduct. Haemorrhage into the adventitial space of blood vessels was a noteworthy feature, especially in the optic thalamus (Fig. 1). The extravasated blood was, as a rule, strictly confined within the peri-vascular space, but occasionally it had penetrated to a short distance into the surrounding brain substance. There was oedema of the brain, shown by dilatation of the perivascular spaces, and an increase in the size of the spaces surrounding nerve cells. Perivascular infiltrations of small round cells ("cuffing") were not found in typical form, but evidence of commencing infiltration was forthcoming. A venule in the optic thalamus had a ring of small lymphocyte-like cells, one layer thick, lying in the dilated perivascular space, closely applied to the vessel wall (Fig. 2). A few other vessels showed three or four similar cells in the perivascular space.

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**Fig. 1.** Blood vessel in optic thalamus showing haemorrhage into perivascular space. (Case 1.) × 150. H. & E.

**Fig. 2.** Venule in optic thalamus, showing early perivascular infiltration. Small mononuclear cells in perivascular space, arranged in a ring around the vessel. (Case 1.) × 300. H. & E.
Changes indicating injury to nerve cells were conspicuous but not extreme. They were best observed in the large ganglion cells in the floor of the fourth ventricle and central grey matter of the mid-brain; also in the larger nerve cells of the thalamus. The changes included swelling of the cell body, the outline becoming convex, chromatolysis with partial or almost complete disappearance of the Nissl substance, an eccentric position of the nucleus, which sometimes bulged beyond the edge of the cell body, and, in a few of the more gravely injured cells, karyolysis, the nucleus staining so faintly as to be almost indistinguishable. These changes were very variable in degree in different cells and those affected were irregularly distributed. In a single group of ganglion cells some might show severe changes while others appeared quite healthy. Occasional nerve cells had three or four satellite cells, but true neuronophagia was not observed. In the pons and medulla many of the large ganglion cells close to the floor of the fourth ventricle contained small strongly eosinophilic granules in their cytoplasm, either aggregated in a clump or dispersed throughout the cell body (Fig. 3). The cells which contained these granules often exhibited in relatively severe degree the various degenerative changes described above. Such granules were not found in any other part. Intranuclear inclusion bodies were not found.

Sections of lung, spleen, kidney and lymph gland showed nothing of pathological significance. Toxic changes were practically absent. In the liver there was an increase of cellular fibrous tissue, infiltrated by lymphocytes, in the portal tracts, and in a few places this tissue had penetrated the lobules. There was also some fatty change in the liver cells. These changes were attributed to congenital syphilis.

Case 2.—C.B., male, aged 1 year and 7 months. He had no illness during infancy other than measles at eight months and occasional attacks of bronchial catarrh. On April 19, 1933, at the age of 1 year and 4 months, he was admitted to the Western General Hospital as a healthy child. He was discharged to the Edinburgh City Hospital with chickenpox on June 4, being readmitted to the Western General Hospital on June 17 in a robust, healthy condition. On July 24, 1933, he was noted to be less active than usual and to have no desire for food.
By evening his face was flushed, his eyes injected and his expression heavy and dull. The tonsils were enlarged and red, the tonsillar glands moderately swollen. Temperature was normal; there was no rash, but, as a precaution, the child was isolated. Temperature was still normal on July 25. The child's condition was one of great agitation which tended to exhaust him so that he was alternately restless and very listless. On being approached he showed intense irritability, and attempts to examine him were resisted with vicious frenzy; he scratched and tore anything within reach, and flung himself about the cot. Pupils were dilated but equal, there was some diminution in arm tendon reflexes, superficial abdominal reflexes were absent, the left knee jerk was increased, and a right extensor toe response was obtained. A true Kernig's sign was not found, but there was definite objection to attempts to elicit it on the left side. Tache pronounced Curious features were the way in which the child screwed up his eyes whenever a hand was brought near his forehead, and a tendency to assume a position of extreme opisthotonus in his endeavour to resist examination. Examination left him extremely exhausted. No localised muscle tenderness was determined. The tongue was moist but heavily coated. Examination of the chest and abdomen was entirely negative. The tuberculin test was positive. The white blood count was 18,000 per c.mm., consisting of polymorphs 57 per cent. and mononuclears 43 per cent. A specimen of stool examined contained no pathogenic organisms. By midnight on the 25th the child looked extremely ill; his expression was dazed, his eyes sunken and ringed; he was definitely drowsy although still able to resist examination violently. The pulse was now very rapid and soft. Lumbar puncture was carried out, and 60 c.c. of clear fluid obtained under pressure. This appeared to result in a slight improvement, but any benefit was only of a temporary nature. By 9 a.m. on July 26 drowsiness had been replaced by a state of intense irritability and restlessness. The patient flung himself about in his cot until, completely exhausted, he lay curled up, his head buried in the pillow. He uttered frequent piercing cries and was obviously in great pain: the lips were ashen, the conjunctivae markedly injected, the right more so than the left, and the pulse continued to become increasingly rapid. Lumbar puncture was again carried out and 10 c.c. of clear fluid obtained under pressure.

At 10 a.m. the child was again examined. Both pupils were contracted, the left more than the right. The eyes were turned upwards and towards the left and blinking was abolished on the left side. A dubious Kernig's sign was elicited on both sides but there was no neck rigidity. The patient continued to utter periodic cries of pain, but these became weaker: he lay continually on his right side, passed into a semi-comatose condition, and died at 12:20 p.m., forty-eight hours from the time of onset of the illness.

POST-MORTEM EXAMINATION (24 hours after death).

Brain. There was intense hyperaemia of the meninges over the whole surface; no thrombosis of blood vessels. The brain substance showed intense congestion of both grey and white matter; the grey matter had a pinkish colour and congested vessels were prominent in the white matter. No haemorrhages or areas of softening were visible.

Spinal cord showed congestion of the meninges.

Facial tonsils were enlarged.

Tracheo-bronchial lymph glands: one contained a few small tuberculous foci.

Liver and kidneys showed very slight toxic changes. No other organ presented anything abnormal.

Microscopic examination. Sections were examined from cerebral cortex, optic thalamus, mid-brain, pons, medulla oblongata and spinal cord. Intense congestion of the brain substance was present in all the parts examined. The adventitial spaces of blood vessels were distended and the pericellular spaces increased in size, indicating oedema of the brain. Haemorrhages into perivascular spaces were numerous in the optic thalamus and present also in pons, medulla and mid-brain; they were not found in cerebral cortex or spinal cord. Typical 'cuffing' of blood vessels with infiltrations of small round cells could not be demonstrated,
but in the dilated perivascular spaces of a few blood vessels in the mid-brain small collections of mononuclear cells were found (Fig. 4). The best examples were in the central grey matter near the aqueduct, and in the region of the substantia nigra. In other parts of the brain and in the spinal cord no such appearance was discovered.

Ganglion cells presented variable appearances. Many showed no alteration. Others were profoundly altered, being swollen, showing chromatolysis of varying degree, and having the nucleus displaced to one side of the cell. Sections stained to demonstrate Nissl bodies (cresyl violet) showed in many cells the condition of central chromatolysis, the Nissl substance having disappeared from the central part of the cell body and being collected in a dense mass or ring at the periphery (Fig. 5). The nucleus of such cells might be healthy, but was usually eccentric in position and sometimes showed karyolysis. These changes in nerve cells were more pronounced in the central grey matter and substantia nigra of the mid-brain than elsewhere, but were found in certain cells in the thalamus, pons and medulla. They were not observed in the cerebral cortex nor in the cord. No inclusion bodies, either intranuclear or extranuclear were found.

Sections stained by Morgan’s method for myelin showed no areas of demyelination.

Sections of liver, spleen and kidney showed no significant changes. Toxic degeneration was very little in evidence. Sections of lung showed nothing except some general hyperaemia.

Case 3.—M.M., female, aged 1 year and 11 months.

Born in the Maternity Ward of the Western General Hospital in August, 1931, she remained in the Hospital until she contracted chickenpox in March, 1933, at the age of 1 year and 7 months. She was readmitted in good health from the City Fever Hospital on May 13, following the attack of chickenpox.

On the morning of July 23, 1933, she was noticed to be less active than usual and without desire for food. Her condition was much the same the next day but her face was flushed and her expression heavy. Temperature was normal, and nothing was found on examination beyond moderate enlargement of the
tonsils and faucial injection. As a precaution the child was removed to the isolation ward.

Complete examination was again carried out on the afternoon of July 25. An extensor plantar response was obtained on the left side; otherwise the superficial and tendon reflexes were normal. The ear drums were healthy in appearance; the urine contained nothing abnormal. The one noticeable change from the previous day was increasing restlessness and irritability. By the afternoon of July 26 this irritability was extreme and made examination difficult. Kernig's sign was not present but the patient resented extension of the legs although there was no apparent muscle tenderness. Superficial abdominal reflexes and the biceps tendon jerks were absent. Sweating of the head was a feature and there was a pronounced tâche. A specimen of stools contained no pathogenic organisms. The tuberculin skin test was negative. Towards evening the restlessness was further increased, and lumbar puncture was carried out, 10 c.c. of clear fluid being obtained under slight pressure with resultant relief.

The next day, July 27, the patient's objection to examination was greater. She flung her head back, rigidly arched her spine, uttered piercing cries and tore at anything within her reach. She appeared in terror of having her head touched and screwed her eyes up in a characteristic way when this was attempted. The pupils were widely dilated and there were dark rings around the eyes. Abdominal and tendon reflexes remained unchanged from the previous day. Examination left the patient extremely exhausted. She occasionally sat up and took an interest in her surroundings but soon relapsed into her former drowsy state. A white blood count gave 12,000 cells per c.mm. of which 60 per cent. were polymorphonuclear and 40 per cent. mononuclear.

The next morning, July 28, the child's general condition showed slight improvement and at times she was seen to smile, but still showed the same maniacal frenzy when any attempt was made to examine her. When undisturbed she was still abnormally quiet and unresponsive. Tendon reflexes were unchanged from the previous day. For the first time there was limitation of neck flexion. Lumbar puncture was carried out and 30 c.c. of clear cerebro-spinal fluid obtained under pressure, after which the restlessness was greatly diminished. A few hours later the child was transferred to the City Hospital. The abdominal reflexes reappeared two days after transfer and the pulse rate remained accelerated for almost two weeks. Otherwise there was nothing to note, and recovery was apparently complete. At the present time her condition is excellent and she shows no residual manifestations of her illness.

Case 4.—E.M.W., female, aged 2 years. The child was first admitted to the Western General Hospital in July, 1932, at the age of one year after a severe attack of measles. No other details of the previous history were available. At the time of admission her condition was poor: this improved greatly during the twelve months she was in hospital, despite the fact that she was subject to recurrent attacks of respiratory and alimentary catarrh. The tuberculin reaction was positive.

On the morning of July 24, 1933, she was noticed to be off colour, apathetic and refusing food. By the afternoon her expression had become heavy, the face flushed and the eyes suffused. Usually of a distinctly friendly nature, she was now very peevish. Temperature was normal. There was an occasional short dry cough. Tonsillar glands were palpable; the tonsils were slightly enlarged and injected. Otherwise the findings on examination were negative. Her condition remained unchanged throughout the next day, but by the afternoon of July 26 her lassitude had greatly increased. During examination irritability was extreme; she flung her head back and assumed the position of marked opisthotonus and uttered repeated shrill cries. Absence of the abdominal reflexes and diminution of the biceps and supinator reflexes were noted and there was a pronounced tâche cerebrale. There was no nuchal rigidity, Kernig's sign was absent, and there was no ocular paresis. The tongue was furred, and the motions were green and increased in frequency but contained no pathogenic organisms. The urine was
normal. A white blood count was 15,200 per c.mm. and a differential count gave polymorphonuclears 65 per cent. and mononuclears 35 per cent.

On the afternoon of the next day, July 27, Babinski's sign was obtained on the right side, while the response on the other side was dubiously extensor. Nuchal rigidity and Kernig's sign were absent but marked voluntary resistance was encountered in testing for these. The abdominal reflexes were still absent, the pupils were now widely dilated, and the expression one of fear. The child was terrified when a hand was brought near her head. Irritability was still extreme and examination left her greatly exhausted. There was no evidence of localised muscle tenderness. The pulse was rapid.

During the night the child became more restless and walked round her cot until, tired out, she lay down. Early in the morning (July 28) she vomited. Examined again at 10 a.m. she resisted with a maniacal frenzy until exhausted. The abdominal reflexes were absent, Babinski's sign was obtained on both sides, and Kernig's sign was found on the right side but not on the left. Vomiting occurred twice during the course of the morning. Lumbar puncture was performed and 30 c.c. of clear fluid obtained under pressure, giving immediate great relief. Three hours later the patient was transferred to the City Hospital. There her progress was uninterrupted; doubtful neck rigidity persisted for a further forty-eight hours and the pulse, which had become rapid while she was still in the Western General Hospital, did not return to normal until ten days after transfer. The abdominal reflexes reappeared two days after admission to the City Hospital. At the present time the child is in excellent health and shows no evidence of any sequelae.

**SUMMARY OF PATHOLOGICAL INVESTIGATIONS**

<table>
<thead>
<tr>
<th>Case number</th>
<th>Initials</th>
<th>Date</th>
<th>C.S.F. Mgrms. per 100 c.c.</th>
<th>Blood W.B.C. Polymorphonuclears Mononuclears W.R. T.R.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I.M.S.</td>
<td>January 25/7/33</td>
<td>... Blood stained</td>
<td>... 18,000; 57% 43%</td>
</tr>
<tr>
<td>2</td>
<td>C.B.</td>
<td>January 25/7/33</td>
<td>20 80 737</td>
<td>... 12,000; 60 40</td>
</tr>
<tr>
<td>3</td>
<td>M.M.</td>
<td>13/7/33</td>
<td>60 25 735</td>
<td>... 12,000; 60 40</td>
</tr>
<tr>
<td>4</td>
<td>E.M.W.</td>
<td>August 26/7/33</td>
<td>22 99 528</td>
<td>... 15,200; 65 35</td>
</tr>
</tbody>
</table>

**C.S.F.** All cases: Cells all lymphocytes, no increase.

**Blood** Cultures sterile: colloidal gold reaction, no precipitate.

(Specimen from Case 1 taken at autopsy).

**Faeces** All cases: no pathogenic organisms isolated.

**Urine** All cases: no microscopical abnormalities.
Clinical summary.

All four children had been in hospital for a prolonged period; two for over three months and two for twelve months. They were all admitted as healthy individuals on the recommendation of the Public Assistance Officer. Three (I.M.S., C.B., and M.M.) were in the same ward, the first two occupying adjacent cots. The fourth child was in a different ward, but was attended by the nurses in charge of the other three cases. Between July 7 and July 11, when the heat was exceptionally great, the four children, along with other inmates of their wards, spent the greater part of each day in the garden adjoining the hospital. Among adult female patients also in the garden were two cases of post-encephalitic Parkinsonism who found a special delight in the companionship of the children. The children I.S. and C.B. were especial favourites and were known to have played for long periods on the knees of one or other of these particular patients. The third child (E.M.W.) was known to have been in similar contact on occasions with the post-encephalitic subjects, but any history of such contact in connection with the fourth child (M.M.) was vague.

The four children fell ill within a period of 36 to 48 hours. The clinical picture presented as the disease ran its course was very similar in all four cases. After an insidious onset extending over a period of some thirty-six hours, characterised by catarrh, lethargy and heaviness of expression, the children became distinctly drowsy but at the same time resisted examination with an almost maniacal frenzy. Nothing abnormal was found on examination of the nervous system five hours prior to death in the first fatal case (I.S.), but in each of the remaining cases Babinski's sign was obtained and the superficial abdominal reflexes were absent. Ready exhaustion, a fear of having the head touched and a pronounced tâche were other constant features. The two surviving patients were afebrile throughout, and in the two fatal cases the temperature only rose during the terminal phase, and in one instance (C.B.) this was preceded by an increase in the respiratory rate. In both fatal cases cerebral crises were noted. Vomiting occurred in two patients. Ophthalmoplegia was seen in only one (C.B.), and then only an hour before death. Kernig's sign and neck rigidity, when they occurred, were rather indefinite and showed a tendency to vary from hour to hour. There were no convulsions and no myoclonic movements. The condition of the two children who died became critical with great suddenness; in those who recovered, the improvement following lumbar puncture was dramatic. The three blood examinations carried out all showed a slight relative polymorphonuclear leucocytosis. The cerebro-spinal fluids taken during the stage of active disease all showed a slight increase in the sugar content and a reduction in the chlorides, unaccompanied by any appreciable increase in cell content. Protein in one surviving case was very slightly increased.
Pathological summary.

The outstanding pathological findings in both cases were remarkably similar. Both showed intense congestion of meninges and brain substance, especially the grey matter, oedema of the brain, perivascular haemorrhages, and degenerative changes in nerve cells. Typical cuffing of blood vessels could not be demonstrated, but evidence of the earliest stage of perivascular infiltration was found in the form of collections of a few small mononuclear cells in the adventitial spaces of certain blood vessels. Perivascular demyelination had not occurred.

Caution is necessary in accepting the changes in nerve cells as a genuine effect of disease. Such alterations are admittedly capable of being produced by post-mortem autolysis or by imperfect fixation. The very unequal incidence of the changes in different cells, however, argues in favour of true ante-mortem degeneration. It was remarkable how, in a single small group, certain cells might be profoundly affected and others, close by, present a perfectly healthy appearance. Such a selective effect, while recognized as a common occurrence in true degeneration, is very unlikely in the case of any factor operating after death.

The minute eosinophilic granules observed in the cytoplasm of certain nerve cells in the floor of the fourth ventricle in case 1 were probably merely products of cell degeneration. They do not appear to be of the same nature as the extranuclear granules described by da Fano and others.

The distribution of the lesions is important. This was similar in the two cases. Congestion and oedema were general throughout the brain, but the graver lesions were found only at the lower levels. Perivascular haemorrhages and nerve cell changes were best seen in the thalamus, mid-brain, pons and medulla; they were not found in the cerebral cortex. The early infiltrations were discovered only in the region of the substantia nigra and central grey matter of the mid-brain in one case, and in the thalamus in the other. The spinal cord, in the one case in which it was examined, showed only a degree of congestion.

Attempts to obtain experimental infection in animals by inoculation of cerebro-spinal fluids from cases 1 and 2 were made by Dr. J. M. Alston, who reported as follows:—

Case 1. Cerebro-spinal fluid was injected intra-cerebrally into two rabbits, two guinea-pigs and six mice. No result was obtained except that one rabbit died seven days after injection. Intra-cerebral injection of two more rabbits from the brain of this animal produced no results.

Case 2. Intra-cerebral injection of cerebro-spinal fluid into two rabbits, two guinea-pigs and four mice was followed by no result except that one rabbit showed nervous symptoms three days after injection and was killed. Two rabbits injected intra-cerebrally with filtrate of this animal’s brain showed no ill effects.

Discussion.

The epidemic nature of the condition is indicated by the almost simultaneous appearance of the initial symptoms, and the occurrence of
all four cases in a single nursing unit. A remarkable feature of the epidemic was the rapidly fatal course of two cases.

**Differential diagnosis.**—On both clinical and pathological grounds the cases may be regarded as a type of acute encephalitis. Clinically this was suggested by the alternation of marked drowsiness and intense restlessness, amounting at times to frenzy; these occurring in the absence of evidence of meningeal irritation such as nuchal rigidity and Kernig's sign. Ophthalmoplegia occurred in one case; vomiting and cerebral cry were noted in two. Further evidence of organic changes in the central nervous system was afforded by extensor Babinski responses and loss of abdominal reflexes. Changes in other reflexes were variable. The sudden unexpected death in the first case, at a time when other children were showing lethargy and irritability, suggested that the condition might be encephalitis of an epidemic nature. The results of the autopsies on the two fatal cases supported this diagnosis; no significant pathological changes were found anywhere except in the brain, and meningitis was not present.

The absence of a pathological picture completely characteristic of any particular type of encephalitis leaves the question of more exact diagnosis open to discussion, and various possibilities have to be considered.

1. **Food poisoning and alimentary infections.**—The fact that among the fifty-one children in the wards from which the cases were drawn no others were similarly affected although all received food from the same source, virtually rules out the possibility of botulism or other form of food poisoning. In all four cases examination of the stools for pathogenic organisms proved negative.

2. **Heat and sunstroke.**—The epidemic occurred at a time of exceptionally hot weather when all the children in the wards spent the greater part of each day out of doors. They were provided with sun-bonnets and kept in the shade. Neither clinical nor pathological facts support a diagnosis of heat or sunstroke.

3. **Acute toxic encephalitis** has been described occurring as an accompaniment of severe infections. The possibility of there being any hidden focus of infection in our cases was ruled out by the afebrile course, the results of blood examination, and the failure to discover any source of toxaemia either clinically, or at autopsy on the two fatal cases. Further, the histological changes did not correspond to those described in acute toxic encephalitis by various observers.

Brain, Hunter and Turnbull described six cases of acute meningo-encephalo-myelitis which they attributed to ‘some unknown toxaemia,’ without evidence of infection. Clinically, these cases resembled ours in certain particulars, but differed notably in the constancy of evidence
of meningeal involvement and in the presence of fever in five of the six cases. On pathological examination the one fatal case showed congestion, oedema, perivascular haemorrhages and nerve cell changes similar to those found in our cases, though more widely distributed; it differed in the complete absence of any evidence of perivascular infiltration. A further point of difference was the presence of very advanced degenerative changes in the liver and kidneys. The one abortive case in this series (case 3) bears a close resemblance to our two recovered cases, particularly in the rapid improvement following lumbar puncture. This case differed from the others in several important particulars, and it seems to us by no means certain that it was of the same nature.

4. Varicella encephalitis.—Two of the children had had an attack of varicella earlier in the year, and had been readmitted from the City Fever Hospital as non-infective, the one ten weeks and the other five weeks before the onset of the illness. The usual interval between the onset of varicella and the appearance of complications involving the nervous system is about nine or ten days; Winnicott and Gibbs, reviewing the literature, state that the extremes are four to thirteen days. It is unlikely, therefore, that varicella had any connection with the condition in these two children, and this is further borne out by the fact that, according to Winnicott and Gibbs, no fatal cases of varicella encephalitis have been reported.

5. Vaccinia.—None of the four patients, none of the other children in the wards, and none of their attendants had been vaccinated during the year.

6. Acute disseminated encephalo-myelitis.—Boyd describes under this title a form of encephalitis quite distinct from the lethargic encephalitis of von Economo. He includes in this category post-vaccinial and post-infectious encephalitis and also a spontaneous type, which forms much the largest group. The clinical picture of this condition, as described by Boyd, shows little resemblance to that observed in our cases. According to him, the essential histological lesion is the presence of areas of perivascular demyelination scattered widely throughout the brain and spinal cord. Nothing at all resembling this was found in our cases.

7. Other epidemic forms of encephalitis.—

A. 'Type B-encephalitis' and 'X-disease.'—Type B-encephalitis has occurred in epidemic form in Japan on many occasions during the last sixty years. X-disease was met with in Australia in 1918 and 1918. Pathologically these conditions show many features in common with the encephalitis lethargica of von Economo, but at the present time authorities are still inclined to regard them as separate diseases. Clinically they closely resemble each other. They appear to be virus infections of the central nervous system tending to occur during
exceptionally hot weather, but otherwise the clinical picture they present does not resemble that of our cases.

B. THE EPIDEMIC IN ST. LOUIS, U.S.A. (1933).—This has been regarded as a type of encephalitis distinct from the lethargic form. The distinction is based upon both clinical and pathological grounds. Paresis when it occurred was only transient, ocular palsies were notably absent, and, so far as can as yet be ascertained, there were no sequelae. The pathological lesions occurred at higher levels, without special localisation in the mid-brain or basal ganglia, and cellular infiltrations occurred with no relation to vessels. Although our cases resembled this type in the initial catarrhal phenomena and in certain features during the later stages, they differed markedly in the absence of fever, the occurrence of ophthalmoplegia and the distinct localisation of the graver pathological changes, including early infiltration, in the bulbar region and basal ganglia.

C. ACUTE SEROUS ENCEPHALITIS.—Under this name Brown and Symmers described ten cases which resembled ours in both clinical and pathological features. Their cases all occurred in children during the summer, ran a rapidly fatal course, and showed catarrhal phenomena and signs of general nervous involvement. They differed from our cases in their febrile nature, in the occurrence of convulsions and in the presence of other localising signs. The pathological data set forth in their paper are scanty, but the changes described, including engorgement of blood vessels of the brain, oedema, perivascular haemorrhages and focal collections of cells, resemble those found in our cases. There is no reference to the exact distribution of these lesions. It is doubtful whether the cases described by Brown and Symmers represent, as they claim, a separate entity.

D. POLIO-ENCEPHALITIS.—In the literature there is general agreement that differentiation between the encephalitic form of polio-myelitis and epidemic encephalitis is uncertain. It has even been suggested that cases hitherto regarded as of the former type should rather be classed as epidemic encephalitis. This view is supported by the fact that the virus of polio-myelitis has not been isolated from a case in which the clinical diagnosis of polio-encephalitis has been made.

The fact that polio-myelitis was not prevalent in epidemic form in the district at the time is in itself an argument against regarding our cases as examples of that disease. The absence of fever, the nature of the changes in the reflexes and the predominance of females among the patients are all facts contrary to those usually associated with polio-myelitis. Another important argument is the bizarre character of the clinical picture and the lack of evidence pointing to cord lesions.

Pathologically there appears to be no criterion by which certain distinction can be made in all cases between epidemic encephalitis and the bulbar form of polio-myelitis. In the Report of the International Committee for the Study of Infantile Paralysis the statement is made
that the histological lesions (in poliomyelitis) cannot be differentiated with certainty from those of epidemic encephalitis. More recently Freeman also has emphasised the similarity of the lesions in the two conditions. Points against the diagnosis of polio-encephalitis in our cases are the relatively slight damage to the nerve cells, and the absence of lesions in the spinal cord in the one case in which it was examined, and the completely inconclusive results of the attempts to transmit the infection to animals. McIntosh considers that these three points are sufficient to distinguish encephalitis lethargica from cerebral polio-myelitis. Kinnear Wilson emphasizes the prominence of haemorrhage in encephalitis as a distinguishing feature in differential diagnosis.

E. EPIDEMIC LETHARGIC ENCEPHALITIS.—As our cases resembled this condition in many features it is necessary to consider these in detail.

a. Epidemic form. It is recognized that it may occur in the form of limited outbreaks in institutions. McNalty and Hall have collected a number of reports of such outbreaks in this country, and Duzar and Balo recorded an institutional epidemic in Budapest.

b. Season. Although epidemic encephalitis has its maximum incidence in the colder months, outbreaks have occurred during hot weather. Hall draws attention to the fact that most of the few outbreaks of encephalitis lethargica of a definitely contagious character have occurred at periods of the year when the disease was not present in epidemic form.

c. Age. Although encephalitis lethargica is generally regarded as a disease which affects adults more often than children, its occurrence in newborn infants, of which several well authenticated cases have been reported, proves that even the youngest are not immune. Furthermore McNalty reported a fatal case occurring in a child aged one year nine months; Netter described a case occurring in an infant of two months; and the eleven cases in the Budapest epidemic were all in infants a few months old.

d. Predisposition. Syllaba and Henner emphasize the importance of predisposition towards infection. Such predisposition was met with in children of unhealthy parentage and they particularly mention that many patients were children of syphilitic parents. Our four children were all poor-law patients; one was a congenital syphilitic and two gave positive reactions to the tuberculin skin test.

e. Result. Our two fatal cases correspond exactly in the matter of age and duration with the case described by McNalty in a female child aged one year and nine months who died after two days' illness. The same authority has recorded improvement following lumbar puncture similar to that which occurred in our two recovered cases.

f. Clinical features. Certain features of the clinical picture already described have been stressed by other observers. Among these are the following:
Duration of the prodromal period. McNalty¹⁹ states that the prodromal period is commonly one to seven days and that, particularly in children, it tends to be brief. In our case signs of active disease were present within 24 to 36 hours of the appearance of initial signs of illness.

Early catarrhal phenomena. These occurring in relation to the throat, conjunctivae and intestine have been particularly emphasized by McNalty¹⁹, Riley²⁸, Duzar and Balo³ and others¹⁸.

Absence of fever. Fever was present only during the terminal stages in the two fatal cases, the other two being afebrile throughout. Kinnear Wilson³¹ and Hall¹¹ remark upon the frequent absence of fever throughout the course of the illness; McNalty¹⁹ considers that afebrile cases do not exist but believes that a rise in temperature may be a late event. Syllaba and Henner⁶ in a review of a thousand cases encountered a number which ran afebrile courses and concluded that the elevation of temperature paralleled the patient’s general condition.

General symptoms and signs. The symptoms in our cases were admittedly vague and the findings noticeably variable. The protean character of epidemic encephalitis is frequently mentioned in the literature³⁴, ²⁸, ¹² and has been emphasized as an observation of especial value in differential diagnosis¹³. Among the few constant findings in our cases was the absence of abdominal reflexes. Raimist²⁷ and Price²⁸ consider this phenomenon to be of diagnostic importance and emphasize that these reflexes return with recovery. The indefinite way in which the prodromal period merged into the stage of active disease corresponds with what McNalty¹⁹ has described as a typical history of encephalitis lethargica. The alternation of irritability and lethargy, so prominent in our cases, is emphasized by Kinnear Wilson³¹ and others. Ophthalmoplegia, which occurred in one of the cases, is a frequent and important finding in lethargic encephalitis.

g. The blood and cerebro-spinal fluid. In two of three of our cases in which an examination of the blood was carried out there was a slight leucocytosis; in all three there was a small relative increase in the number of polymorphonuclear cells. These findings are in agreement with those of Holt¹² and Riley²⁸ in connection with encephalitis lethargica.

According to McNalty¹⁹ and Wilson³¹ the cerebrospinal fluid shows no characteristic changes in encephalitis lethargica. Boyd¹ is in agreement with these authorities but states that the fluid may show a moderate lymphocytosis. Holt¹² maintains that the fluid may be normal during the acute stage but commonly shows an excess of mononuclear cells at a later period. Syllaba and Henner⁶⁰ and Riley²⁸ consider that sugar is often present in excess. The changes present in the fluids obtained from our patients (see table) were in keeping with those recognized by these observers as occurring in epidemic encephalitis lethargica.

h. Pathological features. In certain respects the pathological changes resemble those of encephalitis lethargica:—
The distribution of the lesions. There is general agreement among observers that while congestion and oedema may be universal throughout the brain in encephalitis lethargica, the perivascular lesions and nerve cell changes have a characteristic distribution. The parts most affected are the region of the substantia nigra and central grey matter of the mid-brain, the pons and medulla oblongata, and the basal ganglia, especially the optic thalamus; the cerebral cortex is spared and the spinal cord little involved. This distribution is claimed by McIntosh\(^1\) as one of the most striking features of the lesions. The same fact is emphasized by Zinsser\(^3\) and Freeman\(^8\). This characteristic distribution of the graver pathological changes was found in both our fatal cases.

The nature of the pathological changes. i. The perivascular infiltrations. The paucity of perivascular infiltrations is perhaps the chief objection to a diagnosis of epidemic lethargic encephalitis. These infiltrations are generally recognized as the most characteristic of the lesions. There is, however, to be found in the literature considerable support for the contention that the infiltrations are relatively slow in developing and consequently absent in the early stage of the disease. McIntosh\(^1\) is of this opinion on account of the histological appearance of the lesions and states that ‘several acute cases where death has occurred within a week after the onset of the disease have shown only slight lesions in the brain.’ Gay\(^9\) suggests that ‘perivascular infiltration (cuffing) of mononuclear cells probably does not occur in the earliest stages.’ Michels and Globus\(^23\) observe that ‘in cases of epidemic encephalitis that have run a stormy course with a sudden termination, the predominant histologic picture is that of numerous haemorrhages with an unusual sparcity of typical small round cell infiltrations.’ McNalty\(^2\), referring to rapidly fatal cases, draws attention to the almost completely negative histological findings and the absence of perivascular infiltrations, which he attributes to the fatal issue having occurred before characteristic lesions had time to declare themselves. Duzar and Balo\(^9\), basing their opinion on post-mortem findings in the Budapest epidemic, express the view that characteristic infiltrations are found only in cases of relatively long duration. Kinnear Wilson\(^31\) describes perivascular infiltration consisting of only a few cells—less than one complete layer round—a description which aptly applies to the venule illustrated from case 1 of our series (fig. 2). In our cases the duration of the illness was very short, and perivascular infiltration was at an early stage of development.

ii. Haemorrhage. Reference has already been made (p. 165) to the importance of haemorrhages as a feature distinguishing encephalitis lethargica from poliomyelitis. Zinsser\(^3\) describes them as perhaps the most striking element and states that some pathologists suspect haemorrhages to be the primary lesion.

iii. Changes in the nerve cells. The degenerative changes in the nerve cells found in our cases correspond closely to those described by McIntosh\(^1\) and others. The focal distribution of these changes which was so conspicuous is a characteristic already emphasized by Freeman\(^8\).
Experiments on animals. The results of Dr. Alston’s attempts to transmit infection to animals of various species were negative. This is similar to the experience of the majority of those who have attempted experimental transmission of the virus of epidemic encephalitis. McIntosh and Turnbull \(^{17}\) succeeded in infecting a monkey with material from one of McNalty’s cases, and Levaditi \(^{17}\) claimed success with rabbits, but his results were criticized on account of the likelihood of contamination of the inoculated material with herpes virus. Zinsser \(^{34}\) even goes so far as to suggest that the successful transmission of infection in McNalty’s case throws doubt upon the diagnosis.

**Diagnosis.—** From the clinical point of view these cases almost certainly represented an outbreak of acute encephalitis of epidemic nature. In such an isolated epidemic it was not possible to classify the cases as of any one particular form. Even pathologically, although the condition was clearly acute encephalitis, the findings were not absolutely conclusive as to type. Both clinically and pathologically these cases had many points of resemblance to several of the recorded types of acute encephalitis occurring as epidemics. These types have so much in common with each other that it is possible that they do not in reality represent separate entities, but are rather different manifestations of a single disease process. In the present state of knowledge, our findings would appear to indicate that our cases most closely resembled the lethargic type of epidemic encephalitis (von Economo) in an early stage.

**Source of infection.**—The almost simultaneous occurrence of the four cases seems to indicate a common source of infection rather than case to case transmission. No member of the staff in attendance on the four children reported sick at any time during the month of July. There were no other recognized cases of epidemic encephalitis in the wards. Apart from the possible presence of an unrecognized carrier there is little likelihood that infection was derived from any member of the staff or patient in the wards.

A possible source of infection existed in adult patients with post-encephalitic Parkinsonism with whom the children had associated. The possibility of infection arising from contact with cases of chronic encephalitis has been considered by several authorities. Both Netter \(^{24}\) and Freeman \(^{7}\) favour the view that the later manifestations of the disease are due to the continued presence of the infective agent. Hall \(^{11}\) considers that the occurrence of recrudescence at long and varying intervals provides clinical evidence of persistent infection. There is general agreement that the disease may be contagious in the initial acute stage. Netter and Freeman are definitely of this opinion. According to Hall, although proof is rare ‘contagion may occur to a marked degree.’ If it be recognized that the infective agent persists during the later chronic stage, the possibility of the disease being still contagious must be admitted. Netter recorded several cases in support of this view. These cases have been included in a review of the subject.
by Freeman, who collected seven cases of acute encephalitis which had developed in individuals who had been in close association with patients suffering from the disease in its chronic stage. These observers are inclined to relate the contagion in these cases to exacerbations occurring long after the original attack.

The infection in the cases of our two adult patients with chronic encephalitis dated from acute attacks nine and eleven years before. There was no history of any exacerbation in either case, but it may be mentioned that one of the patients had suffered from an attack of unexplained vomiting shortly before the outbreak among the children. The intimate contact occurring between these patients and the affected children has already been emphasized. On the assumption that the cases of chronic encephalitis lethargica were still infective, the risk of the children contracting infection could hardly have been greater.

If these chronic cases were the source of infection it can be definitely stated that the incubation period in the children was not more than two weeks, as there was no contact between the parties prior to July 7, 1933. McNalty, basing his estimate on records at the Ministry of Health, considers that the incubation period of encephalitis lethargica varies from two days to over two weeks.

It is not possible to dogmatize regarding the probable route of infection, but the presence of faucial and pharyngeal catarrh in every case suggests that the virus gained entry through the mucous membrane of those regions. There is considerable evidence favouring the view that the salivary secretion of patients suffering from chronic encephalitis is infective. The condition of our adult patients was characterized by excessive salivation. As already mentioned, these women frequently fondled the children and actually kissed them. Under these circumstances it seems probable that infection entered by the fauces.

Summary.

The subject of the paper is a small outbreak of acute encephalitis in a hospital, affecting four young children, with two deaths. Clinical details are given, together with the results of examination of the blood and cerebro-spinal fluid. Autopsies were performed on the two fatal cases and full histological examination was carried out. Attempts were made to transmit the infection to animals. Various possibilities in connection with diagnosis are considered. The findings appear to indicate that the cases most closely resembled the lethargic type of epidemic encephalitis. The children had been in close contact with cases of postencephalitic Parkinsonism. The possibility of infection from this source is discussed.

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charge; to Lieutenant-Colonel W. F. Harvey and Dr. W. O. Kermack, of the Royal College of Physicians laboratory, who examined the cerebrospinal fluids; to Dr. I. G. McCrie, who provided us with clinical details concerning the cases of post-encephalitic Parkinsonism; and to Dr. W. D. Henderson, house physician, and Sister M. I. Campbell, without whose whole-hearted co-operation the clinical investigation of the cases could not have been carried out.

REFERENCES.

MENINGEAL TUBERCULOSIS:
BACTERIOLOGY AND PATHOLOGY.*


(From the Departments of Pathology, Bacteriology, and Child Life and Health, Edinburgh University, and the Royal Edinburgh Hospital for Sick Children.)

I. Bacteriology.

In this paper we shall record the bacteriological results so far obtained in an investigation of cases of tuberculosis of the central nervous system which is being carried out on material available at the Royal Hospital for Sick Children and other Edinburgh hospitals.

In the investigation we have examined specimens of cerebro-spinal fluid, not only from cases in which the clinical diagnosis of tuberculous meningitis is established, but also (a) from patients who show only slight clinical evidence, suggestive of an intracranial lesion with, in addition, a positive reaction to the tuberculin skin test, and (b) from cases of active tuberculosis without evidence, clinical or pathological, of infection within the central nervous system. In a few cases lymph glands draining the area in which the primary focus of infection appeared to be situated, obtained from fatal cases of tuberculous meningitis, have been submitted to bacteriological examination.

In the routine bacteriological examination each specimen of cerebro-spinal fluid is injected subcutaneously into the groin of one or more guinea-pigs, and, from one to three months later, the animals are killed and examined for the presence of tuberculous lesions. If an animal is infected, differential media are inoculated with material obtained from the regional lymph glands draining the area injected. Gland material, after preliminary treatment with 5 per cent. potassium hydrate, is inoculated directly on to differential media.

The type of tubercle bacillus isolated is determined by the characters of the resulting growth, and the pathogenic

* Read at a Meeting of the Tuberculosis Society of Scotland on 4th July 1934.
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effects on the rabbit of the intravenous injection of 0.01 mgm. moist weight of growth.

The data at present available refer to:

(1) A group of 47 cases of active tuberculosis, 44 of which were diagnosed clinically as cases of tuberculous meningitis; and (2) the examination of specimens of cerebro-spinal fluid from a group of 20 patients suffering from conditions clinically other than tuberculous meningitis, who showed more or less transient signs of intracranial irritation and reacted positively to the tuberculin skin test.

In the first group of the series the human type of tubercle bacillus was isolated from the cerebro-spinal fluid in 35 cases, and the bovine type of bacillus in 12 cases.

In the second group of the series the tubercle bacillus was isolated from the cerebro-spinal fluid in 3 cases. In two of these cases the bacillus was the bovine type, in one case the human type.

Including the positive results from the two groups of cases, the tubercle bacillus has been isolated from the cerebro-spinal fluid of 50 patients, and the type of bacillus determined. For all ages, the human type of bacillus was isolated in 36 cases or 72 per cent., and the bovine type of bacillus was isolated in 14 cases or 28 per cent.

An analysis of the cases into the age groups 0-4 years, 5-14 years, and over 14 years, gives the following figures for the type of bacillus isolated:

In the age group 0-4 years:

23 cases or 65·7 per cent. the human type.
12 cases or 34·3 per cent. the bovine type.

In the age group 5-14 years:

10 cases or 83·3 per cent. the human type.
2 cases or 16·7 per cent. the bovine type.

In the age group over 14 years:

3 cases, all the human type.

Owing to the less adequate supervision of milk supplies in rural than in urban areas, the possibility of infection with the bovine type of bacillus is greater in country districts than in towns. Only eight of the patients in our series lived in rural areas, and of these 8 cases, three were infected with the bovine
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type of bacillus. Of more significance, owing to the greater number of cases investigated, is the fact that, in spite of the better supervision of milk supplies in towns, of the 42 urban cases investigated, 26·2 per cent. were infected with the bovine type of bacillus.

In 11 of the cases included in the above figures it has been possible to examine bacteriologically tuberculous material obtained from other parts of the body:—

In one case the human type of bacillus was isolated from the cerebro-spinal fluid, and the same type of bacillus was isolated from pus derived from the elbow-joint.

In 2 cases the bovine type of bacillus was isolated from the mesenteric glands, and the same type was isolated from the cerebro-spinal fluid.

In 8 cases the tubercle bacillus was isolated from bronchial glands. In 7 of the 8 cases the bacillus was the human type, and in one case the bovine type. In all of the 8 cases the corresponding type of bacillus was isolated from the cerebro-spinal fluid.

Comment.—In a communication to the Tuberculosis Society of Scotland in 1931, Stanley Griffith 1 gave the following statistics relating to infection of the meninges by the bovine type of tubercle bacillus for England and Scotland:—

For England:—

Of 63 cases at all ages, 30·1 per cent.
Of 23 cases in the age group 0-4 years, 34·8 per cent.
Of 29 cases in the age group 5-14 years, 31 per cent.

For Scotland:—

Of 15 cases at all ages, 13·3 per cent.
Of 12 cases in the age group 0-4 years, 16·7 per cent.

The 3 cases in the age group 5-14 years were infected with the human type of bacillus.

The percentage of cases of bovine infection in our series approximates to the percentage given by Griffith for England, but it is to be noted that his statistics for Scotland included a total of only 15 cases.

He drew attention to the fact that the percentage of meningitis cases due to bovine infection was high and did not vary much at different age periods, in which respect meningeal infection differed from other forms of tuberculosis,
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in which the incidence of bovine infection diminished rapidly with advancing age. In the results which we have obtained to date, the incidence of bovine infection shows a marked diminution with advancing age. Thus, in the age group 0-4 years, 34.3 per cent. of the cases were due to bovine infection, while in the age group 5-14 years, 16.7 per cent. were due to bovine infection.

II. Pathology.

Only two questions concerning the pathology of meningeal tuberculosis will be dealt with: (1) The primary focus of infection; (2) Some observations on pathogenesis.

(1) The Primary Focus of Infection.—Meningeal tuberculosis is a metastatic manifestation of the disease, not a primary form, and in most cases it is possible to find at autopsy the primary site of infection. In children this is usually easy, as meningitis often causes death at a time when the initial infection has not progressed beyond the stage at which it presents the typical characters of the primary complex, and the most advanced lesions in the body are readily identified. In almost all cases in children there is found at autopsy more or less gross enlargement, with caseation, of lymph glands in one of the three principal groups—cervical, thoracic, mesenteric—associated with infection entering by the pharyngeal mucosa, the lungs, and the intestine respectively, often with demonstrable primary foci at these sites, especially in the case of the lungs.

Among the cases referred to in Part I of this paper, in which the type of tubercle bacilli isolated from the cerebrospinal fluid was ascertained, 30 came to autopsy, so that the site of the primary infection could be determined. Among these the principal antecedent lesions were in the thorax in 24 cases (19 human, 5 bovine); in the abdomen in 3 (1 human, 2 bovine); in the cervical glands in 2 (1 human, 1 bovine); undetermined in one (human), an adult patient.

The 5 cases of bovine infection with pulmonary lesions deserve special mention. One exemplified the typical “primary lung complex,” with a small Ghon’s focus in the right lower lobe and caseous enlargement of related thoracic glands; one had tuberculous infiltration near the root of one lung, with related caseous glands; one a chronic cavity in the right upper lobe; one chronic fibroid tuberculosis without cavity in
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the right upper lobe; the fifth an acute tuberculous bronchopneumonia with cavities.

In order to determine the frequency of primary infection in the various situations in a larger series, we collected from records at the Royal Edinburgh Hospital for Sick Children 200 consecutive cases of meningeal tuberculosis in which the site of the probable primary focus was identified at autopsy. The results are as follows:

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of Cases</th>
<th>Per Cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic</td>
<td>135</td>
<td>67.5</td>
</tr>
<tr>
<td>Abdominal</td>
<td>57</td>
<td>28.5</td>
</tr>
<tr>
<td>Cervical</td>
<td>8</td>
<td>4.0</td>
</tr>
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</table>

These figures show that in this series the principal lesions and probable primary focus were in the thorax—i.e. in the lungs, with associated caseous enlargement of thoracic lymph glands—in over two-thirds of all cases. It was found, moreover, that meningitis occurred in nearly 80 per cent. of all cases of thoracic tuberculosis which came to autopsy during the past eleven years, and in only about 50 per cent. of those with primary lesions in the neck or abdomen. Apparently, then, meningeal infection is definitely more likely to occur in cases in which the principal lesions are in the thorax than in those in which such lesions are elsewhere. Two possible reasons for this might be suggested:—(1) The alleged higher virulence of the human type of tubercle bacillus, an allegation the truth of which has not been proved; (2) The anatomical fact that bacilli entering the blood stream from lung lesions would immediately reach the systemic circulation and thus have direct access to the brain and meninges; whereas bacilli entering the blood stream from any other source would have first to pass through the lungs. The importance of this anatomical difference is probably less in the case of heavy blood infections such as produce acute miliary tuberculosis, when the blood is flooded with bacilli and many must pass through the lungs, than in the case of limited blood infections which may set up localised, relatively chronic foci, such as caseous tubercles in the brain.

(2) Some Observations on Pathogenesis.—Interest in this question has recently been stimulated by the work of Rich and McCordock, which has necessitated a revision of the idea, previously generally accepted, that diffuse tuberculous meningitis is, in most cases, the result of direct infection of
the meninges via the blood stream in the course of miliary tuberculosis. These workers showed that the experimental injection even of massive doses of tubercle bacilli into the blood, although it produced severe general miliary tuberculosis, never produced a simultaneous meningitis with its characteristic exudative reaction; but that the introduction of bacilli into the subarachnoid space resulted in typical meningitis. They pointed out also that in the human subject meningitis may occur without miliary tuberculosis, and miliary tuberculosis may occur without meningitis. They argued therefore that, in the natural disease, meningitis does not result from miliary tuberculosis, but from the discharge into the subarachnoid space of large numbers of bacilli from a pre-existent localised caseating focus in the meninges or substance of brain or cord, or in the bones of the skull or spine. They proved by their examination of a large number of human brains that such pre-existent foci can be demonstrated in almost all cases of tuberculous meningitis if careful enough search be made.

During the past fifteen months we have been attempting to confirm this view. So far we have examined twenty-seven brains with meningitis. The method employed is to harden the whole brain in formalin and then to cut it in thin slices—not more than 3 mm. thick—and examine each slice for nodules in the substance, which may be in contact with the meninges or ventricles, or masses or plaques in the meninges, obviously older than the diffuse meningitis. In each case the cord also has been examined in the same way. We have been successful in discovering foci in either brain or meninges, which were definitely older than, and might well have been the source of, the meningitis, in 24 of the 27 cases; and in one other there was found a tuberculous osteomyelitis of lumbar vertebra with infection through the dura mater of the cord.

These observations, so far as they go, support the view of Rich and McCordock, though the mere demonstration of older foci does not prove that these were the source of the diffuse meningitis. But further, we have been fortunate in having been able to study several cases in which death occurred while the meningitis was at a very early stage. In these we found that characteristic exudate was present, not at the base as is the almost invariable rule when the condition is fully developed, but over some other limited area of the brain surface; in one case over the upper surface of one frontal
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lobe; in another over one lateral fissure; and so on. In each of these cases an older caseous mass was found either in the brain substance or in the meninges, from which the exudative meningitis had quite obviously taken origin, and begun to spread diffusely in the subarachnoid space. These cases afford very strong evidence in favour of Rich's view.

From these facts it would appear that many patients who develop tuberculous meningitis have had some previous infection of the central nervous system with tubercle bacilli, which resulted, not in diffuse meningitis, but in the formation of a localised tuberculous lesion in brain or meninges. Rich affirms that, in order to produce diffuse tuberculous meningitis, a heavy infection of the subarachnoid space is necessary, and that a slight infection will produce only localised foci. We have accordingly sought to show that tubercle bacilli may, on occasions, be present in the cerebro-spinal fluid in the absence of diffuse tuberculous meningitis. This attempt was made in cases of two kinds:—

A. Cerebro-spinal fluids were obtained from cases of active tuberculosis in which there was no clinical or pathological evidence of meningitis, and these were injected into guinea-pigs. Such fluids were, of necessity, mostly obtained post-mortem. Three of these fluids have given positive results on animal inoculation, there being no meningitis found at autopsy. One was from a case of severe miliary tuberculosis; in the other cases there was only slight miliary spread, but in one there were several small caseous nodules in the brain. Whether or not these patients were about to develop diffuse meningitis is impossible to say, but they had no detectable meningitis when tubercle bacilli were obtained from the fluid.

B. As it is possible that the infection which produces the initial localised lesions in brain or meninges may sometimes cause clinical manifestations pointing to a pathological process in the central nervous system, we obtained for guinea-pig inoculation cerebro-spinal fluids from cases, not clinically tuberculous meningitis, which presented evidence suggestive of an intracranial lesion and a positive reaction to the tuberculin skin test. Among such fluids three have given positive results. These cases were reported to the Tuberculosis Society in February 1934. The children are still in good health.

Conclusions.—This investigation is still incomplete and dogmatic pronouncements cannot be made at this stage.
But the following tentative conclusions are perhaps justified:

1. Tubercle bacilli may be present in the cerebro-spinal fluid in the absence of diffuse tuberculous meningitis.
2. Diffuse tuberculous meningitis is usually the result of infection of the subarachnoid space from a pre-existent localised focus in brain or meninges, not a direct result of miliary tuberculosis.
3. Such localised foci result from infection of the central nervous system by numbers of tubercle bacilli, too small to produce diffuse meningitis, taking place during periods of bacillæmia.
4. Such limited infections, giving rise to localised lesions, sometimes occasion clinical manifestations of a pathological process within the central nervous system, which may be transient, and from which clinical recovery may be complete, at least for a time.

Acknowledgments.—In the case of one of us (H. J. R. K.), the work reported in this paper was carried out during the tenure of the Kirk Duncanson Fellowship for medical research. Part of the expense of the research was defrayed by grants from the Earl of Moray Endowment of Edinburgh University.

THREE CASES OF TUBERCULOSIS OF THE CENTRAL NERVOUS SYSTEM IN CHILDREN APPARENT CLINICAL RECOVERY

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In the course of an investigation of cases of tuberculous meningitis and glandular tuberculosis, which is being carried out on material available in the Royal Edinburgh Hospital for Sick Children and other Edinburgh hospitals, three cases have been observed which indicate that active tuberculous infection of the central nervous system, associated with the presence of tubercle bacilli in the cerebrospinal fluid, does not necessarily proceed immediately to progressive and fatal tuberculous meningitis. Tubercle bacilli were isolated from cerebro-spinal fluid of these patients, while their subsequent history suggests that the lesion in the nervous system has been at least temporarily arrested.

Examinations are being made of specimens of cerebro-spinal fluid obtained not only from cases in which the clinical diagnosis of tuberculous meningitis is established, but also from patients who show only slight clinical evidence suggestive of an intracranial
lesion with, in addition, a positive reaction to the tuberculin test. In the routine bacteriological examination, each specimen of cerebro-spinal fluid is injected subcutaneously into the groin of one or more guinea-pigs, and from one to three months later the animals are killed and examined for the presence of tuberculous lesions. If an animal is infected, differential media are inoculated with material obtained from the regional lymph glands draining the area injected.

In the three cases recorded in this paper, injection of cerebro-spinal fluid led to infection of the guinea-pigs by the tubercle bacillus. Culturally the following characteristics were noted: (a) In Cases 1 and 3 the growth was of the dysgonic type, indicating infection by the bovine type of tubercle bacillus. (b) In Case 2 the growth was of the eugonic type, indicating infection by the human type of tubercle bacillus.

CASE RECORDS

CASE I.—A. B., aged 1 year and 7 months, was admitted to the Royal Hospital for Sick Children as a case of acute pleurisy. There was a history of cough, fever, and lassitude for eight days, and heavy breathing for three days. Vomiting occurred on the evening of onset of the illness but on no subsequent occasion. His only previous illness was measles at the age of 10 months. At the time of admission the child was in a weak undernourished state, uttered frequent cries, and continually rocked his head as if in pain. The fontanelle was small but tense. Pupils were equal and widely dilated. The Kernig reactions were negative, and there was no nuchal rigidity and no tâche cérébrale. Both ear-drum were red and bulging. Marked percussion note dullness with diminution of breath sounds and vocal resonance were noted at the left base, and aspiration was attempted without result.

The day after admission lumbar puncture was carried out, and water-clear cerebro-spinal fluid obtained under increased pressure. On microscopical examination of the fluid no tubercle bacilli or other organisms were found. There was no increase in cells, and biochemical analysis gave the following results: total protein, 40 mg. per 100 c.c.m.; chlorides, 700 mg.; sugar, 0.060 per cent.; gold test, no precipitate.

After lumbar puncture there was some improvement in the child's condition, and the temperature, which had
varied between 101.2° F. and 102.8° F. since admission, fell on the third day (March 25th) to 98° F. On March 29th the restlessness which had always been a feature became worse, and was associated with a rise in temperature. Paracentesis of the right ear-drum was performed with resultant relief and return of the temperature to normal. The patient was sent home on April 3rd. Three weeks later, on April 24th, he was readmitted on account of marked respiratory distress. The physical signs in the chest were similar to those found on March 23rd, except that there were in addition fine crepitations at both bases. The knee-jerks were diminished, the abdominal reflexes absent, and there was resistance to flexion of the neck. The child was very restless and continually holding his head in his hands. The tuberculin skin test was positive. At the time of readmission the temperature was 103° F., and it continued to swing between 98° F. and 103° F. for five days. Paracentesis of the left ear-drum was carried out on April 29th, blood and pus being obtained, after which the temperature settled and the child's condition greatly improved. The boy was kept in hospital a further week and discharged in good health on May 8th, 1933.

The child was visited in his home on Jan. 17th, 1934, eight months after discharge. He showed signs of bony rickets associated with a moderate pallor and laxity of the ligaments. The abdomen was prominent, but this appeared to be part of the rickets. Since his discharge from hospital the previous May the child had had several colds but otherwise progress had been uneventful.

Case 2.—C. D., a boy aged 2 years 3 months, was admitted to hospital on April 17th, 1933. His only previous illness had been measles in April of the previous year. There was no history of disease in the family, and the housing conditions were good. Five days before admission the boy vomited but appeared to have completely recovered within an hour. Two days later vomiting again occurred and was accompanied by fever and loss of appetite, and the child kept his head held in his hands, as though in pain. Next day (April 15th) he was unable to stand on account of "weakness in the legs." On the 16th he lost the power of his right arm but regained this by the evening. He was extremely irritable during examination following admission to hospital. He appeared to suffer discomfort on palpation of the neck and kept his head inclined to the right side. There was slight resistance to flexion of the neck. A flaccid paresis of the right leg was present associated with loss of tendon reflexes. The knee- and ankle-jerks were diminished on the left side. Plantar responses were both flexor, and
the Kernig tests gave negative results. There was no weakness of either arm.

On April 19th flaccid paresis of the right leg and slight neck rigidity were still present and lumbar puncture was carried out; 50 c.cm. of clear cerebro-spinal fluid were withdrawn under pressure. A small coagulum formed in the fluid on standing. A cell count gave 130 per c.mm., and lymphocytes were in excess of polymorphonuclear cells. No organisms were found on microscopic examination. Biochemical analysis of the fluid gave: total protein, 80 mg. per 100 c.cm.; chlorides, 643 mg.; sugar, 0.132 per cent.; gold test, no precipitate.

On April 21st the temperature was 97.4° F., and remained at this level for three weeks after varying between 97° F. and 99.4° F. during the first four days in hospital. By the 24th neck rigidity had disappeared but the boy still remained abnormally irritable for two weeks after admission. During the patient's fifth week in hospital the temperature showed a slight tendency to irregularity, on one occasion rising to 99° F. About this time the pulse-rate became more rapid, and there was a slight loss in weight. Pulse and temperature settled and the patient was discharged to Challenger Lodge as a case of poliomyelitis on July 6th with paresis of the right leg still present.

The boy was seen on Jan. 21st, 1934, six months after discharge. There was considerable wasting of all the muscles of the right thigh and leg, but limited voluntary flexion and extension at the ankle-, knee-, and hip-joints could be carried out. Knee- and ankle-jerks on the paralysed side were absent; on the left side they were noticeably increased. The plantar responses were both flexor and both Kernig reactions were negative. Nothing else of note was found on examination. The boy was able to move about with the aid of a splint and his general health was good.

Case 3.—E. F., a girl aged 4 years and 6 months, was admitted to hospital on August 3rd, 1933. Ten days previously she had been involved in a motor accident receiving injuries to the legs and left hand; she was not rendered unconscious, and when treated for her injuries nothing was found to suggest the presence of intracranial damage. She appeared to be in normal health until the sixth day after the accident when she was noticed by her mother to be drowsy. The same day (July 30th) she was incontinent. The drowsiness persisted to the time of admission. Throughout the day of July 31st she complained of a severe headache which disappeared by the evening and did not return. On the night of August 2nd she complained of pains in the back
and right side, became delirious, and ran a temperature of 104° F. At the time of admission the child was lethargic and the temperature was 100° F. The next day she was more drowsy and irritable during examination; 10 c.c.m. of clear cerebro-spinal fluid under slight increase of pressure were obtained by lumbar puncture. The fluid showed no increase in cells, and no tubercle bacilli or other organisms were found in it microscopically. Biochemical tests of the fluid gave the following results: total protein, 50 mg. per 100 c.c.m.; chlorides, 720 mg.; sugar, 0.07 per cent.; gold test, no precipitate.

The day after lumbar puncture the child’s condition began to improve; the improvement was maintained and she was discharged from hospital on August 12th after examination had eliminated the possibility of a cranial lesion. Next day she had a severe fit at home which lasted fifteen minutes and was associated with twitching of the right side of the face, right arm, and leg. She was troubled with retching after the fit and remained drowsy for the rest of the evening. She was readmitted to hospital the following day (August 14th) and the same evening had a severe fit, this being followed by vomiting and prolonged drowsiness. Two days later the girl was allowed up, and up to the time of discharge on August 24th was extremely active. Beyond a slight rise in temperature following the fit she was afebrile during the time in hospital after readmission. The tuberculin skin test was positive. The exact nature of the condition was not determined but a tentative diagnosis of epilepsy was made.

On Jan. 17th the girl was seen in her home, five months after discharge. Since leaving hospital she had continued to make uninterrupted progress and when seen was in excellent health. Her previous health is of interest. Between the ages of two and three years she had whooping-cough, chicken-pox, and German measles. At the age of three and a half years she had three severe fits all involving the right side which were never satisfactorily explained and which did not recur. The girl comes of a family known to be tuberculous. She is the second youngest of ten children, two of whom died at the age of six months, one following pneumonia and the other from tuberculous meningitis. Of those alive one sister suffers from abdominal tuberculosis and a brother and sister from pulmonary infection. The father also is tuberculous.

**COMMENT**

Recovery from tuberculous meningitis, though extremely rare, is not unknown. In a careful review
Cramer and Bickel \(^1\) collected 46 cases, including one of their own, which were confirmed either by demonstration of *Bacillus tuberculosis* in the cerebro-spinal fluid or by production of tuberculosis in guinea-pigs by injection of cerebro-spinal fluid, the latter test being positive in 20 cases. In many of these recovery was temporary, and death followed within a few months from recurrence of meningitis or from the effects of tuberculosis elsewhere. In some, permanent sequela remained. Martin \(^2\) collected 20 undoubted cases reported since 1894.

All these seem to have presented fairly definite clinical evidence of tuberculous meningitis, though Cramer and Bickel mention three cases in which the symptoms were abortive; and Martin suggests that recoveries are possibly more frequent than has been believed, and that very mild cases which result in recovery may pass unrecognised.

Those in our series are remarkable for: the absence of the classical evidences of meningitis; the extreme mildness and transience of such nervous symptoms and signs as existed; the absence in two of the three of any definite chemical or cytological change in the cerebro-spinal fluid; and the absence in the same two of any sequelae up to the present time. None of the three was, in fact, at the time of the attack, thought to be suffering from meningitis at all. They seem, therefore, to fall into a somewhat different category from previously reported cases of recovery from tuberculous meningitis. We believe that the proved occurrence of such cases as these may throw new light on the problem of the pathogenesis of tuberculous meningitis.

In an important paper on this subject Rich and McCordock \(^3\) published evidence from which they concluded that the prevalent teaching—that tuberculous meningitis is part of a general miliary (blood-spread) infection—is incorrect. They claimed that careful examination of the brain will show in practically every case that the meninges have been infected from an older focus in the vicinity, most often in the brain substance, from which tubercle bacilli have escaped in large numbers into the subarachnoid space. They contend further that the diffuse exudative reaction
characteristic of meningitis can occur only if there be introduced into the subarachnoid space a number of bacilli in excess of what is likely as a result of even the most severe miliary tuberculosis. They support these contentions by evidence from experiment and from human cases after death.

If this view be correct it follows that a patient who develops tuberculous meningitis has, at some previous time, suffered an infection of his central nervous system by tubercle bacilli, which have set up a localised lesion—probably a caseous nodule (tuberculoma) superficially placed in the brain substance, or a circumscribed caseous focus in the meninges (meningeal plaque). It seems probable that the occurrence of this initial infection might in some instances be marked by clinical evidence, probably slight and transient, of a pathological process within the central nervous system. It is in the hope of obtaining some further light on this problem that we are including in our investigation specimens of cerebro-spinal fluid from children, such as these three, in whom the tuberculin test is positive and who present clinical evidence of meningeal irritation or other nervous lesions, but in whom tuberculous meningitis in the clinical sense is not present and does not develop during the child's stay in hospital.

We are as yet unable to offer proof that this suggested explanation of the facts here recorded is correct and that these incidents in the patients' histories coincided with the setting up of circumscribed lesions in brain or meninges, which may eventually cause meningitis. The subsequent history of these children will be of much interest.

One conclusion, however, seems clear. In the light of the facts recorded it is necessary to recognise that any clinical evidence of meningeal irritation or cerebral lesion, no matter how slight and transient, in a patient in whom the tuberculin reaction is positive, may be an indication of tuberculous infection of the central nervous system, even in the absence of clinically active tuberculosis elsewhere in the body, and of any definite cytological or chemical abnormality in the cerebro-spinal fluid. And the recognition of such an incident in a patient's history as a danger signal
may be a step in the direction of prevention of the deadliest of all forms of tuberculosis.

We wish to express our thanks to Prof. Charles McNeil, Dr. Lewis Thatcher, and Dr. Douglas Nicholson for permission to publish the cases, and for the use of clinical records of patients under their care; also to Lieut.-Colonel W. F. Harvey and Dr. W. O. Kermack, of the laboratory of the Royal College of Physicians of Edinburgh, for cytological and chemical examinations of cerebro-spinal fluids. In the case of one of us (H. J. R. K.) the work reported in this paper was carried out during the tenure of the Kirk Duncanson fellowship for medical research.

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A CASE OF SAGITTAL SINUS THROMBOSIS AND SUBDURAL ABSCESS FOLLOWING NASAL SINUSITIS

BY

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(Edinburgh)

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A CASE OF SAGITTAL SINUS THROMBOSIS AND SUBDURAL ABSCESS FOLLOWING NASAL SINUSITIS

By A. R. MACGREGOR and A. B. SMITH (Edinburgh)

The unusual sequence of events, the difficulty in clinical diagnosis, and the remarkable pathological findings make this case one of considerable interest to ear, nose and throat surgeons.

C.S. (female), aged 8½ years, was admitted to Dr. Scott’s Ward in the Royal Edinburgh Hospital for Sick Children on February 1st, 1935. She had had a bad cold in the head for a week and was first seen by her family doctor four days before admission when she had a rise of temperature, severe headache, and nasal catarrh. On the day previous to admission she developed a swelling of the right upper eyelid and because of this her doctor sent her into hospital. Some years previously she had been in hospital with abdominal tuberculosis but had made a complete recovery.

Her temperature, on admission, was 101° F. and pulse rate 120. She looked ill and her tongue was dry and furred. The right eye was closed because of marked swelling of the upper eyelid and this swelling extended upwards on the forehead. The eye movements were limited but the pupil reacted and the vision was good. On anterior rhinoscopy, pus was seen in the olfactory cleft on both sides. There was also much post-nasal discharge. Both tympanic membranes were normal. X-ray examination showed large frontal air cavities; the right frontal and both maxillary antra were opaque.

Operation.—(A.B.S.) 1.2.35: General anaesthesia. The anterior end of the right middle turbinate was first removed by the snare. An incision was then made through the right eyebrow down to the periosteum. Pus was found below the orbital periosteum; this had come through a fistula in the floor of the frontal air cavity. The floor of the cavity was then removed and the pus in the cavity itself mopped out. A large opening was made into the nose and a drainage tube inserted. The incision was closed with stitches, a small drain being left at the outer angle.

The following morning the temperature had fallen to normal but in the afternoon rose again to 102°. Although the local condition appeared to do well, the temperature remained elevated, swinging between 102° F. and 104° F. Three days after the operation the tube was removed and on the following day the stitches
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were also removed. The swelling of the eye had completely subsided and the incision had healed.

On 6.2.35, it was noticed that the girl could not speak, and also that she had a paralysis of the right arm and right leg, that is, on the same side as the frontal operation.

Mr. Norman Dott was called into consultation and the condition was regarded as a metastatic cerebral abscess in the left cerebral hemisphere. On lumbar puncture clear fluid under pressure was procured. It was decided to wait until the abscess had become walled off before interfering.

On the following day two swellings developed on the head over the left parietal region. These were regarded as being due to osteomyelitis of the skull and an immediate operation was performed.

Second operation.—(Mr. Norman Dott). 7.2.35. General anaesthesia. An incision was made over each swelling on the scalp and two trephine openings were made in the left parietal bone. At both areas pus exuded under pressure from the medulla of the bone and also from the surface of the dura. The dura itself appeared to be intact, and was not incised. A small rubber dam was inserted through each incision which was then closed with stitches. While this was being done the girl collapsed and died.

Bacteriological examination of the pus from the frontal air cavity produced a non-haemolytic streptococcus. A blood culture taken on 5.2.35, also produced a non-haemolytic streptococcus, but culture of the cerebrospinal fluid was sterile although there was an increase of polymorphs.

Post mortem Examination.—The right frontal air cavity had been operated on and contained some blood clot but no pus. The left frontal air cavity contained thick mucopus. There was pus in the ethmoidal air cells and the sphenoidal air cavity on both sides. Both ears were healthy.

There were two foci of osteomyelitis in the left parietal bone; the infected bone had been removed at operation, and the dura mater exposed. Pus was present outside the periosteum around these; the dura deep to them was intact and looked healthy.

There was a large collection of pus in the subdural space on the left side, greatest in amount over the upper anterior part of the parietal lobe and spreading forward to the frontal pole; passing down also on the medial surface of the left hemisphere and beneath the temporal and occipital lobes to the floor of the middle cranial fossa. There was no spread to the right side. Over the affected part of the supero-lateral surface the purulent exudate was adherent to the surface of the brain; elsewhere it was liquid pus which did not adhere to the surface (Fig. 1).

The superior sagittal blood sinus contained septic clot along its whole length; in the anterior half this was almost completely

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FIG. 1.
Left cerebral hemisphere.
A, Area of subdural abscess; B, Thrombosed meningeal veins.

[Face p. 600]
FIG. 2.

× 45. Section from left frontal pole.
A, Septic thrombus in meningeal vein; B, Brain; C, Exudate in subarachnoid space; D, Exudate in subdural space.

FIG. 3.

× 45. Section from area of subdural abscess.
A, Exudate in subdural space; B, Subarachnoid space free from exudate; C, Brain.
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liquefied and appeared as fluid pus. Meningeal veins tributary to the sagittal sinus on the left side, draining the area of the subdural abscess contained septic clot, especially over the frontal pole. On the right side the larger meningeal veins were engorged and some contained recent thrombus which was not septic.

Beyond the area where the leptomeninges were obscured by the subdural collection of pus, there was no leptomeningitis detectable by the naked eye. All the other dural blood sinuses were healthy. In the rest of the body were found only the usual toxic changes and a terminal broncho-pneumonia. There were no pyæmic lesions. Calcified tuberculous glands were present in the mesentery.

Microscopic Examination of a section from the left frontal pole showed septic clot in the meningeal veins and a fibrino-cellular exudate in the subarachnoid space around them (Fig. 2). A section from further back in the area covered by the subdural abscess showed a purulent collection outside the arachnoid and practically no cellular reaction in the subarachnoid space (Fig. 3). A section from the right frontal pole showed the meningeal veins to be greatly engorged, some containing recent uninfected ante mortem clot; a little haemorrhage in the subarachnoid space, and an excess of macrophages but no polymorph reaction. It appears therefore that leptomeningitis was confined to the immediate vicinity of the thrombosed veins on the left side, and had not spread diffusely at the time of death.

Non-hæmolytic streptococci were recovered from the pus in the subdural space.

Discussion.—The chief interest of the case lies in the problem of the pathway of infection. There would seem to be two ways in which the subdural abscess might have arisen: (1) From the frontal air cavity by way of septic thrombosis of the superior sagittal sinus; (2) from foci of osteomyelitis in the left parietal bone.

1. Suppuration in the frontal air cavity is probably the commonest cause of septic thrombosis of the superior sagittal sinus, though cavernous sinus thrombosis is a more frequent occurrence. Turner and Reynolds had no case of sagittal sinus thrombosis, but they mention the possibility and quote Burger as reporting that 23 out of 28 cases of sagittal sinus thrombosis originated in the frontal air cavity. It is therefore reasonable to suppose that the sagittal sinus thrombosis in this case might have originated in this way. In that event the further spread would have been by way of septic thrombosis of the tributary veins of the superior sagittal sinus, setting up suppuration in the subdural space; and thence to the sites of the two foci in the left parietal bone, by way of those venous or lymphatic paths which establish
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continuity between the dura mater and the diploë of the skull bones.

There are two objections to accepting this as the pathway of infection; the unilateral distribution of the subdural infection; and the fact that there was a subdural abscess and not diffuse leptomeningitis. It is difficult to understand why septic thrombosis spreading out from the superior sagittal sinus into its tributary veins should affect only those on the left side; and as these veins run in the leptomeninges, the result of infection passing out from them is more likely to be leptomeningitis than subdural suppuration. It is, in any event, surprising that in the presence of septic thrombosis of these veins and of subarachnoid exudate in their immediate vicinity, no diffuse leptomeningitis occurred. Possibly the development of adhesions helped to limit the spread of infection.

2. The alternative possibility is that the subdural abscess arose from infection passing through the dura from the foci in the parietal bone. In the absence of microscopic examination, too much weight must not be attached to the apparent integrity of the dura. This would explain the unilateral distribution of the subdural suppuration; and the sagittal sinus thrombosis could be explained as following septic thrombosis of its meningeal tributaries from the area of the subdural abscess. On this view the foci in the parietal bone must be attributed to a blood infection, evidence in favour of which is afforded by the result of blood culture two days before death.

On the other hand, clinical evidence suggests that the subdural abscess was present before the development of the bone foci, and that the septicaemia was probably secondary to the intracranial suppuration; while the absence of pyæmic lesions elsewhere in the body casts doubt on the pyæmic origin of the foci in the parietal bone; and the fact that suppuration was definitely more advanced in the anterior part of the superior sagittal sinus suggests an origin in the frontal air cavity.

In the absence of a more exhaustive pathological investigation, it is obviously impossible to reach any final conclusion on these problems. But whatever may have been the pathway of infection, the case presented, during life, a difficult problem in clinical diagnosis and, at autopsy, an unusual pathological picture.

It is with pleasure that we record our indebtedness to Mr. Norman Dott and Drs. C. E. Scott, N. S. Carmichael and J. McNair Murray for their help in this case.

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STAPHYLOCOCCAL PNEUMONIA.
STAPHYLOCOCCAL PNEUMONIA

BY

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That cases of pneumonia occur in which staphylococcus is the sole, or the predominating, infecting micro-organism is well known. Many of the reported cases have been associated with epidemics of influenza. Although generally less frequent than streptococcus haemolyticus and Pfeiffer's bacillus as a cause of pneumonia complicating influenza, staphylococcus aureus has been conspicuous in certain epidemics. Chickering and Park described one of these and noted the very grave and often fatal character of the pneumonia when staphylococcus aureus played a leading role. In such cases it is to be supposed that the staphylococcus is a secondary invader, following upon the epidemic infection which has laid the respiratory tract open to attack. Apart from these occasional epidemics, staphylococcal pneumonia appears to be relatively uncommon. It may be questioned, therefore, whether staphylococcus ever causes pneumonia independently of other micro-organisms, and whether those cases in which it plays a dominant part have clinical or pathological features sufficiently distinctive to justify this condition being regarded as an entity, differing from other forms of broncho-pneumonia. Reimann, in a paper describing six cases, claims 'primary staphyloccic pneumonia' as a clinical and pathological entity. The facts now recorded from a series of ten fatal cases support this claim at least to the extent that they show this type of pneumonia to possess certain constant and distinctive features.

Case reports.

The ten cases were encountered in the pathological department of the Royal Edinburgh Hospital for Sick Children between August, 1935, and May, 1936. During that period there was no influenza epidemic of any serious proportions in the community, and in the hospital the incidence of pneumonia in general, though fairly high during the winter, was not unusual. But the occurrence of so many cases of staphylococcal infection of the lungs (other than pyaemic) within so comparatively short a time is without precedent in the records of the department.

For purposes of description the ten cases may be divided into two groups, according to the stage at which the pathological process was found at necropsy: (1) Four cases with sero-fibrinous pleural effusion, in which the early stages of the process in the lungs were shown; (2) six
cases with empyema or pyo-pneumothorax, in which the pathological process in the lungs had progressed to a later stage.

**Group I.** Case 1. A boy, aged seven weeks, was an under-weight, bottle-fed baby. The fatal illness was of four days' duration, with restlessness, slight fever (99·4° F.) and cough. On admission to hospital on the third day, physical signs indicated consolidation of the right lung.

**Post-mortem Examination** The right pleural cavity contained one ounce of thin turbid fluid and fibrinous exudate; there were numerous sub-pleural haemorrhages. The upper lobe of the right lung was completely consolidated, haemorrhagic and moist. The bronchi in this part contained much thick pus. The other lobes were not consolidated. There was no generalized bronchitis. The left lung and pleura were healthy.

**Bacteriology.** Staphylococcus aureus was obtained in pure culture, post-mortem, from lung, pleural fluid and blood.

Case 2 was that of a girl aged four months. She had had bronchitis two weeks before admission to hospital, but had made a good recovery. The fatal illness was of three days' duration and began with a cough, sneezing, nasal discharge and restlessness, followed by respiratory distress. When admitted to hospital on the third day the infant was cyanosed and very ill. Physical signs indicated consolidation in the left upper and right lower lobes. The temperature was 105·4° F.; the white blood cells numbered 31,000 per c.mm.

**Post-mortem Examination.** Both pleural cavities contained a quantity of slightly turbid serous fluid and fibrinous exudate; there were many sub-pleural haemorrhages. There were large well-defined areas of consolidation in the left upper and both lower lobes; all these were haemorrhagic, with yellow points of suppuration showing through the pleura, and blood-stained pus exuded from the cut surface. Other parts were not consolidated and there was no generalized bronchitis.

**Bacteriology.** Staphylococcus aureus was obtained in pure culture, post-mortem, from lung, pleural exudate and blood.

Case 3 was that of a boy aged three-and-a-half years. He had always been healthy. The fatal illness was of eight hours' duration. He appeared to be quite well in the morning. At noon he asked to be put to bed. He became obviously ill during the afternoon; vomited blood at 6 p.m. and again an hour later; and died at 8 p.m. on the way to hospital.

**Post-mortem Examination.** Both pleural sacs contained one ounce of slightly turbid blood-stained fluid and fibrinous exudate; there were many sub-pleural haemorrhages. The left lower lobe and the base of the right lower lobe were consolidated and very haemorrhagic. There was no pneumonia elsewhere, and no generalized bronchitis. The pharynx and larynx were inflamed.

**Bacteriology.** Staphylococcus aureus was obtained in pure culture from lung and pleural exudate. Blood culture yielded a pure growth of pneumococcus Type II. All cultures were made post-mortem.

Case 4 was that of a girl aged sixteen days, born prematurely by one-and-a-half months and illegitimate. She was feeble and would not take the breast; she was fed with breast milk from a bottle. The fatal illness was of about twenty hours' duration. She refused feeds and was pale and collapsed; blood came from the nose and a black motion was passed. She was moribund when admitted to hospital.
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POST-MORTEM EXAMINATION. The right pleural cavity was full of blood-stained serous fluid; copious sub-pleural haemorrhage made the whole serous membrane crimson. There was a small patch of consolidation at the apex of the right upper lobe, sharply defined, haemorrhagic. The rest of the right lung was collapsed. The left pleural sac and lung were healthy. There was no generalized bronchitis. The upper respiratory passages were not inflamed. The ileum contained altered blood.

BACTERIOLOGY. Staphylococcus aureus was obtained in pure culture, post-mortem, from the right lung, pleural exudate and blood.

The macroscopic characters of these four cases were so similar and so unlike other types of pneumonia that each one, after the first, was recognized at necropsy and tentatively diagnosed as staphylococcal pneumonia before any bacteriological investigation had been carried out. In each there was a pleural effusion of sero-fibrinous fluid, slightly turbid or blood-stained, with numerous sub-pleural haemorrhages. Each had one or more areas of massive consolidation, sharply defined, intensely haemorrhagic, with a soft, moist surface on section which suggested the early onset of suppuration. In each there was an absence of generalized bronchitis and of scattered small patches of consolidation such as are found in the usual forms of broncho-pneumonia. In no case was any focus of infection found to which the pneumonia might have been secondary, nor were there any pyaemic lesions. The other organs showed the usual toxic changes, which were always severe.

The microscopic characters of these four cases were so similar that separate description is unnecessary. The consolidation was due to a combination of haemorrhage and inflammatory exudation. The haemorrhage affected both the alveoli and the coarse stroma. The exudate was
cellular in alveoli and bronchi, with heavy deposits of fibrin in the interlobular septa. Even in the earliest cases there was a strong tendency to suppuration, which might develop anywhere, but especially in the bronchi (see fig. 1), where the walls were destroyed and adjacent alveoli were involved; and in interlobular septa and perivascular stroma, where it spread along, and out from, the lymph vessels. Throughout the affected parts there were extraordinary numbers of staphylococci in large clumps (see fig. 2). Other parts of the lungs showed no pathological changes except some congestion and oedema.

**Group II.** Case 5 was that of a boy aged ten weeks. He was a feeble baby and had been losing weight; there had been an umbilical discharge. The fatal illness was of ten days' duration and began with a sudden rise of temperature to 103.4° F. and consolidation in the left lung. On the day before death 40 c.c. of pus was removed from the left pleural cavity.

**Fig. 2.** Case 4. Masses of staphylococci among haemorrhagic and purulent exudate (x 55)

**Post-mortem Examination.** The left pleural sac showed organized adhesions anteriorly, and posteriorly contained a large quantity of pus. There was a small area of suppuration in the left lung near the base of the lower lobe, from which pus was discharging into the pleural cavity. The rest of the left lung was collapsed. There was no generalized bronchitis. The right lung and pleura were healthy.

**Bacteriology.** Staphylococcus aureus was obtained in pure culture from the pleural pus during life.

Case 6 was that of a boy aged one year. The fatal illness was of three days' duration, with fever (105° F.), cough, dyspnea and blood-stained discharge from the nose. He was moribund when admitted to hospital.

**Post-mortem Examination.** The right pleural cavity contained thin pus and fibrino-purulent exudate. At the anterior border of the right upper lobe a consolidated area of about two cubic inches contained many
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ramifying abscesses, several of which had burst through the pleura. The rest of the right lung was collapsed. The left lung and pleura were healthy. The pharynx and tonsils were inflamed.

Bacteriology. A strongly haemolytic strain of staphylocoecus albus was obtained in pure culture from pleural pus removed just before death.

Case 7 was that of a girl aged four months. The fatal illness was of thirty-six hours' duration, but was preceded by a slight cold and cough for a few days. She became pale and collapsed, with respiratory distress and fever (108°F).

Post-mortem Examination. The right pleural cavity contained a large amount of thin pus and air. A consolidated area of about three-quarters of a cubic inch at the base of the right lower lobe was riddled with ramifying abscesses, one of which had burst through the pleura. The rest of the right lung was collapsed. The left lung and pleura were healthy. There was early fibrinous pericarditis.

Bacteriology. Staphylocoecus aureus was obtained in pure culture, post-mortem, from the pleural pus, but in direct films other organisms also were present, notably streptococci and Gram-negative diplococci of the Neisseria group.

Case 8 was that of a boy aged four months. The fatal illness was of five days' duration, with dyspnoea, cyanosis and fever (104.2°F). The white blood cells numbered 26,000 per c.mm.

Post-mortem Examination. The left pleural cavity contained a large quantity of thin pus, fibrino-purulent exudate and air. A consolidated area at the base of the left lower lobe was riddled with ramifying abscesses, one of which had burst through the pleura. The rest of the left lung was collapsed. There was broncho-pneumonia without suppuration at the base of the right lung.

Bacteriology. Staphylocoecus aureus and pneumococcus were obtained from the pleural pus during life.

Case 9 was that of a boy aged six months. The fatal illness was of twenty-five days' duration, with pallor, panting; cough and sweating. During a feed (cows' milk) he had choked and from that moment there was increasing respiratory distress. He was treated at home, where he developed pneumonia in the left lung. On the fourteenth day he became worse, and on the eighteenth day he was admitted to hospital with an empyema. Skiagrams showed a pyo-pneumotherax, and fifty cc. of pus and air were evacuated from the left pleural cavity. Staphylocoecal antitoxin (B.W. & Co.) was given, ten cc. by the intravenous and ten cc. by the intramuscular route over forty-eight hours, with temporary improvement. Death followed a sudden collapse.

Post-mortem Examination. The left pleural cavity was mostly obliterated by fibrous adhesions, among which were several pockets of thick pus. The antero-inferior portion of the left upper lobe was riddled with ramifying abscesses, several of which had burst through the pleura. The rest of the left lung was collapsed. The right lung and pleura were healthy.

Bacteriology. Staphylocoecus aureus was obtained in pure culture from the pleural pus and blood during life and from the left lung after death.
Case 10 was that of a boy aged seven months. The fatal illness was of two weeks' duration, but had been preceded by measles and bronchitis from which he had never fully recovered. The symptoms of acute illness were cough, dyspnoea and cyanosis. When admitted to hospital, two days before death, his temperature was 101·8° F., and signs of fluid were present at the right base. Forty-five cc. of pus were evacuated from the right pleural cavity.

**Post-mortem examination.** The right pleural cavity contained a large amount of pus and fibrino-purulent exudate. An area of about one cubic inch, just below the apex of the right upper lobe, was consolidated and contained ramifying abscesses, one of which had burst through the pleura. The rest of the right lung was collapsed. The left lung and pleura were healthy. The pharynx was inflamed.

**Bacteriology.** Staphylococcus aureus and B. influenzae, the former predominating, were found in the pleural pus during life. After death, staphylococcus aureus was obtained in pure culture from the right lung, and streptococcus haemolyticus from the blood.

The remarkable similarity of the pathological findings in these six cases cannot fail to be noted. Every case had a unilateral empyema; in three cases there was a pyo-pneumothorax. In every case suppuration had developed in the corresponding lung in a localized area which was never very large and often quite small. Within the affected area in every case multiple ramifying abscesses had formed, one or more of which had burst through the pleura. In all except case 8 there was an absence of generalized bronchitis and of consolidation in either lung apart from the single area involved in suppuration. Case 8, in which there was a mixed infection, showed broncho-pneumonia in the base of the other lung.

**Fig. 3. Case 10. Multiple abscesses in an area of haemorrhagic consolidation (x 7)**
The microscopic characters were almost identical in the six cases. In all but one the abscesses were of an acute type, without evidence of any organization. The exception was case 5, in which some of the cavities had a lining membrane of recent granulation tissue. In many instances some of the cavities were bounded in part by fragments of bronchial wall, or had a traceable connection with bronchi. Sometimes suppurative had originated in lymph vessels in the interlobular septa. Although acute, the abscesses were usually fairly sharply defined. The lung substance between them was collapsed or consolidated, and only occasionally showed spreading necrosis and suppuration. (see fig. 8 and 4.)

![Fig. 4. Case 5. Well defined abscess cavities separated by collapsed lung substance (x 5)](image)

It is obvious that these six cases illustrate a further stage of the pathological process seen in its earlier stage in cases 1 to 4. Both groups show the same localization of the lung lesion to certain well-defined areas, and the same absence of generalized bronchitis and of the disseminated patches of consolidation so constantly found in broncho-pneumonia due to other organisms. The incipient suppuration arising especially, though not only, in the bronchi, which was noted in the cases of group I, had developed in those of group II into a series of ramifying abscess cavities, rupture of which through the pleura had produced empyema. When this happens, if the almost inevitable broncho-pleural fistula communicates with a bronchus which still contains air, pyo-pneumothorax will result, as in cases 7, 8 and 9.
Bacteriological summary.

In nine of the ten cases staphylococcus aureus was isolated, and in one case staphylococcus albus. In six cases no evidence was obtained from the bacteriological investigation that any micro-organisms other than staphylococcus played any part. In cases 7, 8 and 10, although staphylococcus predominated, other organisms accompanied it in the lung or pleural exudate, viz., streptococcus and a coccus of the Neisseria group in case 7, pneumococcus in case 8, and B. influenzae in case 10, in which there was also a haemolytic streptococcus in the blood. In Cases 7 and 10 there was a definite history of a respiratory infection preceding the onset of the fatal illness. In case 8, while no such history was obtained, in addition to the characteristic staphylococcal lesion, there was, in the other lung, an acute broncho-pneumonia without suppuration, which may have been due to the pneumococcus. In these three cases, therefore, it is likely that the staphylococcal infection was superimposed on a previous respiratory infection of another type. In case 3, that rather extraordinary case of a previously healthy boy who died within eight hours of the onset of symptoms, while as far as could be ascertained staphylococcus aureus was responsible for the pulmonary condition, there was a coincident pneumococcal septicaemia. It is difficult to explain how this double infection may have arisen, but clearly it was a peculiarly deadly combination.

Discussion.

It is reasonably certain that the pathological process in the lungs in these ten cases was the result of a primary infection of the respiratory tract, and not of a haematogenous infection from a distant septic focus. In only one case was any antecedent septic focus known to exist (the umbilicus in case 5), and even there no connection was established. Study of the pathological anatomy of the lung lesion leaves little doubt that it is the result of infection which reaches the lung via the bronchi. The intimate relation of many of the abscesses to bronchi, and the severe purulent inflammation of the bronchial walls, even in the earliest cases, together with the absence of septic thrombosis of the pulmonary arteries, are features which almost prove the bronchial and disprove the vascular route. Anatomically the lesions are unlike those of pyaemic infection.

In four cases there was reason to suppose that an antecedent respiratory infection may have predisposed the lungs to attack by staphylococci. In the other six cases, although an antecedent or coincident infection by other organisms cannot be altogether ruled out, there was no evidence that staphylococcus was not alone responsible. In one
case (case 9) there was a strong suggestion in the history that the illness may have been initiated by the baby aspirating milk into the lung. Although there was no suggestive history in any other case, aspiration of food is a possibility, especially in cases 1 and 4, these patients having been feeble, premature babies who did not suck well. Milk often contains staphylococci, and it was noted by Johnson and Meyer that staphylococcal pneumonia in newborn infants might be caused by aspiration of food. But it is probably unnecessary always to seek the cause in any such accidental introduction of staphylococci into the lungs. As with other organisms more commonly associated with respiratory infection, their invasion of the lungs may depend upon predisposition or lowered resistance in the host, or upon their own exalted virulence. The occurrence of so many of these cases in this hospital within a relatively short period possibly indicates a phase of increased virulence among staphylococci. No statistical proof can be produced in support of this suggestion, but surgeons and pathologists working in the same city endorse the opinion that there has been in recent months an increased prevalence of other staphylococcal diseases.

Whether or not the staphylococcus was accompanied by other organisms, in this series of cases the resulting lesions had constant, distinctive and easily recognized characters, quite unlike those of other forms of pneumonia. It is clear that it was the staphylococcal infection which determined the characteristic form of the lesion. It may therefore be claimed that staphylococcal pneumonia (whether 'primary' or not in the sense that the staphylococcus is the first or only bacterial invader) is a definite pathological entity.

Summary.

Ten cases of staphylococcal pneumonia in children are described. Four cases represent the earlier stages, with serous pleural effusion; six the later stage, with empyema.

The children's ages ranged from sixteen days to three-and-a-half years, but eight were under one year.

In nine cases staphylococcus aureus was isolated; in one case staphylococcus albus.

In six cases, as far as bacteriological investigation showed, staphylococcus was the only infecting micro-organism. In four cases there was a mixed infection.

At the earlier stages staphylococcal pneumonia is characterized by massive consolidation of one or more localized areas of one or both lungs, without generalized bronchitis. Haemorrhage and early onset of suppuration are constant features. Suppuration especially attacks the bronchi and lymph vessels.
At the later stage the affected part breaks down into a group of ramifying abscess cavities, one or more of which may burst through the pleura. This gives rise to empyema or pyo-pneumothorax.

The pathological anatomy indicates that infection reaches the lungs via the bronchi. Aspiration of food is a possible cause in some cases, especially in weakly infants.

Staphylocoecal pneumonia is an entity presenting distinctive pathological characters.

Thanks are due to Professor Charles McNeil, Dr. Lewis Thatcher and Dr. J. McNair Murray for permission to publish these cases, and for the use of the clinical records of patients in their wards.

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Pulmonary Tuberculosis in Children

BY
AGNES R. MACGREGOR AND W. A. ALEXANDER

(From the Royal Hospital for Sick Children, the University Department of Child Life and Health, and the Research Laboratory of the Royal College of Physicians, Edinburgh.)
PULMONARY TUBERCULOSIS IN CHILDREN.

By AGNES R. MACGREGOR and W. A. ALEXANDER.

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Introduction.

It is often said that pulmonary tuberculosis is not common in children. It is true that the number of cases admitted to a children's hospital bearing that diagnosis is comparatively small, and that the number of deaths registered as from that cause forms but a small proportion of the total deaths of children from tuberculosis of all types. But it must be recognised that consideration only of clinically manifest pulmonary tuberculosis gives a wholly false and misleading conception of the real importance and frequency of tuberculous lung lesions in children. Vast numbers of cases with primary lesions in the lungs never declare themselves as pulmonary tuberculosis. The fact that the lung lesions are often not clinically detectable, and that illness or death is due to secondary or metastatic manifestations of the disease, have tended to obscure the truth that the lungs play a dominant rôle as portal of entry and as primary site of infection at all ages of childhood.

TABLE I.

Incidence of Primary Thoracic Tuberculosis among all Fatal Tuberculosis. 333 Cases.

<table>
<thead>
<tr>
<th></th>
<th>1922-25 (198 Cases)</th>
<th>1930-35 (135 Cases)</th>
<th>Total (333 Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic</td>
<td>107 (54%)</td>
<td>93 (69%)</td>
<td>200 (60%)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>80 (40.5%)</td>
<td>40 (29.6%)</td>
<td>120 (36%)</td>
</tr>
<tr>
<td>Cervical</td>
<td>11 (5.5%)</td>
<td>2 (1.4%)</td>
<td>13 (4%)</td>
</tr>
</tbody>
</table>
The figures presented in Table I. show that in a series of 333 cases of fatal tuberculosis of all forms examined post-mortem at the Royal Edinburgh Hospital for Sick Children during the period from 1922 to 1935, the disease was found to have originated in the thorax in 60 per cent.; while, when the last six years of the period are separately considered, the percentage of primary thoracic infections rises to 69.

Of the 200 cases of primary thoracic tuberculosis, approximately 80 per cent. terminated with meningitis, and so would, in most instances, appear in registrars’ statistics as cases of non-pulmonary tuberculosis.

It is desirable that the true frequency of primary tuberculous infection of the lungs in childhood should be clearly recognised; for in the great majority of such cases the route of infection is the respiratory tract and the source of infection a human one, often a member of the child’s family. Therefore, important as is the problem of the elimination of bovine infection, the major problem in the control of tuberculosis in children is concerned with the human source and with the prevention of primary infection in the lungs.

This paper attempts to present an account of the origin and development of those tuberculous processes in the lungs which result from a first infection. It is now generally recognised that typical "adult" tuberculosis is the result, not of a first infection, but of later re-infections, endogenous or exogenous; and that in countries with a highly "tuberculised" population it is almost only in children that the "first infection" type of tuberculosis is seen. This type has certain constant characteristics which are in sharp contrast to those of the adult or "re-infection" type, notable among these being the frequently inconspicuous character of the original primary lesion, the early and severe involvement of the lymphatic system, and the tendency to extensive and often fatal spread of infection by the blood stream.

It is recognised that pulmonary lesions of the "adult" type are occasionally met with in children, and represent, as in adults, the result of a re-infection. They occur mostly in older children and have the same characters as in adults, namely, a tendency to the development of chronic, progressive, destructive lesions in the lungs, a predilection for the apical regions, and minimal involvement of the regional lymph glands. These characters serve to distinguish them from the
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forms of pulmonary tuberculosis which result from the progressive evolution of a primary infection.

The development of the disease in the lungs following a first infection is here described in three stages: 1. The "primary complex," by which is understood the original focus in the lung, and the lesions produced in the regional lymph glands secondary to it; 2. localised extensions of the disease in the lung, arising from the primary complex; 3. more widespread disseminations of disease throughout the lungs, representing the advanced and often terminal stages of the process.

Section 1: The Primary Lung Complex.

The frequent occurrence of gross caseous tuberculosis of the lymph glands of the thorax in tuberculous children has long been recognised, and the prevalent belief formerly was that any lesions which might be found in the lungs were secondary to those in the lymph glands. This belief gained a strong hold and has been slow to die. It is sixty years since Parrot in 1876 enunciated his law of "adénopathies similaires," and claimed that, when the lymph glands in the thorax are diseased, there is always present in the lung a corresponding lesion, to which the infection in the glands is secondary. But only within the last decade has the view that thoracic tuberculosis in children originates as a primary lesion within the lung itself gained wide support, and acceptance of it is not even yet universal. Strong evidence in favour of this idea was set forth in 1898 by Küss, in a masterly work which did not gain the recognition it deserved. The work of Ghon (1916) has been more widely recognised; so much indeed that the term "Ghon's tubercle" is now often applied to the "primary lung focus," although he was not, and did not claim to be, the first to describe it. Active interest in the question was of more recent date in this country, where the work of Canti (1919) and others brought it to the attention of British workers. A valuable contribution to the subject is that of Blacklock (1932), in whose report may be found a review of the literature and the results of his own investigations.

Our own experience in a large number of necropsies performed in cases of tuberculosis in children is in complete agreement with that of other observers who have found that, when lymph glands of the tracheo-bronchial or broncho-
pulmonary groups are tuberculous, a primary focus may be found in the corresponding lung almost without exception, provided that a sufficiently careful search be made. This fact has been so fully substantiated by numerous workers that it is unnecessary to recapitulate the evidence in support of it. But as the primary lung complex forms the basis of more extensive lesions which are described in later sections of this paper, a clear understanding of its pathological anatomy is necessary. Some of the essential facts concerning it may therefore be given here.

Macroscopic Characters of the Primary Lung Focus.—The primary lung focus in its simple and most characteristic form, as it is commonly seen at necropsy, is a caseous mass, usually about the size of a pea or smaller, but occasionally considerably larger; sharply defined in proportion to the amount of healing which has occurred at its periphery; often spherical, but sometimes wedge-shaped or irregular; and frequently surrounded by a ring of small “satellite” tubercles, which may be found on the pleural surface also when the focus is superficial in position. Sometimes a line of similar small tubercles can be traced passing inward from the site of the primary focus toward the root, to the nearest regional glands of the broncho-pulmonary group (Figs. 6, 12).

These primary lung foci are often, though not always, situated at or near the periphery of the lung, either immediately, or only a short distance, beneath the pleura. Sometimes they are deeply placed in the centre of a lobe, or are near the root of the lung. The frequency of their occurrence in the various lobes in the cases of the present series is shown in Table II.

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Number</th>
<th>Per cent.</th>
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<tbody>
<tr>
<td>Right upper</td>
<td>37</td>
<td>43.5</td>
</tr>
<tr>
<td>Right middle</td>
<td>8</td>
<td>9.4</td>
</tr>
<tr>
<td>Right lower</td>
<td>19</td>
<td>22.3</td>
</tr>
<tr>
<td>Left upper</td>
<td>8</td>
<td>9.4</td>
</tr>
<tr>
<td>Left lower</td>
<td>13</td>
<td>15.3</td>
</tr>
</tbody>
</table>

It will be seen from these figures that the lung foci were found, in this series of cases, much more frequently in the right upper than in any other lobe. This agrees with the
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findings of Ghon, Blacklock, and some others. The foci have no special predilection for the apices; they are in fact rather infrequently found there, being much more often situated in the lower or outer portion of the upper lobes.

In cases of greater chronicity encapsulation of the focus by more or less fibrous tissue occurs. At this stage, in the case of superficially placed foci, fibrous thickening or localised adhesions of the pleura may be found. The ultimate fate of the focus, if infection be arrested, is to undergo calcification, but this has been a rare occurrence among our cases, particularly in the younger children. Blacklock likewise calls attention to the scarcity of completely healed foci among his cases, in contrast to the findings of certain Continental observers.

The macroscopic characters of the primary focus are, in most cases, so distinctive that it is easily recognisable as belonging to a different period of the disease from any secondary lesions which may be present in the lungs. As a rule, it is only when the secondary lesions are gross and extensive, and the primary focus has been involved in a destructive process, that it is really difficult or impossible to identify it. In the majority of cases the primary focus is single, but cases occur in which two or more similar nodules are found, between which it is not possible to distinguish differences in age. These may be regarded as examples of multiple primary foci.

Sometimes the primary lung focus is found in the form of a cavity (Figs. 9 and 25). This results from liquefaction of the caseous material and its evacuation through the bronchiole with which the focus communicates. Such softening begins in the bronchiole itself and may spread to involve the whole caseous mass. The resultant small cavity is surrounded by a barrier of granulation or fibrous tissue and a zone of satellites, and has more or less caseous material adherent to its walls according to the completeness of the evacuation. Foci which form cavities are, on the average, rather larger than those which remain caseous.

**Microscopic Characters of the Primary Lung Focus.**—In its earliest stage the primary lung focus is a small area of tuberculous pneumonia, in which the alveoli are consolidated with a typical fibrino-cellular exudate and the alveolar walls are swollen and infiltrated with cells. This stage, before the onset of caseation or of any proliferative reaction at the periphery, is seldom seen and was not found in any of our
cases, but has been described by other workers. The earliest focus in any of our cases had already caseated in the centre, and showed some development of tuberculous granulation tissue at the edge of the caseous mass (Fig. 28). But even at a much later stage than this the pneumonic (exudative) character of the original lesion is obvious, because in the caseous centre the outlines of the walls of alveoli, bronchioles and blood vessels are almost always clearly discernible (Fig. 29), and in sections suitably prepared the elastic tissue in these structures is shown to be still stainable and to retain its original arrangement. This is possible only in exudative lesions, as in those of proliferative type either the elastic tissue is destroyed or its original arrangement is so distorted as to be unrecognisable.

It has been suggested that the exudative reaction in tuberculous infection is an expression of the allergic state and is characteristic of the previously infected, sensitised individual. The fact that the primary focus in a subject not previously infected is of this nature would seem to indicate that allergy is not the only factor which can determine the exudative reaction.

It is usual to find a small bronchus entering the caseous nodule, where its walls become involved in caseation and its lumen is plugged with caseous debris. In cases where the primary focus assumes a somewhat wedge-shaped character, this bronchus is often situated at the apex of the wedge, and caseation extends farther along its walls than in the surrounding lung substance (Fig. 26).

Unlike the rapidly progressive and destructive exudative lesions of later infections, the primary lung focus shows, even in the youngest subjects, a tendency to heal. The patch of caseous pneumonia is quickly circumscribed by a zone of tuberculous granulation tissue, in which endothelioid and giant-cell tubercles develop and, in course of time, fibroblasts appear and fibrous tissue is laid down. In the surrounding lung substance beyond this immediate barrier, tubercles develop, which have already been referred to as "satellites" (Fig. 22). These are often found in relation to lymph vessels in the septa and peribronchial and perivascular tissues, and they are to be regarded as the result of lymphatic spread of infection from the primary focus into adjacent tissues (Fig. 23). Sometimes in the lung substance around these tubercles a
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process of interstitial pneumonia develops; the alveolar septa become thickened by a growth of cellular connective tissue and the air-cells are small and lined with conspicuous cuboidal cells. When the primary focus is immediately subpleural, numerous tubercles may be found in the subpleural lymphatics passing to some distance from the lung nodule, or forming a plaque on the pleural surface (Fig. 27). Clusters and rows of similar foci may be found passing inward towards the root of the lung. These bear a constant relation to peribronchial and perivascular lymphatics and mark the line by which infection spread to the regional lymph glands in the hilum (Fig. 24). Blacklock states that such involvement of the peribronchial lymphatics of the bronchiole leading away from the primary lung focus toward the root was not often found in his series. In ours it was quite often found, and also involvement of perivascular lymphatics passing in the same direction. The cases most likely to show it are those in which the primary focus is not immediately subpleural, as when it is very superficial in position the chief channel of spread of infection to the regional lymph glands may be the subpleural lymphatics and not those which accompany the bronchi and blood vessels.

The Lymph Glands in the Primary Complex.—The part played by lymph glands in the primary complex is conspicuous and important. In most cases of this kind great enlargement and extensive caseation of one or more groups of glands in the thorax are found (Figs. 7, 8, 13). The glands which are affected bear a direct and constant relation to the position of the primary lung focus, which depends on well-established anatomical facts.

The lymph glands related to the lungs are in four groups on each side: (1) the broncho-pulmonary or root glands, which are situated between the branches of the main bronchus at the hilum (extrapulmonary), and along the course of the bronchi within the substance of the lung (intrapulmonary); (2) the superior tracheo-bronchial glands, situated on each side in the angle between the trachea and the main bronchus; (3) the inferior tracheo-bronchial glands, situated below the bifurcation of the trachea, in the angle between the two main bronchi; (4) the paratracheal glands, situated on either side of the trachea up to the level of the clavicle.

The broncho-pulmonary glands receive lymph only from
the lung of their own side and have no direct communication with the glands of the opposite side. The superior tracheo-bronchial glands receive lymph from the upper lobe on their own side and from the inferior tracheo-bronchial glands, and have communications with the superior tracheo-bronchial glands of the opposite side. The inferior tracheo-bronchial glands receive lymph from the lower lobe of their own side, and from the right middle lobe in the case of the glands on the right side; and they communicate freely with the corresponding glands on the opposite side. The paratracheal glands receive lymph from the superior tracheo-bronchial glands and there is free communication between the glands of the two sides.

The following general rules may be laid down and will be found to be correct in the great majority of cases. When the primary lung focus is situated in an upper lobe, caseous enlargement will be found affecting the root glands and the superior tracheo-bronchial glands of the same side; if the infection has spread further, the superior tracheo-bronchial glands of the opposite side and the paratracheal glands may be affected, but the disease will be most advanced in the glands nearest the lung focus. When the primary lung focus is in a lower lobe, or in the right middle lobe, the root and inferior tracheo-bronchial glands of the same side will be most affected; if infection has spread further, the inferior tracheo-bronchial glands on the opposite side and the superior tracheo-bronchial and paratracheal glands on the same or both sides may be involved. Occasionally when the primary lung focus is in the lower part of an upper lobe, especially if it be near the interlobar pleura, the inferior tracheo-bronchial glands may show more advanced disease than the superior. In no case will the root glands of the opposite side be involved in the spread of infection from a single primary lung focus. Sometimes the intrapulmonary broncho-pulmonary glands escape, as the infection may pass from the primary lung focus (if it be superficial in position) by the subpleural instead of by the peribronchial lymphatic plexus, and thus arrive directly at the extrapulmonary glands at the hilum.

These rules have been found so reliable that a careful study of the lymph glands in any case provides a guide which greatly simplifies the problem of finding the primary lung focus.
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Thus, with enlarged and caseous glands in the left root and in the inferior tracheo-bronchial groups, the primary lung focus should be sought in the left lower lobe. When the right root and superior tracheo-bronchial glands are most affected, the focus will be found in the right upper lobe, and so on. Examples are shown in the diagrams, which illustrate actual cases (Figs. 1-5).

*FIG. 1.*—Primary lung complex, early stage. Primary focus in right upper lobe. Complete caseation of right broncho-pulmonary glands. Partial caseation of right superior tracheo-bronchial glands.

The Relation of the Lymph Gland Infection to the Primary Lung Focus.—It has been found in this study, as other observers have found, that on histological grounds the disease in the lymph glands can be recognised to be of the same age as, or more recent than, that in the lung focus, but never of longer duration. This fact, together with the distribution of the affected lymph glands in relation to the position of the lung focus, as described above, can only mean that the disease in the glands is secondary to that in the lung and has arisen by extension of infection from it. In cases in which a lung focus is demonstrated, we consider this relation between the lung and the lymph gland lesions to be beyond dispute. But there remain certain cases in which, with caseous enlargement of the tracheo-bronchial glands, no lung focus is found. In such an event several possibilities must be considered: firstly, that a lung focus existed but was overlooked; secondly,
Anterior.

Fig. 2.—Primary lung complex, slightly later stage than Fig. 1. Primary focus in right lower lobe. Complete caseation of right broncho-pulmonary and inferior tracheo-bronchial glands. Partial caseation of right superior tracheo-bronchial glands.

Medial.

Fig. 3.—Primary lung complex, moderately advanced stage. Primary focus in left upper lobe. Complete caseation of left broncho-pulmonary and left superior tracheo-bronchial glands. Partial caseation of left and right inferior tracheo-bronchial and right superior tracheo-bronchial glands.
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**FIG. 4.**—Primary lung complex, advanced stage. Primary focus in left lower lobe. Complete caseation of left broncho-pulmonary glands and of inferior and superior tracheo-bronchial glands on both sides.

**FIG. 5.**—Primary lung complex with two primary foci. Primary foci in right middle and left lower lobes. Complete caseation of broncho-pulmonary and inferior tracheo-bronchial glands on both sides. Partial caseation of superior tracheo-bronchial and paratracheal glands on both sides.
that tubercle bacilli passed through the lining membrane of the respiratory tract without leaving any permanent trace and formed the first lesions in the lymph glands; thirdly, that the glands were infected by lymphatics from some more distant portal of entry, such as the tonsils or the abdomen; fourthly, that bacilli entering the body at any portal, first invaded the blood, and being filtered out in the lungs were conveyed to the lymph glands, there to form their first lesions.

The first of these possibilities must always be considered a probability. The lung foci are often small and are readily missed unless they are specifically sought. Their inconspicuous character caused them to be overlooked by most workers for half a century after they were first described. If they have become quiescent and healing has occurred, they may be even more difficult to find, especially if they are not calcified. Yet among our cases in recent years, since lung foci have been consistently and carefully looked for, there have been very few (apart from cases of gross pulmonary disease, in which all trace of the original primary focus may be destroyed) in which none has been found; so few indeed that we are more ready to believe that a focus was missed than that none existed.

The possibility that in some cases no lung focus is formed and that the primary lesions may arise in the thoracic lymph glands must be admitted. Evidence in support of this view is scanty, and is bound to be unsatisfactory; anyone who advances it can always be charged with having missed a lung focus, and no matter how careful the search it is hard to refute that charge. It is clear that, even if primary infection of the lymph glands can occur, it is only as an exception to the rule.

The view that tuberculous infection frequently gains access to the thoracic lymph glands via the tonsils, mouth or pharynx, and the cervical glands, has often been advanced and has gained influential support. Our experience does not support that view, as far as concerns primary infections in childhood. Facts which are opposed to it are: the almost constant occurrence, in association with tuberculous thoracic glands, of the lung focus described above; the decreasing severity and apparent duration of infection in the thoracic glands in direct proportion to their distance from the lung focus; the frequent absence of any demonstrable involvement of cervical lymph glands; the usual finding, in cases where the cervical
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glands are infected, that disease in them is much less severe than in the thoracic glands, and the absence of histological evidence that it is of older, or even of equal, standing; the frequent lack of continuity between infected inferior cervical glands and the superior group which are nearer the assumed portal of entry; and the fact (mentioned by one of us in a previous paper (Macegregor, 1930), and since confirmed by observation of many more cases) that, when the superior cervical glands are involved in association with thoracic tuberculosis, there is usually an open discharging lesion in the lungs, from which the tonsils would readily be infected by sputum. These facts provide valid reason for excluding the cervical route as a usual channel of infection, but they do not rule it out as an occasional possibility. Cases do occur in which it seems possible that infection might have reached the thorax by that route; and even although, in the great majority of our cases, careful study of the distribution and character of the lesions definitely excluded it as a reasonable possibility, it cannot be categorically denied as an explanation of some of those few cases in which no primary lung focus is discovered.

The view that the thoracic glands may be involved, via lymphatics, from a primary abdominal infection is open to similar objections. It is true that in some cases of obvious primary abdominal tuberculosis the tracheo-bronchial glands become infected, but always definitely less and later than the mesenteric glands; and the disease in them in such cases is incomparably less severe than in those cases which have been described as primary in the thorax.

The possibility of a haematogenous infection giving rise to primary lesions within the thorax has been the subject of much controversy. It was advocated by Calmette (1922) and others of the French school, who believe that most pulmonary infections result from the ingestion of tubercle bacilli, which gain entry through the alimentary mucous membrane and are conveyed to the lungs by the blood stream. The evidence supporting this theory is slender and of doubtful validity; the experiments on which it is based have been subjected to severe criticism, and the consensus of opinion is against it. The rarity of bovine infections among cases with primary thoracic lesions and their relative frequency among those with primary abdominal lesions are facts which certainly suggest that the routes of infection are different. As an
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explanation of those cases without demonstrable primary lung foci, this theory is open to the further objection that bacilli conveyed by the blood stream would reach the lungs first, and would be more likely to form the first foci there than in the thoracic lymph glands.

In conclusion, despite the other possibilities discussed, we are of opinion that, in those few cases in which no primary lung focus is found, such a focus almost certainly existed but was overlooked, either because the search for it was not exhaustive enough, or because some process of healing had rendered it unrecognisable.

The Origin of the Primary Lung Focus.—Of the three possible routes by which tuberculous infection might reach the lungs—air passages, blood stream, lymph paths—the last can be ruled out as far as concerns the foci under consideration. There can be no reasonable doubt that the lesions in the lymph glands are secondary to the lung focus. It is inconceivable that the familiar pathological picture of the "primary lung complex" could possibly result from retrograde spread of infection by lymphatics from glands to lung. Against a hæmatogenous origin of the foci, the general objections considered above again apply. Evidence provided by the character and relations of the lung foci themselves, while not conclusive, points in the same direction. The lesion is of a type (e.g. tuberculous pneumonia) which is usually associated with air-borne infection, although it is certainly possible for lesions in the lungs resulting from blood-borne infection to assume this exudative or pneumonic character; it is, for example, often seen in miliary tuberculosis. It is usually impossible to demonstrate any connection between the lung foci and blood vessels. Blacklock, having investigated the possibility of a vascular origin, summarily dismisses it as lacking any supporting evidence. On the other hand, the lung foci almost always have a clear relation to the air passages, and their histological characters are those of tuberculous pneumonia developing in the alveolar expansions of a small bronchus. Most of the evidence, therefore, supports the view that these foci result from direct inhalation of tubercle bacilli into the lungs from an external source of infection.

Clinical Comment.—It has to be admitted that it is very often impossible to detect the primary lung complex by clinical or radiological means. Small caseous lung foci produce no
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physical signs and cast no X-ray shadow. If they are calcified a skiagram will reveal them; if they have formed cavities or have developed advanced fibrosis they may be detected; but at the earlier, purely caseous stage as a rule they cannot be seen.

In collaboration with Professor Charles McNeil, the writers made a careful study of a large number of cases in which skiagrams taken during life were available and necropsies had been performed. It was found that, even with the post-mortem report, and sometimes the actual specimen, before us, it was often impossible to detect the lung focus in the film. With few exceptions, it was only when the focus was larger than usual, or was much fibrosed or calcified, that it could be located with any certainty. Even the enlarged caseous lymph glands were seldom visible. In the absence of calcification, great enlargement might be present without producing any significant broadening of the mediastinal shadow, especially when it was the inferior tracheo-bronchial glands which were affected.

It is necessary to recognise this limitation of radiological diagnosis. It is sometimes asserted that, in the case of a child who is suspected or known to be tuberculous, the existence of a primary lung focus can be excluded if an X-ray examination of the chest prove negative. We believe this to be a dangerous fallacy. If the primary complex lesions are healing or healed they will probably show in a skiagram, but at the earlier active and therefore dangerous stage they probably will not.

It is only rarely that a child comes under medical observation at the stage when the only tuberculous lesions in the body are those of an early primary lung complex. At that stage there may be singularly little upset of general health, and any slight disturbance which may occur may be disregarded by the parents, its true significance not being even remotely suspected. Most of the children in whom the lung disease was found at the primary complex stage post-mortem in our series were victims of tuberculous meningitis. In many such cases it was asserted that health had been perfect until the onset of symptoms of meningitis.

Section 2: Localised Extensions.

Localised tuberculous lesions affecting an area of lung substance larger than that of the original primary lung focus
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most often arise in immediate relation to that focus. In many cases such lesions become progressive and, although their progress may be slow, they represent a stage in a pathological process which will ultimately become widespread, or, in the event of arrest, will produce permanent structural alteration in the affected lung. In other cases these localised lesions, after persisting for a variable period, may undergo a process of resolution and disappear, leaving little or no trace. As these two types of localised tuberculous extensions present different problems in pathology, they will be considered separately under the headings of (A) Progressive and permanent extensions, and (B) Extensions capable of undergoing resolution. Cases coming under the second heading are of the type to which the term "epituberculosis" has been applied.

(A) Progressive and Permanent Extensions. — These usually originate directly from the primary complex, when the lesions composing this remain active and progressive. Most often they represent the evolution of the primary lung focus into a larger lesion. They may also arise as a result of infection from the root lymph glands extending outward into the lung.

(a) Extensions originating in the Primary Lung Focus.— These may be of two distinct histological types, exudative or proliferative. In the first, the affected part is consolidated with an inflammatory exudate which later caseates, the process being a tuberculous caseous pneumonia. In the second, the lung substance is more or less completely replaced by tuberculous granulation tissue and tubercles, the condition being largely of the nature of an interstitial pneumonia. The pathogenesis of the lesion is different in the two types.

Areas of Caseous Pneumonia.— In some cases the primary lung focus, instead of remaining in the form of a compact caseous nodule which is limited by the proliferation of granulation tissue as has been described, becomes more actively progressive. Increased activity of infection in the focus may result in caseation spreading to involve the barrier ring of granulation tissue and tubercles at the periphery of the central area of caseous pneumonia. Subsequent reaction on the part of the tissues may succeed in forming a new barrier of granulation tissue and again checking the advance of the caseating process. A focus in which this sequence of events has occurred may be recognised by the fact that, whereas in its central
portion the alveolar structure of the caseous material can be distinguished and the elastic tissue retains its normal arrangement, in the peripheral part of the caseous area this is not so, as this part was occupied by proliferative lesions before it underwent caseation, and therefore had lost its original architecture. But often when infection is active in the primary focus, caseation extending from the centre destroys the cellular barrier and is unchecked by new proliferative reaction. In such case fresh areas of tuberculous pneumonia may develop beyond the original margin of the primary focus but contiguous with it, and thus rapidly increase its size, often in an irregular manner. This is a process of direct extension through the alveolar tissue.

The development of similar areas of massive caseous pneumonia sometimes results from involvement of the wall of a bronchus within the area of the primary focus, and the passage of infected material into neighbouring branches (Fig. 14). The close and constant relation of the primary lung focus to a bronchus has already been pointed out. Where this bronchus enters the focus its wall becomes caseous and its lumen filled with exudate. Liquefaction of the caseous centre of the focus is not uncommon and provides a ready means of spread of infection by the air passages. There is little doubt that many localised extensions which have the character of caseous pneumonia arise in this way. At a later stage, when further excavation of the pneumonia areas occurs, this lesion is likely to develop into a more widespread tuberculous broncho-pneumonia.

It is obvious from the character of the changes which occur in the tissues in lesions of this kind that resolution is impossible without permanent alteration of the lung structure. Not only the exudate but the lung substance itself caseates, and in the event of healing taking place there could be no return to normal structure, but at best fibrous replacement, or cavity formation with subsequent fibrosis and necessarily extensive scarring.

Areas of proliferative infiltration originate as an extension of the cellular reaction which occurs constantly around the primary lung focus and leads to the formation of satellite tubercles and a barrier of tuberculous granulation tissue. At the earlier stages of such lesions it is sometimes obvious that spread along lymph channels plays an important part (Fig. 25).
Later on the proliferation of tuberculous granulation tissue and tubercles may be so diffuse that large areas of lung are massively consolidated (Figs. 15 and 17), and any relation to lymph paths is completely obscured. That this proliferative process does not arise through organisation of a previous caseous pneumonia is shown by the persistence of atrophied or collapsed alveoli, with thick cellular walls and cubical lining cells, throughout the area wherever the alveoli have not been completely obliterated by the formation of tubercles. Such an appearance obviously could not develop in a part where all alveolar structure had previously been destroyed by caseation.

The natural evolution of these proliferative lesions is in the direction of progressive fibrosis. Fibrous tissue forms around and replaces the tubercles; the originally cellular walls of the remaining alveoli become densely fibrous; the interlobular septa and peribronchial and perivascular stroma are converted into dense fibrous masses intersecting the part. Whether it is possible that these proliferative infiltrations may sometimes undergo absorption by a process of resolution, and leave the affected part relatively normal and capable of function, can only be a matter for speculation. At the later stages, when definite fibrosis has supervened, absorption can hardly be accepted as possible. Even at the earlier stage of massive cellular proliferation it seems very unlikely, in view of the known tendency of tubercles to heal by fibrous organisation. It is probable that the most favourable end-result of this type of lesion would be a contracted fibrous scar, representing a permanent loss of functioning lung substance.

The exudative and proliferative types of localised extensions have been described above as separate and distinct processes; but it must be recognised that in any given case they may be combined. Secondary areas of caseous pneumonia may develop around the primary focus, and these be surrounded by granulation tissue and tubercles in the same way as the original lesion. In this way an extensive area, even a whole lobe, may be massively consolidated with a combination of exudative and proliferative lesions, while other parts of the lung remain unaffected.

(b) Extensions originating in the Root or Tracheo-Bronchial Lymph Glands.—Localised areas of tuberculous pneumonia may result from erosion of a bronchus by a
caseating lymph gland in or near the root, and aspiration of infected material into the lung (Fig. 14). The lymph glands being so constantly and so severely involved at an early stage of the primary infection, this might be expected to be a relatively common occurrence. Actually, in the series of cases on which this study is based, it has rarely been seen. When it does occur it is likely to give rise to a massive infection, first in the area of distribution of the affected bronchus, but probably leading speedily to cavity formation and more widespread dissemination.

The root lymph glands may be responsible for a more chronic lesion in the lung, of a proliferative type, spreading out from the root. It is a debatable question to what extent infection of the lungs from the root glands occurs by means of a spread of infection in retrograde direction along afferent lymph vessels. We have not found definite evidence of the occurrence of this process. The spread from lymph gland to lung is more often direct, the tuberculous process within the gland destroying the capsule and extending into the adjacent lung substance, causing the production of tuberculous granulation tissue, sometimes followed by caseation, and thus producing a more or less extensive infiltration which spreads out from the root (Fig. 16).

Clinical observation proves that even in young children localised lesions of considerable extent may exist for long periods without showing much alteration in size or giving rise to a spread of the disease to other parts of the lungs. But as long as active and progressive disease exists in such a lesion there is obviously a risk of wider dissemination. Unless the course of a case is cut short by tuberculous meningitis or some other rapidly fatal form of the disease, it is not common to find the lungs at necropsy the seat of an extensive localised lesion and free from more recent disseminated foci. It would seem therefore that, if the localised lesion fails to heal, its almost inevitable ultimate consequence is dissemination of the disease throughout the lungs. Lesions of the caseous pneumonic type are the more prone to give rise to widespread tuberculous broncho-pneumonia, owing to the likelihood of cavities developing in them. But even with proliferative infiltrations the risk is present. Often in the midst of the affected area the original primary focus may be found as a small cavity, from which infection may spread to other parts.
by way of the bronchi; not uncommonly, among the granulation tissue, tubercles form in the walls of bronchi and caseate into the lumen, offering further chances of dissemination. In very chronic proliferative infiltrations the bronchi often show cylindrical enlargement, which may be in part secondary to fibrosis, but is certainly in part the result of tuberculous bronchitis which has destroyed tissue in the bronchial wall. Thus, although in proliferative infiltrations the process is to a large extent interstitial, it is unusual to find no evidence of lesions open to the air passages in some part of the affected area.

(B) Localised Extensions which are capable of Resolution.

—It is recognised as a result of clinical experience that even extensive localised lesions in the lungs of tuberculous children do not invariably run a rapidly progressive and fatal course, but may persist for long periods without evidence of active spread and without much disturbance of general health, and may ultimately disappear leaving no trace, or only slight radiographic evidence of scarring. Attention was directed to cases of this type by Eliasberg and Neuland in 1920, when the term "epituberculosis" was first used. They considered that the recognition of such cases is important because their occurrence proves that even extensive lung lesions in tuberculous children do not necessarily carry an ominous prognosis. The original authors and some who followed them laid stress upon complete disappearance of the lesion as the criterion of "epituberculosis." In the cases which they reported the infiltrations in the lungs cleared up and left no trace detectable by X-rays, except some widening of the mediastinal shadow which was attributed to enlarged tuberculous lymph glands. Later observers have confirmed the occurrence of cases of the type described by Eliasberg and Neuland—that is to say, cases of extensive pulmonary infiltration which run a benign course and result in clinical recovery; but it is evident from case reports that disappearance of the lesion is not necessarily complete, and that a certain amount of scarring may remain. Yet, even when this is so, it is indisputable that large areas which are at one time shown by X-rays to be involved in a dense infiltration may ultimately resume a normal radiographic appearance, proving that extensive lung lesions in tuberculous children may undergo absorption and disappear.

Concerning the pathology of such lesions very little is
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certainly known. The problem is obviously a difficult one and hardly capable of complete solution by the methods of morbid anatomy. The real criterion which distinguishes an infiltration of the type to which the term "epituberculosis" is applicable from a chronic tuberculous lesion which, up to a point, may run a similar clinical course but causes grave permanent structural alteration, is the fact that the epituberculous lesion, or at least the greater part of it, disappears. If it has not disappeared at the time of death, it cannot be known whether it would have disappeared had the patient survived. Published reports of cases stated to be of this nature are open to the objection that the lesions, not having disappeared, had not fulfilled the conditions necessary for inclusion in the category of epituberculosis. The cases run a benign course; patients seldom die with half-resolved infiltrations. Thus pathologists can very seldom have an opportunity to examine a case which could confidently be regarded as one of epituberculosis. It is, therefore, not surprising that at least three different suggestions have been put forward to explain the pathological process concerned, and that no agreement has been reached. The three suggested explanations are (1) collapse; (2) a non-tuberculous pneumonia; (3) a true tuberculous process.

(1) Collapse.—Occlusion of a large bronchus by pressure exerted on it by an enlarged caseous lymph gland at the root of the lung, causing collapse of the corresponding portion of lung substance, has been thought by some observers to explain the clinical and radiological findings. Relief of the occluding pressure, when the disease in the lymph gland begins to heal, permits re-entry of air and rapid re-expansion of the affected part. This theory has gained a good deal of support and it offers a simple explanation of the phenomena. It is favoured by Miller (1934) who, in a review of the subject, concludes that "the evidence seems to favour the view that the changes in the lung in epituberculosis are due to collapse secondary to pressure on a bronchus by a tuberculous lymph gland." It is strongly supported by the case reported by Morloch and Pinchin (1933). Their patient, a boy of 14 years, presented characteristic clinical and radiological evidence of epituberculosis. Bronchoscopic examination revealed a tumour pressing into the lumen of the bronchus of the right upper lobe, which was the seat of the infiltration. A piece of the
tumour was removed and microscopic examination proved it to be a caseous tuberculous lymph gland. Four days later a skiagram showed that the upper part of the affected lobe had cleared, suggesting that the lung had re-expanded in that area.

It is, however, doubtful whether this can be accepted as the whole explanation of all cases. Occlusion of the bronchus would have to be complete, otherwise not collapse but emphysema would result; and despite the great frequency of gross enlargement of tuberculous bronchial lymph glands, it is, in our experience, unusual to find at necropsy any evidence that they have in any way interfered with the passage of air, let alone produced collapse by complete occlusion of a large bronchus.

Collapse of otherwise normal alveoli in the vicinity of a tuberculous area seems to be more often due to occlusion of smaller bronchi by inflammatory exudate, caseous material or encroachment by tuberculous granulation tissue. In this way the extent of a lesion, as seen by X-rays, might be considerably increased, while much of it would disappear on relief of the bronchial occlusion.

(2) A non-tuberculous pneumonia, with delayed resolution.—This was the view advanced by Eliasberg and Neuland in their original description of epituberculous infiltrations. It has been suggested that the interference with lymph flow which results from tuberculous disease of the lymph glands which drain the part may favour delay in resolution of a simple non-specific pneumonia. The occurrence of non-tuberculous pneumonia in a lung which contains tuberculous lesions is quite common. In some cases the non-specific pneumonia is found only in and immediately surrounding the tuberculous area. This may indicate a special proclivity towards infection in that part. We have not, however, personally observed this combination in any case in which the area of consolidation caused by non-tuberculous pneumonia was known to have existed for any considerable time. No doubt, when found, it is often merely a recent terminal pneumonia. But it may well be that a non-specific pneumonia consolidation, which ultimately, after long delay, undergoes resolution, is the explanation of certain cases of the type under discussion.

(3) A Tuberculous Process.—On the assumption that the
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process under discussion is a specific tuberculous one, there are two possibilities with regard to its pathogenesis. It may be (a) a reaction, perifocal or otherwise, to products of the tubercle bacillus, dependent on allergy; or (b) an unusual type of reaction to the presence of living tubercle bacilli. It has been asserted that lesions of the kind under discussion occur only in persons who react to the tuberculin test, i.e. who are allergic to products of the tubercle bacillus. Radiological and post-mortem evidence agree that it is usual to find tuberculous lymph glands at the root of the affected lung. It may therefore be assumed that the area of consolidation arises in relation to a primary lung focus. These facts suggest that it may be a perifocal allergic reaction. This view is supported by cases such as that reported by Langer (1922-3) in which, following the administration of 1/10 mgm. of tuberculin, an infiltration demonstrable by X-rays as a dense shadow appeared over a whole lobe, accompanied by a systemic reaction, the shadow disappearing after fourteen days. A reaction of this type is induced in an allergic subject by the action of tuberculostatic toxins rather than of the bacilli themselves. The resulting exudate is poor in, or even free from, living bacilli, and so might well fail to undergo caseation and be capable of absorption by resolution. Recent experimental work by Oppenheimer (1935) showed that "epituberculous infiltrations" can be produced in allergic animals by intra-tracheal injection of killed cultures of tubercle bacilli. It is deduced from this that the natural lesion results from rupture into a bronchus of a caseous lymph gland which contains few, if any, living bacilli, but is rich in tuberculo-protein.

Evidence in support of the view that these lesions are not always due to purely allergic or "tuberculo-toxic" reaction is afforded by reports of cases in which tubercle bacilli were obtained from the affected part by lung puncture. Gorter and Lynac report such a case, but as tubercle bacilli were obtained on only one occasion by lung puncture, and as necropsy about eighteen months later revealed a fairly extensive caseous mass, evidently a primary lung focus within the affected area, it is possible that the exploring needle entered that caseous nodule and from it obtained the bacilli which were found. Less open to this objection is the case reported by Spence (1932), who obtained tubercle bacilli on two occasions by lung puncture at widely separated parts of the affected area,
Spence believed that it is unlikely that on each occasion the needle struck the primary focus, and considered that "the evidence suggests that the whole lesion in so-called epituberculous infiltration is a caseous tuberculous process." According to a personal communication received in December 1935, this child "appears to be in perfect health, but there is an X-ray 'scar' in the area of the original lesion." As the X-ray shadow illustrated in the published report is a dense and extensive one, a considerable measure of resolution must have taken place, and the diagnosis of epituberculosis is fully justified. For reasons already stated, Spence's conclusion that the whole process was a "caseous tuberculous" one may be doubted; but the evidence which this case affords that tubercle bacilli may be present in considerable numbers throughout the "epituberculous infiltration" cannot be lightly dismissed.

In view of such evidence that pulmonary consolidation capable of resolution may be due to a specific tuberculous process, it is necessary to consider what its histological character may be. In an earlier section of this paper the opinion has been expressed that, in the case of caseous pneumonic consolidation, absorption by resolution, with restoration of the affected lung to normal, is impossible; and that in the case of proliferative infiltrations of the usual kind it is more than unlikely. That is to say, it is reasonably certain that tuberculous lesions which undergo caseation or any material amount of fibrosis are not capable of absorption by resolution. In that case it follows that areas of consolidation which undergo absorption and leave little or no clinical or radiological trace, if they be in fact tuberculous, must be of a different character from those which pathologists recognise in fatal cases.

It has been suggested that these lesions may be of the nature of the so-called "gelatinous infiltration" of Virchow, which is probably the same condition as that described by Grancher in 1883 as "spleno-pneumonia." Kaufmann (1929) describes this condition as "an airless, grayish red gelatinous consolidation" in which microscopically "the most striking detail is marked congestion and especially exudation of serous and, to a less extent, fibrinous materials; cellular admixtures . . . are relatively sparse." These exudates are often very poor in tubercle bacilli and, in Kaufmann's opinion, do not necessarily undergo caseation and may disappear by absorption. Other authors have doubted this. Eliasberg and Neuland
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(1921), for example, were of opinion that an extensive gelatinous pneumonia always caseates. There is no doubt that at the periphery of every area of caseous pneumonia there is a zone of consolidation with sero-fibrinous and cellular exudate, not materially different from that described in "gelatinous infiltration," and that this exudation seems to be but a preliminary to caseation, and there is no type of pulmonary tuberculosis in which caseation is so rapid and extensive. Doubtless the onset of caseation depends in large measure upon the number of tubercle bacilli present, and in some cases bacilli may be very sparse in an exudate of this type. But it is certainly not at all usual to find at necropsy any large area consolidated with this kind of exudate and not showing a considerable amount of caseation.

During the course of the present study occasional cases of undoubted tuberculosis have been seen in which there was extensive consolidation in one or both lungs without caseation, cavitation or fibrosis, but in which the microscopic characters of the affected parts differed from those described as characteristic of "gelatinous infiltration." The macroscopic appearance of such parts, which might extend to a whole lobe, was greyish or reddish, uniform, not unlike that of acute lobar pneumonia, though less dry and "granular" on section; the part was airless, firm to the touch and not particularly oedematous. Microscopic examination (Fig. 32) showed the alveoli completely filled with large mononuclear cells, without either fibrin formation or any appreciable amount of serous fluid. The cells were either desquamated alveolar epithelium, or more probably histiocytes, or both. It was sometimes impossible to demonstrate either tubercle bacilli or other micro-organisms in sections prepared from lungs affected in this way; if present, tubercle bacilli were never numerous. The process is possibly the result of a "tuberculo-toxic" or allergic reaction. There is nothing in its histological character to render resolution impossible or even improbable. It does not seem to possess the tendency to rapid caseation manifested by the sero-fibrinous exudates of the more usual forms of pneumonic tuberculosis. That it may have some tendency to organisation is indicated by the occasional finding of intra-alveolar tubercles, sometimes with giant-cells, which may have progressed to the stage of fibroblastic proliferation. But although this fact is interesting because it affords grounds to regard the process as a specific
tuberculous one, there is no reason to suppose that organisation is an inevitable development. Over the greater part of the affected area it is usual to find the alveolar walls distinct, thickened only by swelling and free from fibrosis as well as from caseation.

It is of interest to record that, in a section of lung kindly sent to us by Dr H. C. Cameron, from the case of a child who died of tuberculous meningitis after an illness which corresponded in most essentials to “epituberculosis,” a large amount of the consolidation, which affected an extensive area of lung in the vicinity of a tuberculous focus, was produced by a mononuclear cell reaction, with occasional intra-alveolar giant-cells (Fig. 33), precisely similar to that found in our own cases. The experimentally produced epituberculous infiltrations described and illustrated in Oppenheimer’s paper appear to have had somewhat the same character. It seems possible, therefore, that at least in some cases this peculiar type of non-caseating and non-fibrosing tuberculous reaction may be the histological basis of “epituberculous infiltrations.”

Section 3: Widespread Disseminations.

Widespread dissemination of tuberculous disease throughout the lungs occurs in two distinct types of cases of which the pathogenesis is different. The widespread disease may be due to a local spread of infection within the lungs, arising from a primary lung lesion; or it may result from infection spread by the blood stream from a pre-existent focus which may or may not be in the lungs. The latter type, although not necessarily a result of a primary lung infection, is included in this study because, in common with other manifestations of miliary tuberculosis, it is peculiarly characteristic of the “childhood” or first-infection type of the disease, and because, in some of its forms, it is apt to be confused with other types of pulmonary tuberculosis.

(A) Disseminations arising from Spread within the Lungs.—These cases are those in which tuberculous infection originating in the lungs runs an unfavourable course, but in which the development of the local disease is not cut short by fatal metastatic lesions such as meningitis, and there proceeds to its final stages. The cases vary greatly in duration from the first onset to the final event, but the last phase is usually
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a more or less acute tuberculous broncho-pneumonia with cavitation, in which the principal channel of spread of infection is the bronchi. When examined post-mortem the disease is usually bilateral, but often of unequal extent and severity on the two sides. It is remarkable for how long a time it may remain confined to one lung, even in young children.

In an earlier section of this paper it was explained how, in the original primary lung focus and in the localised extensions which may develop from it, the walls of bronchi may become involved in a caseating process, cavities may form, and infective material be discharged into the air passages. As has been pointed out, this risk is present even in the case of the more chronic proliferative process, though doubtless less than in extensive caseous pneumonic lesions. It is, therefore, remarkable that examples of massive widespread tuberculous broncho-pneumonia are not more common than they are.

In this type of tuberculosis the approximate site of the original primary lung focus is often recognisable as a relatively chronic cavity, or an area of proliferative infiltration with more or less fibrosis; and also by the greater caseous enlargement of the regional lymph glands of the part. As is to be expected, in most cases it is evident that some amount of localised extension in the vicinity of the primary focus had occurred, and may have been present for some time before the disease became widespread; a fact which is often confirmed by clinical observation. Usually at the time of death the areas of caseous pneumonia have become confluent throughout a wide extent of the lung substance. The more severely affected lung may be completely solid but for numerous ragged and ramifying cavities (Figs. 10 and 19), and only in the more recently involved parts are there found small discrete patches of broncho-pneumonia. These are areas of exudative tuberculosis, of which the centre is formed by a bronchus or bronchiole, and the periphery by alveoli filled with sero-fibrinous and cellular exudate. The characteristic cells are of large mononuclear type, but polymorphs may be numerous in very acute cases. Caseation sets in early and involves the exudate, the walls of the central bronchus and the alveolar septa. The patches may correspond to the alveolar expansions of a terminal bronchiole, but often they consist of a ring of alveoli which surround a rather larger tube and have been infected by a spread through the caseating wall. The process
is thus in part a tuberculous peribronchitis. The obvious relation of the patches to the distribution of the bronchial tree is an essential feature (Fig. 18).

Very widespread tuberculosis of a really chronic type is not common in the lungs of children. Most of the chronic lesions which were seen post-mortem in the present series were strictly localised and of small extent. This is to be expected, as the chance of healing after the disease has become widely disseminated in the lungs is obviously slight in the case of the relatively non-resistant child. There are exceptions to this. In a case recently observed, the whole left lung was involved in a tuberculous process of an exceptionally chronic character, with formation of a vast cavity which destroyed almost the whole upper lobe. The disease was limited to the left side until the terminal phase, when an acute tuberculous broncho-pneumonia supervened in the right lung. In this case, however, the disease had characters resembling those of the adult type, and was probably a manifestation of reinfection. It is probable that most cases in which there are extensive chronic destructive lesions in the lungs are to be explained as examples of "adult type" tuberculosis in the child.

In the acute cases also, when there is severe and widespread pulmonary tuberculosis, the question arises of what part, if any, is played by repeated exogenous re-infection in the pathogenesis of the disease. Does the whole trouble arise from the progressive spread of infection from a single primary focus, or are new infections from without responsible for at least a part of the widespread dissemination? The question is difficult to answer with any certainty. On the one hand, it is often possible to trace, with at least a fair degree of plausibility, the progressive evolution of the pulmonary lesions from their origin in the primary focus. On the other hand, many children who develop this grave type of pulmonary tuberculosis have been exposed to the risk, or indeed the certainty, of repeated heavy infections, perhaps from a tuberculous mother or other member of the household. While some authorities doubt the occurrence of exogenous "super-infection" in persons who possess active tuberculous lesions, there is little doubt that continued residence in a heavily infected tuberculous environment does unfavourably influence the course of a child's illness. The effects of later infections are not the same as those of the first infection. The "primary
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complex” can apparently never be produced a second time in any individual. But it would be hard to find proof that new infections entering from the environment contribute nothing to the progress of the disease. Even if it were certain that they do not of themselves produce new foci, it is possible that they may do injury, after the manner of an overdose of tuberculin, by activating existing lesions.

(B). Disseminations resulting from Blood-Spread Infections.—For convenience of description these may be classed, according to duration, as acute and subacute or chronic milary tuberculosis.

(a) Acute milary tuberculosis in its characteristic and most acute form is seen in cases in which the miliary (blood-spread) infection coincides with the onset of tuberculous meningitis and death occurs within a month. The involvement of the lungs is but a part of a general dissemination of infection throughout the body, and the primary focus need not be pulmonary. The clinical character of the cases is not that of pulmonary tuberculosis, and in a study of that condition they are of little interest. The characteristic lesions are minute grey tubercles, in which caseation has barely begun, scattered more or less uniformly over all parts of the lungs (Fig. 20). Microscopically they occur in two forms. Sometimes they are sharply defined, typical, proliferative giant-cell tubercles; sometimes they are minute areas of exudative tuberculosis having the same microscopic features as patches of tuberculous broncho-pneumonia except that they do not form around a central bronchus. It is alleged that the allergic state of the patient and the heaviness of the miliary infection determine of which type the reaction will be in any given case, the exudative type being usual in a highly allergic patient with a heavy infection.

(b) Subacute or chronic milary tuberculosis is of greater interest from the point of view of pulmonary disease. Of this also there are two histological forms, proliferative and exudative, of which the latter is the more likely to give rise to clinical evidence of pulmonary tuberculosis. Both are found in cases in which the blood-spread infection has not been accompanied by the simultaneous development of tuberculous meningitis, and has not been severe enough itself to cause early death, so that time is afforded for the milary lesions to develop.
The proliferative foci have the same haphazard distribution which characterises acute miliary tubercles; they are more or less equally scattered throughout both lungs. They vary in number in different cases but are often less numerous than in the severer cases of acute miliary tuberculosis, and usually much less numerous than in cases of the exudative type to be described below. They are typical giant-cell tubercles, in which a considerable amount of fibrosis may develop, according to their age. They often form clusters, resembling the "staphyloid" arrangement which is generally held to be characteristic of lymph-spread tuberculosis in the lungs (Fig. 17). This is due to the fact that, in course of time, "satellite" tubercles arise around the focus which originally formed where the blood-borne bacilli alighted (Fig. 31). Further, infection may spread from this original "blood-spread" focus into the nearest lymphatics, which are never far away, so that many of the satellites form in the position of lymph paths (peribronchial, perivascular, etc.). Thus the resemblance to a lymph-spread infection becomes very close. It is probable that many cases of this kind, where there are numerous "staphyloid" clusters of tubercles widely disseminated throughout both lungs, have been mistaken for examples of lymph-spread infection on account of this resemblance; and that this misconception has helped to perpetuate the theory that tuberculous infection can pass freely in retrograde fashion along the lymph vessels from the root glands to all parts of the lungs. In the many cases of this type in which both lungs are similarly affected but the root lymph glands are involved only on one side or not at all (e.g. when the primary focus is extrathoracic), the idea that the "staphyloid" tubercles in the lungs are entirely the result of lymph-spread infection is obviously incorrect.

Lesions of this type can be numerous and widespread in the lungs without giving rise to physical signs detectable on clinical examination. This is because most of the lesions are shut off by tissue proliferation from communication with the air passages, and the alveoli surrounding and separating them are free from exudate and fully aerated.

The exudative foci in certain cases, not excessively uncommon, give rise to a notable form of pulmonary tuberculosis. The lungs are not necessarily the site of the primary lesions, but they usually are, probably because the close connection of
the tracheo-bronchial lymph glands with the venous blood stream makes them a frequent source of heavy blood infections. The appearance of the lungs is striking. They are voluminous and heavy and contain little air. In every part they are studded with innumerable caseous foci, which vary in size from a pin-head to perhaps half a centimetre in diameter in different cases, but are often fairly uniform in any one case (Figs. 11 and 21). The condition is always bilateral and of practically equal severity in the two lungs. Each caseous focus is surrounded by a greyish zone of consolidation, and these may coalesce and exclude air from a large area; but any extensive confluence of the caseous centres is unusual. Cavity formation is rare; when it occurs in this type of case the cavities are usually small excavations along the walls of bronchi, quite different from the large ragged cavities of caseous broncho-pneumonia. The root and tracheo-bronchial lymph glands are infected but are usually not grossly enlarged or completely caseous, unless they were previously affected by participation in the "primary complex." In other organs foci resulting from blood-spread infection are present and are of a size and type comparable to those in the lungs. The spleen in particular is much enlarged and studded with big caseous tubercles.

Microscopically, the lung lesions are typical exudative tubercles, the centre being caseous, the periphery formed of alveoli consolidated with sero-fibrinous and cellular exudate. Both macroscopic and microscopic appearances thus resemble those of tuberculous broncho-pneumonia, and cases of this type are often wrongly included in that category. Only a careful study of the distribution of the tubercles reveals their true nature. They do not bear the constant relation to a central bronchus which is the essential feature of broncho-pneumonia; their distribution is that of other types of miliary tubercles, though their larger size makes this less obvious. The microscopic picture is further complicated by the fact that the walls of bronchi may become involved in caseation spreading from a nearby focus; infected material may thus enter the bronchus and pass to other branches, adding true broncho-pneumonic lesions to those resulting from the blood-spread infection (Fig. 30). This process is met with even in cases of acute miliary tuberculosis, when the foci are of exudative type. It plays a much more important rôle in the
longer-standing cases, when the lesions caseate more extensively and time is afforded for bronchial spread. It affords one reason why so often the lungs are much more heavily involved than the other organs, such as the spleen, in which the infection, brought by the blood, finds no such supplementary channels of spread within the organ. It is responsible for such cavitation as occurs in this type of case. In their terminal stages, therefore, these cases present a combination of miliary and broncho-pneumonic lesions, but their pathogenesis is quite different from that of tuberculous broncho-pneumonia due directly and entirely to air-passage spread of infection. Therefore it is desirable to separate them from the latter by including them, as cases in which the essential mode of spread is by the blood, in the category of miliary tuberculosis.

Distinctive features of this type of case are the following: both lungs and all parts of each lung are uniformly involved; the tubercles are of exudative type, but are not essentially related to bronchi (except in the case of secondary broncho-pneumonic lesions); there is no advanced open lung lesion to which the disseminated foci are obviously secondary, as there usually is in true tuberculous broncho-pneumonia; there are caseating tubercles of corresponding age and type in other organs.

These cases vary greatly in duration. There may be only a brief illness lasting two or three weeks and resembling acute broncho-pneumonia rather than tuberculosis, but most cases run a longer course. A child may live for some months after the lungs have been proved by X-ray examination to be involved in widespread disease of this kind, and even in such a case there may be no massive confluence of caseous areas and no cavity formation. It is, however, unlikely that recovery, or even a temporary arrest of the disease, could occur.

Summary.

A pathological study is presented in which the results of primary tuberculosis in the lungs of children are described and illustrated.

The impression that tuberculosis of the lungs is uncommon in childhood is erroneous and is due to the fact that in many cases the lung lesions do not become clinically manifest, or are overshadowed by the results of secondary spread.
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In fatal cases of tuberculosis in children the primary lesions are found in the lungs more often than in any other site.

The development of tuberculous disease in the lungs following a first infection is described in three stages: (1) the primary lung complex; (2) localised extensions; (3) general disseminations.

The anatomical characters of the primary lung complex are described. The origin of the primary lung focus and its relation to infected regional lymph glands are discussed.

Localised extensions of the primary lung complex arise either from the lung focus or from the lymph glands. Their modes of origin and their histological characters are discussed. The problem of “epituberculosis” is considered and some suggestions as to the pathological characters of the infiltrations are made.

Widespread dissemination of tuberculosis in the lungs is due either to bronchial or to blood spread. The distinctive pathological features of each type are discussed.

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REFERENCES.


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DESCRIPTION OF FIGURES.

FIG. 6.—Primary lung complex. Primary focus in lower lobe, a caseous nodule with satellite tubercles. Line of lymph-spread infection marked by a row of tubercles passing towards root. Two intrapulmonary root glands enlarged and caseous.

FIG. 7.—Primary lung complex. Primary focus in left lower lobe, a small caseous nodule with satellite tubercles. Gross caseous enlargement of root glands and inferior and superior tracheo-bronchial glands on left side, and of one right superior tracheo-bronchial gland.

FIG. 8.—Primary lung complex. Primary focus (A) in left upper lobe. Massive caseous enlargement of left root and inferior tracheo-bronchial glands, and of superior tracheo-bronchial and paratracheal glands on both sides. Terminal miliary tuberculosis of exudative type.

FIG. 9.—Primary cavity (excavated primary focus) in upper lobe, surrounded by a small area of "proliferative infiltration." Small caseous root glands. Subacute disseminated haematogenous tubercles.

FIG. 10.—Confluent tuberculous broncho-pneumonia with multiple acute cavities.

FIG. 11.—Subacute miliary tuberculosis of exudative type. Soft exudative tubercles simulating tuberculous broncho-pneumonia, distributed uniformly throughout the lung.

LARGE LUNG SECTIONS.

FIG. 12.—Early primary lung complex. Primary focus in lower lobe. Early caseous enlargement of root glands. Small tubercles in lymphatics forming rows passing between primary focus and glands.

FIG. 13.—Primary lung complex. Very small primary focus (A) in right lower lobe. Caseous enlargement of root glands and of inferior and superior tracheo-bronchial glands. Terminal miliary tuberculosis. (Upper lobe and much of lower lobe omitted from section.)

FIG. 14.—Localised extension of exudative type. A roughly wedge-shaped area (A) in upper lobe, extending from root to pleura, is consolidated with caseous pneumonia. Probably caused by massive infection of a large bronchus by rupture of a root gland or caseous lung focus. Terminal acute miliary tuberculosis.

FIG. 15.—Localised extension of proliferative type. A broad band of tuberculous granulation tissue passes across middle of upper lobe from root to pleura. The scattered patches of consolidation near the apex are terminal non-tuberculous broncho-pneumonia.

FIG. 16.—Localised extension from root glands. A group of caseous glands lies deep in root and is continuous with a mass of tuberculous granulation tissue in adjacent lung substance. Primary focus (not shown in section) was at base of lower lobe. Terminal acute miliary tuberculosis.

FIG. 17.—Massive tuberculous infiltration of proliferative type affecting whole of right upper lobe. Primary cavity at apex, opening on pleural surface. Caseous glands at root. Subacute haematogenous tubercles with "staphyloid" arrangement in lower lobe.

FIG. 18.—Acute tuberculous broncho-pneumonia with large acute cavity at apex, confluent consolidation of upper lobe, and small discrete patches (bronchial spread) in lower lobe. Enlarged caseous tracheo-bronchial glands.
Fig. 19.—Tuberculous broncho-pneumonia with massive confluence over whole lung. Primary cavity in lower lobe. Small recent cavities at base. Very large caseous inferior tracheo-bronchial gland.

Fig. 20.—Acute miliary tuberculosis. Small sharply defined foci uniformly distributed all over lung.

Fig. 21.—Subacute haematogenous tuberculosis of exudative type. Relatively large caseous foci surrounded by exudate, diffusely distributed in all parts of lung. Enlarged caseous glands in root.

Photomicrographs.

Fig. 22.—Primary lung focus. A small, sharply defined caseous nodule surrounded by tuberculous granulation tissue and satellite tubercles. It is near the pleura, which shows a fibrous adhesion. (×4.)

Fig. 23.—Primary lung focus. A well-defined caseous nodule with a few satellites. Tubercles surrounding a vein passing towards the root mark the line of spread of infection. (×4.)

Fig. 24.—Primary lung focus and lymph spread. Small caseous nodule with satellites. Tubercles in peribronchial and perivascular lymphatics form a distinct “line of infection.” (×4.)

Fig. 25.—Early primary cavity and incipient proliferative extension. The cavity is an excavated primary focus. Surrounding lung substance consolidated by tuberculous granulation tissue which forms strands passing out from cavity, suggesting lymph spread. (×4.)

Fig. 26.—Primary lung focus, partially calcified. To show intimate relation of focus to a bronchus (A). (×12.)

Fig. 27.—Subpleural primary focus. Caseous plaque on pleura overlying it. (×6.)

Fig. 28.—Edge of relatively early primary lung focus, showing part of caseous centre and zone of granulation tissue separating it from aerated alveoli. (×70.)

Fig. 29.—Caseous centre of primary lung focus. Alveolar walls and network of fibrin in consolidated alveoli clearly distinguishable, indicating exudative character of the original tuberculous process. (×100. Stain: Azan.)

Fig. 30.—“Soft” or exudative miliary tuberculosis. A small bronchus invaded from without and filled with caseous debris. To illustrate origin of secondary tuberculous broncho-pneumonia in cases of haematogenous tuberculosis. (×50.)

Fig. 31.—Subacute haematogenous tubercle in lung surrounded by a cluster of satellite tubercles of more recent origin, producing “staphyloid” appearance. From a case of primary abdominal tuberculosis without involvement of thoracic lymph glands. (×20.)

Fig. 32.—Area of lung consolidated with large mononuclear cells and intra-alveolar giant cells, without caseation or fibrosis. This may be the histological character of “epituberculous infiltration.” (×110.)

Fig. 33.—Section from Dr Cameron’s Case of epituberculosis. Consolidated area adjacent to tuberculous focus. Alveoli filled with large mononuclear cells; intra-alveolar giant cells; no caseation or fibrosis. (×110.)
Tuberculosis of the Central Nervous System, with Special Reference to Tuberculous Meningitis

BY

A. R. MACGREGOR AND C. A. GREEN

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TUBERCULOSIS OF THE CENTRAL NERVOUS SYSTEM, WITH SPECIAL REFERENCE TO TUBERCULOUS MENINGITIS.*

A. R. MACGREGOR and C. A. GREEN.

From the Departments of Bacteriology and Child Life and Health, Edinburgh University.

(Plates LXXXI.-LXXXIII.)

Part I. Bacteriology.

Interest in the bacteriology of tuberculous meningitis is centred mainly in the determination of the incidence of the human and bovine types of tubercle bacillus in these cases. In 1934, Griffith, surveying a series of 251 cases collected over a period of 30 years from England and Scotland, noted the relative proportions of human and bovine type infections to be 73.3 and 26.7 per cent. respectively. In Scotland the bovine incidence was 40.5, in England 24.3 per cent. In 1936 Griffith and Menton recorded that 5 of 12 cases investigated in Staffordshire were of bovine origin, while Blacklock and Griffin (1935) found this type in 18 per cent. of 72 cases in the West of Scotland. Munro and Scott (1936) recorded the bovine incidence in a series of 50 cases occurring in the East of Scotland to be 36 per cent. The regional variation in the proportional incidence of the two types is thus seen to be marked, and as it is probably an index of the state of milk supplies, the results of all similar enquiries should be fully recorded. Further points dealt with in this section include the relation of type of

* Since 1933 a combined bacteriological, pathological and clinical investigation of certain problems related to tuberculous meningitis has been carried on in Edinburgh. For the sake of completeness the enquiry included as many cases as possible from the principal hospitals in this district, which serve the south-east of Scotland. During the first eighteen months the bacteriology was done by Dr H. J. R. Kirkpatrick; on his departure it was taken over by Dr C. A. Green. Dr Kirkpatrick's results were published in a preliminary communication by Macgregor, Kirkpatrick and Craig (1933) and, except when expressly stated, they are not included in the results given in the bacteriological section of this paper. Results of the pathological studies given in that communication are included in the pathological section of this paper, and the bacteriological findings referred to in that section include Dr Kirkpatrick's cases. The clinical side of the investigation was in the hands of Dr W. S. Craig, who also performed some of the necropsies. Unforeseen circumstances have caused publication of the clinical study to be postponed. This paper presents the results of the bacteriological and pathological investigations.
bacillary infection to age-group incidence and to the site of primary infection.

Methods.

Guinea-pig inoculation. The presence of blood or coagulum in each specimen was noted. If less than 5 c.c., the entire volume was injected subcutaneously into the left groin of a single guinea-pig. Repeat specimens were each inoculated into a fresh guinea-pig. Inoculated animals were examined at weekly intervals and killed when enlargement of the inguinal glands had progressed sufficiently, and before ulceration could occur. If no evidence of infection was noted the animal was kept for a period of three months and then killed. Absence of lesions at necropsy was recorded as a negative result. Animals dying as a result of intercurrent infection within 14 days of injection and failing to show either macroscopic or microscopic evidence of tuberculosis were recorded as "no result."

The distribution of macroscopic lesions was noted in positive animals and pus from the inguinal glands draining the site of injection was taken for microscopic examination and culture. In no instance was spontaneous tuberculous infection found in the test animals.

Culture from guinea-pig gland pus. Sterile saline was added gradually to the gland pus to form a uniform thick suspension and to this was added an equal volume of 6 per cent. HCl. After 30 minutes' acid treatment at room temperature the reaction was made neutral to litmus by the addition of 4 per cent. NaOH. The deposit following 20 minutes' centrifugation at 3000 r.p.m. was inoculated by pipette on two tubes each of (1) Löwenstein-Jensen, (2) Dorset egg and (3) glycerol egg media. The cultural appearances were noted after 4 weeks' incubation at 37° C. and, if required, the strain was then used for rabbit inoculation.

Direct culture. Later in the investigation an attempt was made to ascertain the value of direct culture in the detection of tubercle bacilli in cerebro-spinal fluid. As before, the presence or absence of blood or coagulum was noted and the specimen was then thoroughly shaken in a test tube until any coagulum present was well broken up if not entirely dispersed. Half the volume was then taken for guinea-pig inoculation as above, while the remaining half was centrifuged at 3000 r.p.m. There was a considerable risk that many of the specimens contained organisms other than tubercle bacilli. To eliminate possible contamination the specimen was centrifuged at 3000 r.p.m. for 30 minutes and the clear supernatant fluid pipetted off, leaving 1 c.c. in which any deposit was resuspended. To this was added 1 c.c. of 6 per cent. HCl, the mixture thoroughly shaken and, after being left at room temperature for 15 minutes, made neutral to litmus by the addition of 4 per cent. NaOH. The treated specimen was again centrifuged, the bulk of the supernatant fluid poured off and a thick suspension of the deposit inoculated on culture media as before. The cultures were examined at intervals of 3 days and the date of the first appearance of distinct growth noted. After 4 weeks' further incubation at 37° C. the cultural characters on all media were finally described.

Rabbit inoculation. The final differentiation of strains into human and bovine groups was made by rabbit inoculation. In the rabbit test either the direct culture from the cerebro-spinal fluid or the guinea-pig gland culture was used, depending on which proved the most suitable. In practically all cases which were positive on direct culture, this growth was used for the determination of virulence.

Between 5 and 10 mg. of a 4-weeks-old culture was emulsified in an agate mortar, sterile saline being added slowly in the proportion of 1 c.c.
TUBERCULOUS MENINGITIS

Inoculated films from containing approximately by to every 1 mg. of culture in order to secure as fine a suspension as possible, by no means always an easy process. The test rabbits were all fully grown adults and each was injected intravenously with 0·1 c.c. of the emulsion containing approximately 0·1 mg. moist weight of culture. At the same time, tubes of Löwenstein, Dorset egg and glycerol egg were inoculated from the same suspension. Each animal was kept in a separate cage to avoid the risk of cross infection and killed at the end of eight weeks if the virulence of the strain was not such as to cause death before that time. At autopsy the distribution of macroscopic lesions was noted and microscopic examination of films from the lesions was carried out to confirm the presence of tubercle bacilli.

In the event of a rabbit dying before the eighth week without any of the generalised lesions of the bovine type of infection, the test was repeated with the subculture prepared at the time of the first rabbit injection. The appearance of these subcultures after 4 weeks’ incubation at 37°C. proved a useful confirmation of the growth characteristics of the strain.

Results of guinea-pig inoculation.

Specimens of C.S.F. were injected into guinea-pigs from 141 subjects and in 80 of these one or more of the fluids produced tuberculous lesions in the inoculated animals, while in 61 the guinea-pigs died of intercurrent infection or were negative at autopsy three months after injection. Of the positive series, single specimens of fluid were received from 40 cases. Two specimens were injected from each of 36 cases and in 28 of these both inoculated animals became infected: in 6 of the remaining 8 of these double-specimen cases one animal was positive and the other died within 14 days of infection without the appearance of lesions; in 2 cases, one guinea-pig was infected and the other remained healthy even after three months. In one of the latter cases the negative specimen was withdrawn two days before and in the other case two days after the positive fluid. From 4 cases three specimens of fluid were available: in one case all three specimens were positive; in two instances two specimens were positive; in one case only one specimen was positive. It will be seen therefore that in 69 cases which comprised the 40 single-specimen cases, the 28 double-specimen cases with positive results, and the one triple-specimen case in which all three animals were positive, the examination of a single specimen was sufficient to establish the bacteriological diagnosis, but in the remaining cases two or more specimens were required. In the 6 double-specimen cases in which one of the inoculated animals died of intercurrent infection, this difficulty might have been obviated by the use of two animals to each specimen. Nevertheless five specimens of fluid were encountered which gave negative results although specimens taken from the same case a few days preceding or following the removal of the negative specimen were found positive. These facts serve to
emphasise the importance of the examination of multiple specimens if these are available in a doubtful case.

Results of direct culture.

The eugonic human type of tubercle bacillus was cultured from 42 specimens of cerebro-spinal fluid taken from 27 cases. The relative value of the different media used is indicated in table I.

Table I.

Results of direct culture on various media of cerebro-spinal fluid from cases of tuberculous meningitis.

<table>
<thead>
<tr>
<th>Strains</th>
<th>Result of culture on</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L.</td>
</tr>
<tr>
<td>Human type</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
</tr>
<tr>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>16</td>
<td>+</td>
</tr>
<tr>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Bovine type</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>


Successful results were obtained in all 42 specimens on Löwenstein-Jensen medium, in 25 specimens with glycerol egg and in 16 with Dorset egg medium. On the Löwenstein-Jensen medium the growth of the human type was heavy and luxuriant, the colonies being dry and mammillated and pale yellow to golden brown in colour. The period of incubation at 37°C at which a growth visible to the naked eye first appeared varied considerably. No growths were readily seen in the first 10 days; from 11 to 14 days 3 strains appeared; from 15 to 18 days 11 strains; from 19 to 22 days 13 strains; from 23 to 26 days 13 strains; and from 26 to 30 days 2 strains. The majority of cultures of this type appeared between the 15th and 26th days, the shortest and longest incubation period being 11 and 28 days respectively.

The dysgonic bovine type was isolated from 6 specimens from 6 cases; the results are included in table I. Dorset egg and Löwenstein media were successful in 5 and 4 specimens respectively of this limited series. The cultural appearances of the bovine strains on the Löwenstein medium were in marked contrast to those of the human type, the growth consisting of small, smooth, hemispherical colonies, with moist, glistening surface and pale yellow to almost white in colour.
Results of direct culture compared with those of guinea-pig inoculation.

In this series five guinea-pigs dying within 2 weeks of inoculation were discarded as giving no result. From the remaining 54 cases in which both methods of isolation were attempted, 38 specimens (32 human, 6 bovine) gave positive results in both tests, and 16 (12 human, 4 bovine) were positive on animal inoculation but negative on culture. In no case was the animal inoculation test negative and direct culture positive. But in view of the possibility of the loss through intercurrent infection of inoculated animals, the maximum number of positive results is to be secured if both methods of isolation are practised in every case. Positive results in direct culture are secured within 2 or 3 weeks, at which period only a presumptive result can be given by the animal method, depending on the degree of enlargement of the regional lymph glands. A further advantage of direct culture is the immediate recognition of bacillary type by the cultural appearances.

Results of rabbit inoculation.

Using the above methods 80 strains of tubercle bacilli were isolated in all from the cases examined. Of these 61 proved to be relatively avirulent for rabbits while 19 were highly virulent. Two strains were encountered which grew luxuriantly on glycerinated media and in this respect resembled the human type, but on animal inoculation were found by repeated tests to be highly virulent for rabbits. The virulence test in rabbits being taken as the final criterion, the incidence of the two types of tubercle bacillus in the series was: human 76 per cent., bovine 24 per cent.—figures almost identical with those given by Griffith for England and Scotland together.

Type of bacillary infection in relation to age-group incidence.

To make the following sections more complete, 50 typing results obtained by Dr J. R. Kirkpatrick have been combined with 73 of the present group for whom clinical data were available. The first decade of life was the period of greatest frequency for the onset of tuberculous meningitis in the series examined (chart 1). Considering this period more closely, only two cases, both of human type, were below 6 months of age. In the second 6 months 17 cases occurred, the highest figures for any similar period. The incidence in the second year of life, 18 cases, was roughly half that in the second 6 months. Approximately the same number of cases were spread over the next 3 years, i.e. age period 2-4 years inclusive, as in the first 2 years, indicating a further fall in the yearly incidence.
That the greatest risk of tuberculous meningitis is in the first 5 years of life is illustrated by the total of 73 cases for that period, as contrasted with 24 cases for the second half decade. Cases were scattered with diminishing frequency throughout subsequent decades, the oldest patient being aged 64 years. In the age groups 0-4 years and 5-14 years, the incidence of bovine infection was 30.1 per cent. and 21.2 per cent. respectively, again almost equalling the corresponding figures of 31 per cent. and 23 per cent. given by Griffith.
Type of bacillary infection in relation to site of primary infection.

The data available for consideration on this point were used to construct chart 2. From this it will be seen that in 82.2 per cent. of 73 cases in which the organism isolated from the central nervous system was of human type, the primary focus of infection was intrathoracic. In 13.7 per cent. this type of infection had developed from an initial focus in the abdomen, in 1.4 per cent. from cervical glands, while in 2.7 per cent. it could not be stated whether the abdominal or thoracic lesions were of longer standing. The bovine type of organism was isolated from 37.5, 56.3 and 6.2 per cent. respectively of thoracic, abdominal and cervical primary foci. Reviewing this figure from another aspect table II indicates that 90.9 and 9.1 per cent. respectively of the primary thoracic cases terminating in tuberculous meningitis were caused by human and bovine type infections. Primary abdominal cases, only 19 of which were noted, were divided almost equally between the two types. These figures again draw attention to the probable origin of our bovine cases of tuberculous meningitis. Another interesting point
revealed by this survey is that of the 16 cases of bovine infection encountered, 6 were apparently of primary thoracic origin.

**Table II.**

*Site of primary focus in relation to type of bacillary infection.*

<table>
<thead>
<tr>
<th>Site of primary focus</th>
<th>No. of cases</th>
<th>Type of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Human.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Per cent.</td>
</tr>
<tr>
<td>Thoracic</td>
<td>66</td>
<td>60 (90.9)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>19</td>
<td>10 (52.6)</td>
</tr>
<tr>
<td>Cervical</td>
<td>2</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Thoracic or abdominal</td>
<td>2</td>
<td>2 (100.0)</td>
</tr>
</tbody>
</table>

**Type of bacillary infection in relation to distribution of cases.**

Finally we have noted the incidence of the two types of infection in relation to the urban or rural distribution of the cases. Griffith and Smith (1935), in noting the exceptionally high proportion of bovine thoracic cases of tuberculosis in the north-east of Scotland, have indicated that this is in the main due to cases occurring in rural districts, where a much higher proportion of non-pasteurised milk is taken as compared with the city. Our own figures are too few on which to generalise but they do lend support to Smith's findings. Thus 61 or 98 per cent. of 62 cases from which the human type of bacillus was isolated from the C.S.F. were town-dwellers compared with 75 per cent. of 29 bovine type cases (table III). Of the 8 cases occurring in rural dwellers 7 were bovine and 1 human.

**Table III.**

*Distribution of human and bovine type cases.*

<table>
<thead>
<tr>
<th></th>
<th>Town.</th>
<th>County.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human type</td>
<td>61 (98 per cent.)</td>
<td>1 (2 per cent.)</td>
</tr>
<tr>
<td>Bovine type</td>
<td>22 (75 per cent.)</td>
<td>7 (25 per cent.)</td>
</tr>
</tbody>
</table>

**Summary of part I.**

1. The ideal method for the isolation of tubercle bacilli from the cerebro-spinal fluid is the utilisation of both direct culture and guinea-pig inoculation.

2. If direct culture is adopted, Löwenstein-Jensen medium is likely to be of more service than the routine media more commonly used.
3. Animal inoculation yields a larger proportion of positive results than direct culture, but considering the individual case, determination of the result is much slower, taking 4-6 instead of 2-3 weeks.

4. In a series of 80 cases of tuberculous meningitis the infecting organism was found to be of the human type in 76 per cent, and of the bovine type in 24 per cent.

5. Of these cases 2 per cent. occurred in the first 6 months of life, 14 per cent. in the first year and 81 per cent. within the first decade.

6. The human type of organism was responsible for 91 per cent. of primary thoracic cases terminating in tuberculous meningitis, the bovine type for 9 per cent. By contrast, the two types were responsible for approximately equal numbers of cases terminating in meningitis with an initial focus of infection in the abdomen.

**Part II. Pathology and pathogenesis.**

Interest in the pathogenesis of tuberculous meningitis was reawakened by the publication in 1933 by Rich and McCordock of observations which seemed to disprove the generally accepted doctrine and suggested a new conception. Previously it had been almost universally believed and taught that tuberculous meningitis was usually the direct and immediate result of acute miliary tuberculosis, and that it was only in occasional cases that an older tuberculous focus in or in close relation to the central nervous system was responsible for infection of the leptomeninges.

Rich and McCordock were dissatisfied with this explanation on the grounds that tuberculous meningitis and acute miliary tuberculosis often occur independently of each other, and that in experimental animals intravenous injection or even injection into the carotid artery never produced an immediate tuberculous meningitis, although acute miliary tuberculosis was constantly produced. They expressed the opinion that in acute miliary tuberculosis the number of bacilli set free in the subarachnoid space is very small, insufficient to evoke the intense exudative reaction which is characteristic of tuberculous meningitis and capable of producing only circumscribed tubercles in the meninges or brain. They advanced evidence to show that direct introduction of tubercle bacilli into the subarachnoid space produced in experimental animals a diffuse exudative meningitis resembling in all particulars the natural disease. They also claimed to have proved that in the human subject the development of tuberculous meningitis depends on the escape into the subarachnoid space of large numbers of bacilli from a pre-existent focus, by demonstrating in almost all of a large number of human brains the existence of caseating tuberculous lesions, in or in close relation to the central nervous system, which had discharged into the subarachnoid space or ventricles. The focus responsible for the meningeal infection was most often a caseous nodule superficially situated in the brain substance, but it was sometimes in the meninges or in an adjacent bone.

Certain other workers who, since the publication of the observations of Rich and McCordock, have pursued the same line of enquiry, examining human brains by the same method, have not produced the same results.
Ragins (1935-36) examined 47 brains from tuberculous subjects, 39 of whom died of tuberculous meningitis, and concluded that of the 39, 82.05 per cent. seemed to have been due to direct haematogenous spread and only 17.95 per cent. gave indication that older lesions in the central nervous system had caused the diffuse infection of the meninges. Radmann (1935), who examined 10 brains from typical cases of tuberculous meningitis, found that 3 cases supported Rich and McCordock's conception while the remainder failed to do so, and he concluded that the new conception holds good in cases of tertiary tuberculosis, but that in the primary stage meningitis occurs as a direct result of blood-borne infection without prior formation of "solitary tubercles."

In view of such divergent opinions it is desirable that further observations should be recorded by independent workers. The present study is intended to be a contribution towards the solution of this problem and of certain other problems which arise out of the new conception of the pathogenesis of tuberculous meningitis.

If the view of Rich and McCordock is right, even in a substantial proportion of cases, it follows that many victims of tuberculous meningitis have, at some time prior to the onset of meningitis, suffered an infection of the central nervous system by tubercle bacilli, which did not immediately give rise to diffuse meningitis but produced a localised lesion which subsequently infected the meninges. It was felt, therefore, that an investigation confined to the examination of typical cases of tuberculous meningitis would be incomplete. For this reason there were included in the study not only cases of declared and proved tuberculous meningitis, but also cases of active tuberculosis affecting any part of the body, in which there was no clinical evidence of involvement of the central nervous system and in which meningitis was not found at necropsy. The investigation of these cases included examination of the brain and spinal cord for "Rich foci" and, as often as possible, examination of the cerebro-spinal fluid by microscopic, cultural and biological methods for the presence of tubercle bacilli.

Further, as it seemed possible that the occurrence of the first infection of the central nervous system, which sets up localised lesions, might occasionally be marked by symptoms or signs of cerebral or meningeal injury or irritation, an attempt was made to demonstrate the presence of tubercle bacilli in the cerebro-spinal fluid of patients who presented such symptoms and signs, of a transient character and not followed by the development of fatal tuberculous meningitis, and who reacted to the tuberculin skin test.

The material included in this study was as follows.

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>88</td>
</tr>
<tr>
<td>Tuberculosis without meningitis</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>112</strong></td>
</tr>
</tbody>
</table>
Cerebro-spinal fluids examined for tubercle bacilli.

<table>
<thead>
<tr>
<th>Meningitis (post-mortem cases)</th>
<th>73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis without meningitis (post-mortem cases)</td>
<td>20</td>
</tr>
<tr>
<td>Reactors who survived or did not die of tuberculous meningitis</td>
<td>45</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>138</td>
</tr>
</tbody>
</table>

Method of investigation of post-mortem cases for the presence of localised foci of tuberculosis in or closely related to the central nervous system.

This part of the study included the complete examination of 112 brains of tuberculous subjects, *i.e.* from 88 cases of tuberculous meningitis, in 10 of which the meningitis was at a very early stage, and 24 cases in which no exudative meningitis was found at necropsy, though some of them exhibited localised tubercles in the meninges or brain substance. In the great majority of cases the necropsy was performed by or in the presence of one of us (A. R. M.), or by Dr W. S. Craig. The necropsies were as complete as possible and included examination of the ears and other possible sources of infection in the skull and, whenever practicable, of the spinal canal and its contents. Attention was paid to the presence and severity of any accompanying miliary tuberculosis, and in all cases in which a complete necropsy was made microscopic sections of representative organs were examined to confirm the macroscopic observations on this point and to determine the type of the miliary tubercles.

The detailed examination of all the brains was carried out personally by one of us (A. R. M.). The method advocated by Rich and McCordock for the detection of foci antecedent to meningitis was followed. The brains were hardened by being suspended in Kaserling's fluid for one month or more. They were then cut in thin slices, which were examined for nodules in the substance or deposits in the meninges which appeared to be older than the diffuse meningitis, when such was present, or for the presence of any evidence of tuberculous infection when meningitis was absent. The free-hand method of cutting was employed, using a long thin-bladed knife. With practice it was possible to cut slices of almost even thickness, not more than 2-3 mm. thick. As the nodules which it was desired to find were often very small, thin sections were essential. It was found best as a rule to cut the slices in the coronal plane.

Very small nodules in the substance were sometimes difficult to see as their colour was not in sharp contrast to that of the brain tissue. They could be detected more readily by holding the thin slices up against a strong light. Often they were detected by touch, their relatively firm consistence making them easy to feel even when very small.

Deposits in the meninges representing infection of longer standing than the diffuse meningitis were more difficult to recognise than nodules in the substance. The mere quantity of tuberculous exudate which may be present at any given point gives no indication of the duration of the pathological process there. The more chronic meningeal deposits were distinguished from recent exudate by their yellower colour and firmer consistence. Often their detection depended on touch rather than sight, owing to their firmer consistence. It was always necessary to confirm macroscopic impressions of greater chronicity by microscopic examination. The difficulty of detection was increased by the fact that these older meningeal deposits were often situated in deep fissures and buried in masses of recent exudate.

Although every precaution was taken to make the search exhaustive,
it is not possible to claim that nothing was overlooked. Much care and patience are required if reliable information as to the frequency of these lesions is to be obtained, but short of microscopic examination of the whole brain in serial section, it is not possible to avoid all risk of missing some of them.

In all cases microscopic sections were made from the meninges at the base of the brain, from any nodule in the substance which was so placed as to be a possible source of infection of the meninges or cerebro-spinal fluid, from any deposit in the meninges which was suspected to be older than any diffuse meningitis present and from portions of the choroid plexus. In all cases when the spinal cord was available it was included in the microscopic examination.

Results of examination of 88 brains with tuberculous meningitis.

Foci of tuberculous infection antecedent to the exudative meningitis were found in 74 of these 88 brains. In addition, in 4 cases in which no older foci were found in the central nervous system, tuberculous disease of the spine was present. Thus in 78 (88.6 per cent.) of the 88 cases tuberculous foci antecedent to the meningitis were shown to be present in or in close relation to the central nervous system. The situation of these foci was as follows.

| Foci originating in substance of brain or cord | 18 cases |
| Foci originating in meninges | 32 " |
| Foci situated both in substance and in meninges | 24 " |
| Foci situated in the spine | 4 " |

In 10 cases no tuberculous focus older than the diffuse meningitis was found in any situation from which a direct spread to the meninges or cerebro-spinal fluid could possibly have occurred.

From these results it may be concluded that in the great majority of cases tuberculous meningitis does not arise as an immediate result of the first arrival of tubercle bacilli in the central nervous system, but is preceded by a limited infection which produces only localised lesions. Proof that antecedent foci of the type discovered are actually the source of the exudative meningitis requires more precise evidence. Foci situated deep in the substance of the brain and those which, though superficially placed, are very chronic and encapsuled by fibrous tissue, or over which the meninx shows no active exudative inflammation, are unlikely to be responsible for the meningitis. Those situated near the meningeal surface, in contact with the meninges, showing no fibrous encapsulation and surrounded by recent exudate, may be accepted as a very probable source. Only in those cases in which it can be clearly demonstrated that the meningitis has spread out from a focus, or that a focus has discharged directly into the cavity of a ventricle, can it be regarded as certain that the focus is the source of the meningitis.

When these rules are applied to the 78 cases in which foci were found, the result is as follows. In 10 cases, owing to the position
of the foci in the brain, or their character, or the lack of recent exudate in relation to them, it was not permissible to regard any of the foci which were discovered as the source of the meningitis. In 3 of the 4 cases of spinal tuberculosis a full examination of the spine and cord was not made, so that the origin of the meningitis from the spinal lesion can only be conjectured; in the fourth case infection of the spinal meninges from the vertebral lesion was clearly traced. Of the 64 remaining cases, in which older foci were present in the brain or meninges, their causative relation to the meningitis was very probable in 6 and practically indubitable in 58.

Thus the origin of the exudative meningitis from an older focus in or in close relation to the central nervous system was conclusively demonstrated in 59 (67 per cent.) of the 88 cases and in a further 6 it was extremely probable, making 65 (74 per cent.) in all. In the remaining 23 cases (26 per cent.) a local origin of the meningitis was not established. In 3 of these the most likely source was spinal tuberculosis. In 10 others, foci antecedent to the meningitis were found in the brain or meninges, but the origin of the meningitis was not traced to them. In the remaining 10 no older foci were found.

Among the 88 cases there were 10 in which the meningitis was at a very early stage and its mode of origin was particularly obvious. In every case a localised and not quite recent tuberculous lesion was demonstrated, from which the recent exudative meningitis had obviously arisen. In these cases the meningeal exudate was not found in those situations in which it is most plentiful in fully developed tuberculous meningitis; it was found only in the vicinity of and spreading out from the older focus. In no case was any exudate found at the base of the brain, even microscopically. The concentration of exudate at the base in typical fully developed cases depends on the fact that infection is distributed throughout the subarachnoid space by the cerebro-spinal fluid, and the exudate tends to collect in greatest amount in the large subarachnoid cisterns at the base. This happens no matter at what point the infection is introduced into the subarachnoid space, provided that the meningitis has time to develop to a sufficient extent. It does not mean, as has sometimes been suggested, that the meningitis begins at the base. Theories of pathogenesis which depend upon the idea that because the exudate is most plentiful at the base it must have appeared there first are founded upon a wrong conception. The facts revealed by the ten early cases in this series show conclusively that at the earliest stage the distribution of the exudate depends entirely on the position of the focus responsible for infection of the subarachnoid space. This fact is illustrated by the following notes on representative cases among those with early meningitis.
Case 111. Boy aged 7 months. Pulmonary tuberculosis. The brain showed no exudate at the base. Meningitis was limited to an area on the lateral surface of the left parietal lobe, where typical tuberculous exudate spread out in lines from a central point where a small hard nodule lay in a sulcus, not involving the brain substance. Microscopically it was a partly caseous, partly organised tuberculous deposit, indubitably older than the recent exudate which surrounded it.

Case 188. Man aged 25 years. Abdominal tuberculosis. The brain showed no exudate at the base. Typical exudate and small tubercles were present over the distribution of the left middle cerebral artery, passing outwards and upwards from the left lateral fissure. The stem of that fissure and several small tributary sulci were filled with a mass of very dense caseating exudate. In contact with this mass were several small caseous nodules which had originated in the superficial cortex and which had ulcerated through and discharged into the meninges in the sulci.

The 23 cases in which the meningitis was not traced to an antecedent localised focus failed to afford support for the new conception of the pathogenesis of tuberculous meningitis. It is of interest to enquire whether they afforded support for the older view and could be attributed to direct haematogenous spread. In the following table the facts with regard to the presence and severity of accompanying miliary tuberculosis in these 23 cases are set forth.

<table>
<thead>
<tr>
<th>Number.</th>
<th>Military tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>absent.</td>
</tr>
<tr>
<td>No antecedent foci found</td>
<td>10</td>
</tr>
<tr>
<td>Non-discharging foci</td>
<td>10</td>
</tr>
<tr>
<td>Spinal lesions without proved connection</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
</tr>
</tbody>
</table>

From this it appears that miliary tuberculosis was absent in 8 of the 23 cases and of very slight degree in 7 others. Thus, in 15 of the 23 cases in which a local source was not demonstrated, evidence of a direct haematogenous origin as an alternative was almost equally lacking. This fact suggests that, at least in these 15 cases, a local source of infection of the meninges was missed. There remain only 8 of the 88 meningitis cases which had no demonstrated local source and which had a miliary tuberculosis sufficiently severe to be acceptable as a likely source of the meningitis.

In this series the proportion of cases in which the meningitis was traced to a local source is not as high as in that of Rich and McCordock. Nevertheless the facts and figures here presented support the conception of the pathogenesis of tuberculous meningitis.
advanced by them and show that in a large majority of cases it can be demonstrated that exudative meningitis arises from a pre-existent localised tuberculous focus and not as an immediate result of miliary tuberculosis.

Description of the anatomical characters of the localised tuberculous lesions in the central nervous system.

Lesions of several distinct kinds were found, alone or together, in the cases of this series.

(1) Caseous nodules originating in the substance of the brain or spinal cord were found in 42 of the cases with meningitis. In 24 of these there were in addition deposits in the meninges which were older than the exudative meningitis. The nodules in the substance were tuberculous masses, completely caseous in the centre, with granulation tissue at the periphery and fibrosis in proportion to their chronicity. In some cases small nodules were formed entirely of hyaline fibrous tissue. No calcified nodule was found in any case of meningitis. The size of the nodules varied from 1 mm. to 6 cm. Most often they were less than 1 cm. in diameter, 3-5 mm. being common (figs. 1, 2 and 4). Those which gave rise to meningitis were usually comparatively small and relatively acute, the cellular barrier at the margin of the caseous centre being poorly developed or non-existent. In a few cases very large tuberculomata which had existed for a long time, but were still active and growing, caused a terminal meningitis. The nodules were usually multiple. In 6 cases a single nodule in the substance was found, unaccompanied by meningeal deposits; and in a further 6 a single nodule in the substance was accompanied by one or more deposits of corresponding age in the meninges. The largest number discovered in one brain was 130 and several brains had 30 to 40 nodules. When they were very numerous they were usually small and of fairly uniform size.

The nodules occurred in all parts of the central nervous system, in both grey and white matter. The distribution of 459 nodules the exact position of which was noted is given in the table on p. 628.

The cerebellum, alleged to be the commonest site of tuberculomata, often contained nodules, though it showed no greater frequency than certain lobes of the cerebrum. In cases where multiple nodules were scattered throughout the brain, those in the cerebellum were often rather larger than those in other parts and had an irregular shape and the appearance of a more active spreading character. This may be because a tuberculous nodule in the cerebellar cortex cannot enlarge to any size without coming into contact with pia mater in some of the many small sulci between the folia, and, infection spreading relatively easily in the meningeal
spaces, the area of the lesion increases more readily than in those which do not come in contact with the meninges.

<table>
<thead>
<tr>
<th></th>
<th>Right.</th>
<th>Left.</th>
<th>Both sides.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe</td>
<td>51</td>
<td>55</td>
<td>106</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>57</td>
<td>44</td>
<td>101</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>42</td>
<td>42</td>
<td>84</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>13</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>Central white matter</td>
<td>11</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>6</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Whole hemisphere</td>
<td>180</td>
<td>169</td>
<td>349</td>
</tr>
<tr>
<td>Mid-brain</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Pons</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Medulla oblongata</td>
<td>...</td>
<td>...</td>
<td>3</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>...</td>
<td>...</td>
<td>96</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>...</td>
<td>...</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>459</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nodules in the spinal cord were rare. The cord was examined in 60 cases and in only 2 was a single nodule found.

As regards the responsibility of these nodules for producing meningitis, those are chiefly of interest which are so placed that they come in contact with the meninges or erode the wall and discharge into the cavity of a ventricle. As most cerebellar nodules involve the meninges at an early stage, in many cases the meningitis was traced to one in the cerebellar cortex. In the cerebrum most of those which caused meningitis were in the cortex, involving the meninges on the superficial surface, or in the walls of sulci. In the latter case they had often produced an exudative meningitis limited in the first instance to the sulcus affected and becoming generalised only at a later date (fig. 2 B). In such a case the position of the nodule was often indicated on the outer surface by a group of tubercles in the meninges, much larger than the minute grey foci which always accompany diffuse meningitis, or by a firm caseous plaque sealing the mouth of the affected sulcus. It thus appeared that in many cases the diffuse meningitis did not immediately follow rupture of a caseous nodule into the subarachnoid space, but that this gave rise first to a localised exudative meningitis in the immediate neighbourhood, in which bacilli would multiply freely and which gradually extended until, perhaps on reaching the mouth of the sulcus, it gained access to a larger area and spread rapidly to produce diffuse meningitis (fig. 7). If it be true, as Rich and McCordock assert, that to produce diffuse meningitis a large number of bacilli must be simultaneously discharged into the subarachnoid space, it may be doubted whether the rupture of one, often tiny, caseous nodule, as described by them, could always discharge enough bacilli to produce such a result. But if it be conceived that the rupture of the tiny nodule may initially produce
Fig. 1.—Two small caseous nodules in cerebral cortex, each invading a sulcus. The one marked A set up exudative meningitis which spread out from it on the surface. Natural size.

Fig. 2.—(A). Small caseous nodule in cerebral cortex, touching sulcus; no infection of meninges. (B). The same, but sulcus filled with recent exudate; meningitis in this case was limited to this sulcus. (C). Area of tuberculous meningo-encephalitis. Natural size.

Fig. 3.—Cerebral hemisphere showing thick exudate and tubercles over parietal lobe, spreading out from point A, where there was an older meningeal deposit beneath the surface. ×3.
Tuberculous meningitis

Fig. 4.—Small caseous nodule in cortex of cerebellum, invading a sulcus where pia shows cellular infiltration. ×10.

Fig. 5.—Chronic meningeal nodule with caseous centre surrounded by fibrosis. The cortex has been slightly invaded at one point. ×8.

Fig. 6.—Area of tuberculous meningo-encephalitis involving a sulcus and the surrounding brain substance. A vein in the mass is thrombosed. Punctate haemorrhages in adjacent tissue. ×10.
Fig. 7.—A small caseous nodule (A) near surface of cerebrum has invaded the subjacent sulcus (B), which contains caseous and organising exudate surrounded by recent exudate. This has spread to the surface at (C), causing diffuse meningitis. ×4.

Fig. 8.—Artery in chronic meningeal deposit, showing endarteritis obliterans. ×110.
exudative meningitis in a limited area, in which bacilli would multiply rapidly, it may readily be supposed that when this reservoir of active infection ultimately bursts its bounds, the resulting discharge of bacilli is likely to be much more adequate. It is not suggested that this sequence is invariable or that diffuse meningitis cannot directly follow the rupture of a small caseous nodule. But in this series evidence that localised exudative meningitis in the vicinity of a nodule had preceded diffuse meningitis was commonly found, and this seemed to be the usual sequence when the nodule was in such a position that its rupture infected in the first instance the meninx in the depth of a large sulcus.

Another position in which nodules may produce infection of the cerebro-spinal fluid is the walls of the ventricles, when they erode the ependyma and discharge into the cavity. In one case of this series a nodule was found to have done this by ulcerating through the floor of the fourth ventricle. This case was remarkable for the unusual quantity and density of exudate at the base of the brain and for the presence of relatively large meningeal tubercles in the region of the cisterna magna and on the tela choroidea of the fourth ventricle. In another case there was a nodule in the head of the left caudate nucleus projecting into the cavity of the left lateral ventricle, but it was covered by intact ependyma.

(2) *Foci or deposits originating in the meninges*, of older standing than the diffuse meningitis, were found in 56 of the brains with meningitis. In 24 of these there were in addition nodules in the substance as already described. The meningeal lesions were of two distinct types:—

(a) *Circumscribed compact tubercles* having the structure of typical proliferative tuberculous foci, with central caseation, endothelioid and giant cells and more or less fibrosis in proportion to their chronicity (fig. 5). These were found on the superficial surface of the brain, in the depths of sulci and occasionally in the choroid plexus. They were usually quite small, often no more than 1-2 mm. in diameter. Most often they were multiple.

(b) *Deposits of tuberculous exudate* in the meninges with more or less organisation according to their chronicity. These were found either on the outer surface, where they appeared as flat yellowish plaques often surrounding a blood vessel at the mouth of a sulcus, or occupying a sulcus without appearing on the surface. These deposits usually showed advanced caseation, but even in the caseous material the exudative character of the process was obvious under the microscope, the fibrin of the exudate being readily recognised. Organisation of the exudate might lead to the replacement of much of it by fibrous tissue or tubercles. In almost all cases arteries involved in these meningeal deposits showed proliferative endarteritis, which in some instances led to their
total occlusion (fig. 8). Especially when they occurred in sulci these deposits often caused some involvement of the cortex of the brain, but in many instances this was clearly secondary to the meningeal infection and there was no evidence of the existence of a nodule in the substance which might have given rise to it.

These meningeal lesions were found in all parts of the brain, the superficial ones most often on the supero-lateral surfaces of the cerebral hemispheres and occasionally on the cerebellum. Those which were hidden in sulci were most often in deep fissures such as the lateral, hippocampal, choroidal or parieto-occipital; but they might occur in small relatively shallow sulci. The position of a deposit deep in a sulcus was often indicated by relatively large tubercles on the surface along the line of the affected sulcus or its tributaries. When these deposits occurred in large sulci such as the lateral fissures they were sometimes quite extensive, spreading along the rami of the fissure and into a number of small tributary sulci. In such cases microscopic examination of various parts of the deposit revealed differences in age which made it evident that there had been a gradual spread of the localised meningitis during a considerable time. In other cases the older deposit was quite small and was buried in a mass of recent exudate which made its recognition difficult (fig. 3). In such a case suspicion of the presence of an older deposit might be aroused merely by the fact that the exudate on one side (e.g. in one lateral fissure) was much more plentiful than in the corresponding position on the other side. Palpation might then reveal a harder mass in the midst of the recent exudate, which subsequent microscopic examination would prove to be a relatively chronic meningeal deposit. There were cases in which these chronic deposits were shut off by firm adhesions between the walls of affected sulci. This explains how they were able to exist for considerable periods without infecting the general subarachnoid space. As such adhesions would most readily form in the case of deposits far beneath the surface in deep sulci, it can be understood why the best examples were found in the larger fissures.

Obviously, if localised meningeal deposits are not quickly shut off by the formation of adhesions, it will not be long before they spread and produce diffuse meningitis. In such a case, as the diffuse meningitis follows quickly after the formation of the localised deposit, the latter will be difficult or impossible to distinguish. It is possible that some of the cases in which no lesions antecedent to the meningitis were discovered may be explained in this way, rather than as exceptions to the rule of Rich.

(3) Tuberculous "meningo-encephalitis." This term is applied to a type of lesion which involves both the meninges and the underlying brain substance to some depth in a spreading caseating
Tuberculous meningitis (figs. 2 C and 6). The areas were of irregular shape, spreading along the walls of sulci, and sometimes they were quite extensive. Often it was impossible to tell whether the process began in the brain substance or in the meninges; frequently the appearances suggested the latter. The lesions were relatively chronic but always active, with spreading caseation at some point, and these cases provided some of the clearest examples of the local origin of diffuse meningitis. The position of the lesion was usually indicated on the superficial surface of the brain either by a caseous mass visible in the cortex or by a meningeal plaque or clusters of relatively large tubercles in the meninges; but the lesion itself was usually much more extensive than appeared on the outer surface.

Under the microscope the meningeal part of the lesion was found to consist of a mass of partly organised, partly caseous tuberculous exudate, while in the brain substance it took the form of irregularly spreading caseation with more or less formation of tuberculous granulation tissue at the margins. In the more chronic examples most of the meningeal exudate had been organised and replaced by granulation tissue with tubercles or by dense fibrous tissue. The arteries involved in these areas invariably showed endarteritis, sometimes with great narrowing or complete obliteration of the lumen by proliferated fibrous tissue in the intima; sometimes caseation involved the wall from without. Veins showed similar changes, caseation of the walls being commoner than in the arteries; often the lumina of veins were filled with masses of caseous thrombus.

(4) Tuberculous nodules in the choroid plexus. As Rich and McCordock pointed out, in most cases of tuberculous meningitis small foci may be found in the choroid plexus. These are part of the diffuse meningitis, not antecedent to it, and they have no significance in relation to pathogenesis. In a few cases nodules of a more chronic character occur in the choroid plexus, and these may be the originators of diffuse meningitis. In this series such nodules were found in 4 cases, twice in the choroid plexus of the fourth ventricle, once in the right lateral ventricle and once in both lateral ventricles. They were caseous or fibro-caseous nodules or clusters of conglomerate tubercles forming small masses of tuberculous granulation tissue. Owing to their intimate relation to the cerebro-spinal fluid in the ventricles, such lesions are very favourably situated to set up diffuse meningitis. Nevertheless, despite the importance attached to them by certain observers in the past, they seem to be rather rare and much less often responsible for setting up tuberculous meningitis than the lesions in the brain substance and meninges described above.
The origin of localised tuberculous foci in the central nervous system.

Localised lesions of all the types described may be regarded as the result of sporadic spread of infection by the blood stream from an active tuberculous lesion in some distant part of the body. Rich and McCordock suggest (p. 27) that some are “the result of the early dissemination of bacilli which so commonly takes place during the primary infection.” Clearly this must be so when the subjects are young infants. It is not certain whether the localised exudative meningeal deposits are the direct and immediate result of blood-borne infection, or whether they are preceded by a circumscribed tubercle which subsequently disappears in the larger lesion. The nodules in the substance and the scattered meningeal tubercles are clearly haematogenous. In this series, when they were numerous, there were invariably haematogenous lesions of corresponding age and type in other organs, such as liver, spleen etc. When they were few, analogous visceral foci were not always found, but it must be admitted that the other organs were not examined with the scrupulous care which was devoted to the brain and cord.

It seems clear then that the direct result of haematogenous infection of the central nervous system is, at least in most instances, the production of these localised lesions in the brain and meninges and not diffuse tuberculous meningitis. The interval which must elapse between the setting up of the localised lesions and the development from them of diffuse meningitis varies within wide limits and is not necessarily long. It is known that in many cases tuberculous meningitis in children arises only a short time after the primary infection has been received. Wallgren (1935) considers that the greatest risk of meningitis is during the first three months after infection. If this is so, the meningitis must often follow very shortly after the first occurrence of haematogenous spread to the central nervous system. Indeed it is not difficult to believe that the greatest risk of meningitis may arise soon after the localised lesions have formed, when they begin to caseate and are not yet surrounded by a protective tissue reaction.

Observations on the association of miliary tuberculosis with tuberculous meningitis.

It is common knowledge that tuberculous meningitis and acute miliary tuberculosis are very frequently associated with each other. A high proportion of cases in which tuberculous meningitis was accompanied by miliary tuberculosis was noted in the series of Rich and McCordock (64 out of 82 cases of meningitis), and also in that of Blacklock and Griffin (202 out of 241 cases of
malingitis). In the present series, in 84 of the 88 cases of tuberculous meningitis a complete necropsy was done. The frequency and severity of miliary tuberculosis are shown in the following table.

<table>
<thead>
<tr>
<th>Miliary tuberculosis</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>14</td>
</tr>
<tr>
<td>Slight or very slight</td>
<td>27</td>
</tr>
<tr>
<td>Moderate</td>
<td>25</td>
</tr>
<tr>
<td>Heavy or very heavy</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
</tr>
</tbody>
</table>

Thus miliary tuberculosis was present in 70 (83.3 per cent.) and absent in 14 (16.7 per cent.) of the 84 cases. In the 14 negative cases its absence was confirmed by microscopic examination of the various organs (lungs, liver, spleen, kidneys) in which it is mostly constantly found.

These figures, like those of the other observers quoted, show that the association of meningitis and acute miliary tuberculosis is common enough to suggest that the two have some connection with each other. It is one of the difficulties in the way of accepting the theory of Rich and McCordock as applying to all cases, that it fails to explain this very frequent association. Blacklock and Griffin, while expressing general agreement with the observations of Rich and McCordock, comment that their work “does not fully explain . . . the very frequent association of generalised miliary tuberculosis with tuberculous meningitis.”

There would seem to be three possible ways of reconciling the Rich hypothesis and these facts.

(1) As noted by Rich and McCordock, when what is commonly described as generalised acute miliary tuberculosis is present along with tuberculous meningitis, it has not necessarily arisen simultaneously with the meningitis; microscopic examination may show that most, or even all, of the miliary foci are of longer duration than the meningeal exudate. This would mean that the meningitis did not arise as the immediate result of the blood-borne infection which produced the miliary tuberculosis but at a later date. Such cases are explained by Rich and McCordock as resulting when tubercle bacilli in any of the sparsely scattered miliary tubercles in the brain or meninges continue to proliferate so that larger caseous foci develop, which later may discharge bacilli into the subarachnoid space and so establish diffuse meningitis. Neither Rich and McCordock nor Blacklock and Griffin state in what proportion of their cases the accompanying miliary tuberculosis was entirely, or mostly, older than the meningitis. In the present study special attention was given to this matter, with the following results.

It was found that among the miliary tubercles (using that term in a wide sense) were haematogenous visceral foci of a great variety
of ages. For convenience of description these may be grouped under three headings—acute, subacute and chronic. Acute miliary tubercles were minute foci visible to the naked eye as grey specks, and microscopically showing only early caseation or none, and no fibrosis. Subacute tubercles were either larger foci showing more advanced caseation and appreciable fibrosis, or small partly fibroed nodules. Chronic tubercles were larger nodules showing advanced caseation and fibrosis, or small completely fibroed foci. Of these only the acute tubercles could be regarded as being of approximately the same age as the diffuse meningitis; the others were definitely older. It was possible to classify under these headings the haemato-genous visceral foci of 62 cases in which the microscopic examination was sufficiently complete. Acute miliary tubercles were present in 54 cases; subacute in 33; chronic in 14. In 35 cases haemato-genous foci of distinctly different ages were present, 4 showing lesions which clearly belonged to all three groups. In very few cases did all the miliary foci appear to be of the same age. It seems that miliary tuberculosis does not often arise all at one time as the result of a single eruption of tubercle bacilli from an infected focus into the blood stream. Even cases where a really heavy terminal blood infection was most obvious usually presented clear evidence of previous invasions of the blood stream.

In 8 of the 62 cases no acute miliary tubercles were found but only subacute or chronic haematoegenous foci or both. This means that in 22 (29 per cent.) of the 76 cases of meningitis which were adequately examined (including the 14 without any miliary tuberculosis) there was no miliary tuberculosi which could be regarded as of the same duration as the meningitis. Further, in 25 other cases acute miliary tubercles of an age corresponding approximately to that of the meningitis were present in exceedingly small numbers. Thus, in 47 (61.8 per cent.) of the 76 completely investigated cases, miliary tuberculosis of an age corresponding to that of the meningitis was either absent or so slight as to be almost negligible. It would seem from this that the simultaneous occurrence of tuberculous meningitis and miliary tuberculosis is not quite as constant as is generally believed. Yet the whole problem cannot be dismissed in this way. In 29 of the 76 cases (38 per cent.) acute miliary tubercles were present in moderate or large numbers and in 25 others (33 per cent.) the meningitis was accompanied by a simultaneous slight miliary spread.

(2) It is possible that the occurrence of an invasion of the blood stream by numbers of tubercle bacilli from a progressive focus in any part of the body may occasion an awakening of activity—a perifocal reaction—which causes an extension of caseation in pre-existent tuberculous foci. Any such reaction in and extension of a pre-existent caseous focus in the meninges or
near the surface of the brain might cause such a focus, hitherto
capsulated, to discharge into the subarachnoid space and produce
diffuse meningitis. In this event the occurrence of general miliary
tuberculosis and the onset of exudative meningitis might be almost
simultaneous, although the former would not be the direct cause
of the latter, the occurrence of which would still depend on the
presence of an older local focus.

(3) It is possible that in some cases the meningitis may itself
be the source of the blood infection which produces acute miliary
tuberculosis. It is recognised that any active tuberculous lesion
may be the source of miliary tuberculosis. In the case of meningitis,
there is an exudate rich in bacilli, in free communication with the
cerebro-spinal fluid and surrounding many meningeal veins. Bacilli
in the exudate could gain access to the blood stream either through
the arachnoid villi into the dural blood sinuses or through the
damaged walls of meningeal veins or capillaries. The passage of
tubercle bacilli from the subarachnoid space into the dural sinuses
through intact Pacchionian bodies along with the cerebro-spinal
fluid may be doubted. There is greater likelihood when the
Pacchionian bodies are involved in the tuberculous process.
Examination of these structures from the supero-medial margins of
the cerebral hemispheres in a number of cases of tuberculous
meningitis showed them not infrequently to be affected and under-
going caseation. In such an event it seems not improbable that a
leak of tubercle bacilli into the venous blood stream might take
place. The meningeal veins provide another possible source. At
the base of the brain, where exudate is usually thick, and in such
places as the lateral fissures, meningeal veins are often embedded
in masses of exudate and involved in caseation. In some cases
they have been seen filled with caseous thrombus. In the older
meningeal deposits severe damage to vein walls is usual. Similar
involvement of veins in relation to tuberculous lesions elsewhere
(e.g. in lungs or lymph glands) would be accepted as a probable
source of miliary spread. Proof is hard to obtain through histo-
logical study, but several cases in the present series afforded
evidence which is at least suggestive. Two examples are given.

**Case 239.** Boy aged 2½ years. Tuberculous meningitis was definitely
traced to a relatively chronic caseous deposit in the right lateral
fissure. The primary focus of infection was in the upper lobe of the right lung—a
small cavity healed by fibrous scarring and showing no active disease.
The regional lymph glands related to this were calcified and showed no
appearance of activity. There were large numbers of very small miliary
tubercles in all the organs usually affected. Microscopically these were all
of very recent origin, some being compact cellular foci, some so early as to
be as yet without the characteristic features of fully formed tubercles;
many were too small to be visible to the naked eye.

In this case the lesions of the primary lung complex appeared to be
quite inactive and very unlikely to have given rise to a severe miliary infection such as was present. There was no likely source of the miliary tuberculosis except either the chronic meningeal deposit or the diffuse meningitis. The miliary tuberculosis was recent enough to have arisen within the period of duration of the diffuse meningitis.

**Case 209.** Man aged 50 years. The meningitis had originated from a nodule which had produced a localised meningitis in the right lateral fissure and later a diffuse meningitis. There was chronic pulmonary tuberculosis with cavities in both lungs which showed little activity. No hematogenous visceral tubercles were seen at necropsy. Microscopically, various organs were found to contain large numbers of very small and recent but typical acute miliary tubercles.

In this case no miliary tubercles were large enough to be visible to the naked eye. It is uncertain how long it takes for a tubercle in the human subject to become visible to the naked eye; the time is usually estimated at from two to three weeks. If that is correct the miliary tubercles in this case can be regarded as less than three, and possibly less than two weeks old. Thus the miliary infection almost certainly took place after the diffuse meningitis had developed. As the pulmonary disease was of a chronic and not at all active character, the meningitis seemed to be the most likely source of blood infection.

These observations do not permit any conclusions to be drawn. The evidence can only be regarded as suggesting that the miliary tuberculosis in these cases took origin from the meningitis, as in each case it appeared to be of shorter duration than the meningitis, and only the lesions in the central nervous system were active enough to be likely to give rise to a heavy infection of the blood.

It could not be shown in the present series that the occurrence or the severity of miliary spread depended in any way upon the duration of the meningitis. It is always difficult to determine exactly the duration of tuberculous meningitis, as the onset of characteristic clinical symptoms and signs probably does not coincide with the onset of the pathological process. But a study of the clinical histories of the 14 cases without miliary tuberculosis did not reveal any significant difference between them and the cases with miliary tuberculosis as regards duration of symptoms and signs of meningitis.

**Observations on tuberculous subjects without meningitis.**

The object of including these cases in the study was to discover (a) whether persons who die of tuberculosis without having developed meningitis often have tuberculous lesions in the central nervous system, the characters of such lesions and the types of case in which they are found; (b) whether tubercle bacilli are ever present in the cerebro-spinal fluid of such persons; and (c) the relation, if any, between the presence of tubercle bacilli in the cerebro-spinal fluid and the nature and site of lesions in the central nervous system.
It was rarely possible to obtain cerebro-spinal fluid during life from patients who subsequently died and could be included in this group. Such patients seldom presented clinical indications for lumbar puncture. The samples of cerebro-spinal fluid used for bacteriological examination had, as a rule, to be obtained post-mortem, by cisternal puncture performed before the necropsy was begun. This is unfortunate, as it is impossible to know whether, or how soon, meningitis would have developed had the patient lived longer. Nevertheless, the findings are of some interest. The essential particulars regarding the 25 cases which form this group are set out in the accompanying table.

**Post-mortem cases of tuberculosis without meningitis.**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Tub. lesion</th>
<th>C.N.S. focus</th>
<th>Military</th>
<th>T.B. in C.S.F.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>3/12</td>
<td>P.L.C.</td>
<td>?</td>
<td>Slight</td>
<td>Bovine</td>
<td>Brain not fully examined</td>
</tr>
<tr>
<td>44</td>
<td>3/12</td>
<td>P.L.C.</td>
<td>Choroid</td>
<td>Severe</td>
<td>Human</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>7</td>
<td>Pulmonary</td>
<td>Absent</td>
<td>Slight</td>
<td>No result</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>1</td>
<td>P.L.C.</td>
<td>Substance</td>
<td>Slight</td>
<td>Present</td>
<td>T.B. not typed</td>
</tr>
<tr>
<td>98</td>
<td>3/12</td>
<td>P.A.C.</td>
<td>Substance</td>
<td>Severe</td>
<td>Present</td>
<td>T.B. found microscopically</td>
</tr>
<tr>
<td>101</td>
<td>8</td>
<td>P.L.C.</td>
<td>Substance and meninges</td>
<td>Severe</td>
<td>Human</td>
<td>Subacute miliary</td>
</tr>
<tr>
<td>103</td>
<td>2½</td>
<td>P.L.C.</td>
<td>Substance and meninges</td>
<td>Absent</td>
<td>No result</td>
<td>P.L.C. healed. Brain nodule calcified</td>
</tr>
<tr>
<td>105</td>
<td>26</td>
<td>Pulmonary</td>
<td>Absent</td>
<td>Absent</td>
<td>Human</td>
<td></td>
</tr>
<tr>
<td>109</td>
<td>9/12</td>
<td>P.L.C.</td>
<td>Absent</td>
<td>Absent</td>
<td>Human</td>
<td></td>
</tr>
<tr>
<td>112</td>
<td>4/12</td>
<td>Pulmonary</td>
<td>Meninges</td>
<td>Severe</td>
<td>Human</td>
<td></td>
</tr>
<tr>
<td>117</td>
<td>19</td>
<td>Pulmonary</td>
<td>Substance and meninges</td>
<td>Absent</td>
<td>No result</td>
<td>Meningal nodule calcified Lobar pneumonia. P.L.C. healing</td>
</tr>
<tr>
<td>135</td>
<td>13</td>
<td>P.L.C.</td>
<td>Substance</td>
<td>Absent</td>
<td>Absent</td>
<td>Lobar pneumonia</td>
</tr>
<tr>
<td>154</td>
<td>35</td>
<td>Pulmonary</td>
<td>Absent</td>
<td>Absent</td>
<td>Human</td>
<td></td>
</tr>
<tr>
<td>157</td>
<td>11</td>
<td>Pulmonary</td>
<td>Substance</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>164</td>
<td>7/12</td>
<td>Pulmonary</td>
<td>Substance and meninges</td>
<td>Severe</td>
<td>Human</td>
<td>Lobar pneumonia</td>
</tr>
<tr>
<td>165</td>
<td>50</td>
<td>Pulmonary</td>
<td>Meninges</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>168</td>
<td>2½</td>
<td>P.L.C.</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>169</td>
<td>2¼</td>
<td>P.L.C.</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>181</td>
<td>6/12</td>
<td>Pulmonary</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>183</td>
<td>55</td>
<td>Pulmonary</td>
<td>Absent</td>
<td>Absent</td>
<td>No result</td>
<td></td>
</tr>
<tr>
<td>197</td>
<td>7/12</td>
<td>P.L.C.</td>
<td>Meninges</td>
<td>Severe</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>198</td>
<td>44</td>
<td>Pulmonary</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>53</td>
<td>Pulmonary</td>
<td>Absent</td>
<td>Absent</td>
<td>No result</td>
<td></td>
</tr>
<tr>
<td>203</td>
<td>26</td>
<td>Pulmonary</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>214</td>
<td>3/12</td>
<td>P.L.C.</td>
<td>Absent</td>
<td>Severe</td>
<td>No result</td>
<td></td>
</tr>
</tbody>
</table>

P.L.C. = primary lung complex.
P.A.C. = primary abdominal complex.

No result = no examination, or premature death of animal and no culture made.
Occurrence of tuberculous lesions in the central nervous system in tuberculous cases without meningitis.

The brain in one of the 25 cases was not completely examined for localised tubercles though it was ascertained that there was no diffuse meningitis. The other 24 brains were subjected to the same detailed examination as was carried out on those with meningitis and of these, none of which showed any exudative meningitis either to the naked eye or microscopically, 11 had tuberculous lesions in the brain substance, meninges or choroid plexus, as follows:

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foci in substance of brain</td>
<td>3 cases</td>
</tr>
<tr>
<td>Foci in meninges</td>
<td>3 cases</td>
</tr>
<tr>
<td>Foci in both substance and meninges</td>
<td>4 cases</td>
</tr>
<tr>
<td>Foci in choroid plexus only</td>
<td>1 case</td>
</tr>
</tbody>
</table>

The ages in the "no meningitis" group ranged from 3 months to 55 years. The ages of those who had tuberculous lesions in the central nervous system ranged from 3 months to 50 years, but only one was over 20 years, while seven were under 4 and one was 8 years old. Among the 13 who had no tuberculous lesions in the central nervous system, six were over 20 years, while five were under 4. As might be expected, the younger patients were more prone to have the brain or meninges affected, but the older were not altogether immune.

Of the 11 cases with lesions in the central nervous system, miliary tuberculosis was severe in 7 and slight in 1; in 3 cases no haematogenous foci were found except in the central nervous system. Among the 13 cases without lesions in the central nervous system, miliary tuberculosis was severe in 1, slight in 2 and absent in 10. It appears from this that a severe blood infection usually sets up demonstrable lesions in the central nervous system, that a slight blood infection may or may not do so and that haematogenous foci may occur in the central nervous system even in cases in which no evidence of blood-spread infection is found elsewhere by means of careful necropsy and microscopic examination and in which discovery of sporadic haematogenous lesions in the other organs would require an investigation as detailed as that to which the brains were subjected.

To summarise, of the 24 cases 11 had miliary tuberculosis to some extent and of these 8 had lesions in the central nervous system; in 13 no haematogenous foci were detected elsewhere and of these 3 had lesions in the central nervous system. It may be concluded that in most cases in which tuberculous infection spreads by the blood, lesions are set up in the central nervous system which can be demonstrated if sufficient care be taken; and this may be
so even when the blood-spread infection is of minor degree. As the likelihood of blood spread is greater in young subjects, so the frequency of foci in the central nervous system is also greater in them. But in older patients also, at any stage of the disease while infection is active, sporadic blood spread, often very scanty, does occasionally occur, and so haematogenous foci in the central nervous system may be found at any age and in any type of case.

Occurrence of tubercle bacilli in the cerebro-spinal fluid in tuberculous cases without meningitis.

The cerebro-spinal fluid was examined microscopically and either culturally or biologically or both in 20 cases in this group. In 9 cases tubercle bacilli were recovered by cultural or biological methods; in 1 case they were found microscopically but animal inoculation failed. Thus in exactly half the cases tubercle bacilli were demonstrated in the cerebro-spinal fluid. Seven of the 10 were cases in which tuberculous foci were found in the central nervous system, 2 were cases in which no foci were found and one was the case in which the brain was not fully examined for foci. Six were cases of severe and 2 of slight miliary tuberculosis and 2 were without miliary tuberculosis. There were 2 cases in which tubercle bacilli were isolated from the cerebro-spinal fluid and in which neither foci in the central nervous system nor miliary tubercles in other organs were discovered. These are referred to below. In one case of the 10 the cerebro-spinal fluid was obtained 14 days and in one case 4 days before death; in the rest it was collected post mortem.

Among the 10 cases in which no tubercle bacilli were demonstrated in the cerebro-spinal fluid, foci were found in the central nervous system in 2 and not found in 8. Miliary tuberculosis was severe in 1 case and absent in 9.

The number of cases is too small to permit positive conclusions to be drawn, and the fact that the cerebro-spinal fluid was obtained after or only a short time before death makes caution necessary in interpreting these observations. The facts set forth suggest that in cases of miliary tuberculosis, especially but not only when it is a heavy infection, tubercle bacilli may be present in the cerebro-spinal fluid even when there is no meningitis; and that even in the absence of miliary tuberculosis tubercle bacilli may occasionally occur in the cerebro-spinal fluid when active tuberculosis is present elsewhere in the body. It cannot be stated whether or not this would apply to specimens collected a longer time before death or whether meningitis would have developed in our cases had the patients lived a little longer. In one case tubercle bacilli were present at least two weeks before death and meningitis did not
develop. This is an interesting question on which much more numerous observations are required.

The character of tuberculous lesions in the central nervous system in relation to the occurrence of tubercle bacilli in the cerebro-spinal fluid.

As indicated above, there were 7 cases in which tuberculous lesions were found in the central nervous system and tubercle bacilli were proved to be present in the cerebro-spinal fluid, 4 cases in which lesions were present in the central nervous system but tubercle bacilli were not found in the cerebro-spinal fluid and 2 cases in which no lesions were found but tubercle bacilli were isolated. Thus of 25 cases of the "no meningitis" groups, 13 gave evidence, either in the form of lesions or by the presence of tubercle bacilli, that infection had reached the central nervous system.

(1) The character of the lesions when tubercle bacilli were present.
The lesions in 6 of the 7 cases were small nodules in the substance or pia-arachnoid. In each case one or more nodules were situated either in the meninges or in contact with the pia in a sulcus. In 5 cases the foci were fairly recent, without much fibrosis, and the pia adjacent to them showed a slight reaction with increase of large mononuclear cells and sometimes lymphocytes. In one case (no. 98) the nodules, though small, were much more chronic and well fibosed. In the remaining case (no. 44) the only evidence of tuberculous infection found in the central nervous system was a number of minute compact acute miliary tubercles in the choroid plexus. This was the only case in the "no meningitis" group in which any involvement of the choroid plexus was found. In all these cases except one (no. 58) there was severe miliary tuberculosis. In one case (no. 44) the miliary tubercles were all minute grey foci of very recent origin. In the other 5 cases they were of longer standing and larger, having developed into small nodules with caseous centres. In the remaining case (no. 58) miliary tuberculosis was very slight. The central nervous system foci were five small caseous nodules in the brain substance, two in contact with pia in a sulcus, fairly recent, without fibrosis and with a small amount of cell reaction in the adjacent pia.

(2) The character of the lesions when tubercle bacilli were not found.
One of the 4 cases was similar to several in which tubercle bacilli were found—a case of severe miliary tuberculosis in which several tubercles were present in the meninges on the surface of the cerebrum. In this case the premature death of the guinea-pig used for the isolation of tubercle bacilli from the cerebro-spinal fluid invalidated an important part of the bacteriological examination. In another case, with chronic fibrosed tubercles in brain and
TUBERCULOUS MENINGITIS

meninges, no cerebro-spinal fluid was available for examination. Of the remaining 2 cases one had a calcified plaque in the meninges, the other a calcified nodule in the brain substance. Thus both cases in which a valid negative bacteriological result was obtained had only healed foci in the central nervous system. All these last three cases were without miliary tuberculosis.

Cases without foci in the central nervous system in which tubercle bacilli were isolated from the cerebro-spinal fluid.

Case 109 was that of a female infant, aged 10 months, who died in a wasted condition with a progressive primary lung complex spreading in the right lung as tuberculous bronchopneumonia. No tuberculous lesions were found either at necropsy or microscopically outside the right lung and related lymph glands; there was no miliary tuberculosis. Case 154 was that of a man aged 35 years who had chronic pulmonary and renal tuberculosis, with a psoas abscess originating from the kidney. There was no spinal tuberculosis. Miliary tuberculosis was absent and a complete examination of the central nervous system revealed no tuberculous lesion anywhere.

In these two cases nothing was found to explain the presence of tubercle bacilli in the cerebro-spinal fluid. It may be that some focus in the central nervous system was missed. Otherwise it can only be supposed that a bacillæmia occurred too short a time before death to permit formation of miliary tubercles, and that this allowed tubercle bacilli to escape into the cerebro-spinal fluid. If this is so it means that bacilli can be released from the blood into the cerebro-spinal fluid before tubercles are formed, and not only by discharge from a caseating focus. This may be suggested by some of the cases discussed in a previous paragraph, especially by case 98, in which all the foci found in the central nervous system were so chronic and well fibrosed that they were unlikely to have discharged tubercle bacilli and in which it seemed more probable that the bacilli found in the cerebro-spinal fluid had arrived as a result of a more recent, perhaps terminal, tuberculous bacillæmia.

Results of examination for tubercle bacilli in the cerebro-spinal fluid of tuberculin reactors.

There were 45 patients in this group, of whom 9 presented clinical evidence of active tuberculosis; the rest were recognised to be tuberculous only by the use of the tuberculin test. The cerebro-spinal fluids were obtained by lumbar puncture, which was performed for diagnostic purposes on account of various symptoms or signs of cerebral or meningeal irritation. No patient presented the classical clinical picture of tuberculous
meningitis nor did any develop a fatal meningitis while under observation.

In 3 of these 45 cases tubercle bacilli were recovered from the cerebro-spinal fluid by animal inoculation. None of the 3 children was diagnosed clinically to be suffering from active tuberculosis, though in one case the symptoms (thought to be due to poliomyelitis) might be explained as due to a cerebral tuberculoma. An account of these 3 cases was published by Macgregor, Kirkpatrick and Craig (1934). Over two years after the isolation of the tubercle bacilli from the cerebro-spinal fluid all three children were in good health, though paresis remained in the case of supposed poliomyelitis.

In 2 other cases among the 45 the cerebro-spinal fluid on a single occasion produced a spider-web coagulum and cytological changes very suggestive of tuberculous meningitis, but no tubercle bacilli were found or recovered and later specimens were normal in all respects. One was a case of pulmonary, the other of spinal tuberculosis, both in young children. In both cases at the time when the abnormal fluid was obtained there was definite clinical evidence of meningeal irritation, which afterwards passed off. Although proof by finding tubercle bacilli in the cerebro-spinal fluid was not obtained, it is reasonable to suppose that at these times infection occurred in the central nervous system, setting up a tuberculous process which produced the cytological changes in the cerebro-spinal fluid but which was quickly arrested and presumably localised.

In the 3 cases in which the occurrence of infection in the central nervous system was proved by recovery of tubercle bacilli from the cerebro-spinal fluid, the effects of that infection can again only be conjectured. In the light of knowledge gained from the study of the post-mortem cases, it seems more than probable that the incidents which led to the discovery of the bacilli coincided with the setting up of localised lesions in the central nervous system, such as might subsequently give rise to diffuse meningitis. In the spinal case there may have been a localised infection of the spinal meninges from the diseased vertebrae. It is suggested that in these 5 cases the infection was detected at the stage of the setting up of "Rich foci" in the central nervous system.

It is not to be supposed that in all cases it is possible to detect this early stage of meningeal or cerebral tuberculosis. More often than not it appears to pass unobserved and is probably unobservable. Yet the fact that in 5 out of 45 cases examined, evidence, conclusive or suggestive, was found of the occurrence of this stage, surely shows that the possibility of detecting it in occasional cases is not so very remote. For further light on this interesting and important question, many more cases would need to be examined than are likely to be encountered by individual workers, even over a long
period. It is a problem more likely to be solved by the collective experience of many observers.

General conclusions (part II).

The results of this study are in agreement with the view of the pathogenesis of tuberculous meningitis advanced by Rich and McCordock. It was shown that in a great majority of cases tuberculous meningitis had arisen from a pre-existent localised lesion in or near the central nervous system and not directly as part of a simultaneous acute miliary tuberculosis.

The usual effect of miliary tuberculosis in the central nervous system is to set up isolated tubercles in the brain or meninges. These do not immediately produce exudative meningitis but may do so later when they become caseous and themselves represent "Rich foci."

There is evidence to show that tubercle bacilli may be released into the cerebro-spinal fluid during the course of tuberculous bacilleuria. This is most likely to happen when tubercles are formed in close relation to the cerebro-spinal fluid but may occur in the apparent absence of such lesions. The presence of tubercle bacilli in the cerebro-spinal fluid does not necessarily imply the presence or indicate the immediate development of diffuse meningitis, but it is probable that localised lesions will be formed. This suggests that for the production of diffuse meningitis a large number of bacilli and a suitably allergic subject are necessary, and that in default of either the result of infection will be at worst a localised lesion. As a rule, the number of tubercle bacilli released into the cerebro-spinal fluid in acute miliary tuberculosis seems to be insufficient to produce the diffuse exudative reaction.

Localised lesions in the central nervous system may be set up by haematogenous infection of a mild sporadic type, not meriting the name of miliary tuberculosis. There is evidence that on such occasions tubercle bacilli may be present, probably temporarily, in the cerebro-spinal fluid, that occasionally clinical symptoms and signs may mark the occurrence of this initial infection and that such incidents are not necessarily followed by the development of fatal tuberculous meningitis.

It follows from this that tuberculosis of the central nervous system, in common with other forms of the disease, may be arrested and undergo clinical cure, even when the cerebro-spinal fluid has been infected, provided that the lesions remain localised and that the diffuse exudative reaction does not take place.
Summary of part II.

1. Eighty-eight cases of tuberculous meningitis were examined for evidence of tuberculous lesions in or near the central nervous system antecedent to the exudative meningitis. Evidence was found in 78 cases.

2. In 65 cases (74 per cent.) it was reasonably certain that the exudative meningitis had arisen from a localised lesion. In one case the responsible lesion was in the spine; in the rest it was in the brain or meninges.

3. In 23 cases (26 per cent.) a local origin of the meningitis was not proved, but in 15 of these a direct haematogenous origin was unlikely.

4. The localised lesions in the central nervous system took the form of caseous nodules in the substance of brain and cord, tubercles or deposits of tuberculous exudate in the meninges or choroid plexus, and areas of tuberculous meningo-encephalitis. The characters, sites, frequency and origin of each of these are discussed.

5. It is concluded that the results of this study support the view of the pathogenesis of tuberculous meningitis advanced by Rich and McCordock.

6. The relation of miliary tuberculosis to tuberculous meningitis is considered. Various ways of explaining the frequent association of these two conditions in accordance with Rich's theory are suggested.

7. Twenty-five cases of tuberculosis without meningitis were examined for evidence of infection of the central nervous system. In 11 of 24 brains localised tuberculous lesions were found. In 10 of 20 cerebro-spinal fluids tubercle bacilli were demonstrated. The significance of these observations is discussed.

8. Cerebro-spinal fluids from 45 patients who presented symptoms of cerebral or meningeal irritation and who reacted to the tuberculin skin test were examined for tubercle bacilli and other evidence of tuberculous infection. In 3 cases tubercle bacilli were isolated and in 2 others the cerebro-spinal fluid showed cytological changes strongly suggestive of tuberculous infection. In no case did fatal tuberculous meningitis develop. The significance of these observations is discussed.

We are indebted to all who, during this investigation, gave us access to cases or supplied us with specimens of cerebro-spinal fluid and especially to the members of the honorary visiting staff and the resident medical officers of the Royal Edinburgh Hospital for Sick Children, the pathologists to the Royal Infirmary of Edinburgh and Dr Charles Cameron, Superintendent of East Fortune Sanatorium. Thanks are due also to Professors Charles McNeil, T. J. Mackie and A. Murray Drennan for their helpful criticism and advice.

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RICH, A. R., and MCCORDOCK, H. A.
THE CLINICAL COURSE AND PATHOLOGY OF BURNS AND SCALDS UNDER MODERN METHODS OF TREATMENT

BY

W. C. WILSON, AGNES R. MACGREGOR, AND C. P. STEWART

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THE CLINICAL COURSE AND PATHOLOGY OF BURNS AND SCALDS UNDER MODERN METHODS OF TREATMENT*

BY W. C. WILSON,† AGNES R. MACGREGOR, AND C. P. STEWART†

In 1933 a short report on the treatment of men burned in colliery explosions was rendered to the Ministry of Mines by a committee under the Chairmanship of Sir David Wilkie. The report, though concerned mainly with measures to lessen the high death-rate from burns sustained in colliery explosions, contained also some details of an investigation into the causes of death in burns. The observations reported therein were at variance with views which had been expressed in recent literature on the subject, and, as these views have subsequently gained new adherents, it seemed desirable that the work initiated by the committee should be continued and extended. The present paper is a record of the continued investigation into the causes of the systemic disturbances and of death after burns under the conditions of modern methods of treatment. Our study of the clinical course has, it is hoped, provided a fuller description and a clearer definition of its stages than has hitherto been available; in the section on the pathology of burns, consideration has been given to aspects not previously emphasized. We have recorded our conclusions as to the causes of death after burns, and made some reference to treatment and its future developments.

THEORETICAL CONSIDERATIONS

In the following short survey of theoretical aspects, we shall refer only to literature which deals particularly with the causes of the systemic disturbances and of death after burns. A more comprehensive account of the subject may be found elsewhere. It is customary and convenient to discuss the clinical course in respect of stages because at successive periods after injury the systemic disturbances differ in nature and probably in causation. For the purpose of the present discussion we shall employ a classification in common use, whereby the clinical course is divided into four stages. The first is shock, which occupies a variable period during the first twenty-four hours; the second is toxemia, which may continue till the 4th or 5th day; the third is sepsis or bacterial intoxication; and the fourth is healing. In this section we shall mention only the aetiology of each stage.

1. Shock.—Shock which follows injury by burning so closely resembles shock following severe trauma that there seems no reason to doubt that aetiologically the conditions are essentially similar. The aetiology, however, is not yet fully determined.

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† In receipt of a part-time grant from the Medical Research Council.
The important work of the Medical Research Committee which investigated surgical shock and allied conditions during the late war, is too well known to require detailed recapitulation at this time. Shock was divided into ‘primary’ and ‘secondary’ shock; the first was attributed to derangement of the vasomotor mechanism by afferent nerve-impulses; the second was thought to be probably due to the action of a histamine-like depressor substance which had been absorbed from the injured tissues—that is, secondary shock was considered to be of the nature of a toxæmia. The theory of the nervous origin of primary shock has not been seriously questioned. That of the toxic origin of secondary shock has, however, become scarcely tenable in view of subsequent investigation. In large part the theory rested on experiments by Cannon and Bayliss in which shock was produced by trauma to muscles. Among subsequent investigators there has been general agreement that Cannon and Bayliss, in suggesting that absorption of toxins was the probable mechanism of shock production, had underestimated the effects of local loss of blood or loss of blood and plasma combined. According to O'Shaughnessy and Slome they had failed also to exclude properly the influence of afferent nerve-impulses. Experiments devised to test for depressor substances in blood from a traumatized limb have also given negative results.

At present three alternative explanations, two of which are revivals of older theories, obtain greater favour. The first is that secondary shock is due mainly to loss of blood or plasma, or both, at the site of injury. The second is that it is due mainly to nociceptive nerve-impulses, and that local escape of fluid into the damaged tissues is a subsidiary factor. The third, which has been suggested by Cannon on the basis of experiments by Freeman, is that hyperactivity of the sympatho-adrenal system plays at least a contributory part. Those who hold that secondary shock is essentially of nervous origin naturally dispense with a classification into primary and secondary shock.

Needless to say, each theory has been suggested as an adequate explanation for shock following burns, although for only one has any evidence been offered in support; Blalock and also Harkins concluded that the local loss of plasma in the burned area was sufficient to produce a pronounced fall in blood volume, and that it was probably the chief factor in the causation of shock.

It would be outside the scope of this article to criticize these theories or to detail the evidence for and against each. It seems to us that the possibility of a toxic factor in the causation of shock in man has not yet been entirely excluded.

2. Toxæmia.—The next stage, that of ‘toxæmia’, has been at least appropriately named, because in its fully-developed form the condition resembles an overwhelming poisoning. Three mechanisms have been suggested as the cause of the systemic disturbances:

a. The Action of Toxins which have been formed in the burned area and absorbed into the circulation; the evidence for this mechanism has been reviewed previously.

b. Anhydramia or Increased Concentration of the Blood.—Underhill has been the most active proponent of this view, according to which large quantities of fluid escape from the blood into the burned area, and in consequence the blood concentration and viscosity increase to such a degree as to impair circulatory efficiency. The importance of anhydramia as a cause of systemic disturbances has been much stressed in recent years, and it is commonly believed that
enormous quantities of fluid can be lost from the circulation into an extensively burned area.

Other points in Underhill's thesis are that absorption from burned tissues is greatly reduced, that chlorides as well as water are retained in the burned area, and that the blood-chlorides are depleted. To the combination of fluid and chloride depletion of the blood Underhill has attributed all or most of the systemic disturbances of burns during the first few days, and he has rejected emphatically the possibility of toxin formation or absorption from burned tissues. There is also evidence that in man the blood-chlorides may diminish and other changes in blood-chemistry occur. 10, 11

It may be stated, however, that clinical experience in general does not support Underhill's contentions, because fluid administration in itself will not prevent toxæmia and death, 1 and, under certain conditions of treatment, fatal toxæmia can occur without evidence of serious anhydramia. 23, 30 Still more decisive evidence is contained in this paper.

c. Bacterial Infection of the Burned Area.—Aldrich, 4 who was as sceptical as Underhill of a specific burn toxin, substituted the haemolytic streptococcus for anhydramia as the chief causal agent. His further claim that the application of gentian violet instead of tannic acid to the burned area greatly diminished the incidence of streptococcal infection has not been universally accepted. 24, 18

The present trend of opinion seems to be towards Underhill's view that increased concentration of the blood is the main, if not the sole, cause of symptoms in the stage of toxæmia; some support, 6 however, is given to Aldrich's belief in the predominating influence of haemolytic streptococcal infection. An attitude of scepticism or reserve towards a specific burn toxin has become fashionable.

3. Sepsis.—That bacterial invasion of the burned area is of frequent occurrence and a source of great danger is well-known, and that the haemolytic streptococcus is the most usual agent of serious infection is a common experience. The only points in dispute are the time of onset and the frequency of serious infection. Aldrich stated that streptococcal infection was common and that it occurred early, often within twenty-four hours. The usual estimate has placed the onset towards the end of the first week.

4. Healing.—This stage requires no discussion here.

METHOD OF INVESTIGATION

Our investigation was directly towards the points which, as indicated in the foregoing section, were most in dispute. As will be seen, it has yielded information mainly in relation to the causation of toxæmia and the incidence and time of onset of bacterial infection.

From more than two hundred cases of burns which came under our care or were specially referred to us for the purposes of the investigation, we selected for study 65 cases in which the injuries, by reason of their extent and severity, seemed likely to prove serious. The observations were therefore concerned almost exclusively with severe and dangerous injuries, and the majority, 57 of 65, were in children below 12 years of age. In 41 instances the injuries were scalds, in 24 burns by fire. Twenty-three (15 scalds and 8 burns) of the 65 patients died, and post-mortem examination was obtained in 20. Additional pathological material was obtained from 13 other
fatal cases, in most of which the clinical course was observed by us, but circumstances did not permit of special clinical investigation.

Observations were made on blood-pressure, heart-rate, respiration-rate, rectal temperature, and blood and urinary changes. Blood examination included concentration, as estimated by the haemoglobinometer (Haldane), leucocyte counts, sedimentation rate (Landau’s micro-sedimentation method), bacterial cultures, and chemistry. The usual blood-chemistry investigation comprised chlorides, carbon-dioxide combining power, and plasma proteins; in some cases additional estimates were made, such as non-protein nitrogen, urea, cholesterol, inorganic phosphorus, serum calcium, potassium, sodium, van den Bergh reaction, and icteric index. The burned areas were examined at intervals for bacterial growth by anaerobic and aerobic cultures. Cultures were taken from small incisions made through previously sterilized portions of the coagulum. In a few cases gastric acidity was measured.

The post-mortem examinations included the brain, thyroid, parathyroid glands, lymph-glands, burned and unburned skin, and all thoracic and abdominal organs; bacteriological cultures from blood and burned areas were made.

As the investigation proceeded, its scope was extended, and thus the studies were more complete in later than in earlier cases of the series. In addition to the selected cases, many others were investigated for a limited period, till it was clear that they would yield no information of special value.

The main principles and details of treatment may be described here; treatment was the same for all cases unless otherwise stated in case reports. Immediately the patient was admitted to hospital, morphine or heroin was administered, and as soon as practicable the local treatment of the burned area was carried out under nitrous oxide, oxygen, and ether anaesthesia. All loosened epidermis was removed by gauze soaked in warm normal saline solution, and to the raw surface 20 per cent tannic acid with the addition of 1 per cent gentian violet (in some cases 1–1000 acriflavine) was applied. Two applications of the coagulating solution were made, and the area was dried by a current of hot air from a hair-drier after each application. Immediate coagulation of the surface layer of the burned area was thus produced. Thereafter the area was exposed to the air under a heating cage (see Fig. 618) and supervision was carried out as previously described. In many cases intravenous infusions were given during the early stages; these and other adjuvant measures are mentioned in individual case reports and in the discussion on treatment.

To present the results in the most convenient form, we shall give first a general description of the clinical course and of the pathology of burns as they were exemplified by our cases, and later we shall detail the evidence for our conclusions by quoting illustrative cases.

**CLINICAL COURSE**

The severity of the constitutional disturbances which followed injury by burning was influenced by many factors, of which the most important were the age of the victim, the extent of skin surface involved, the depth and situation of the burn, and the time which elapsed between the infliction of injury and the institution of treatment. In any group of cases, however, in which these and other factors were fairly constant, very conspicuous differences in the clinical course were observed. There seemed little doubt that the main cause of such differences was
individual variation in susceptibility to the effects of injury. In a proportion of
the cases selected for study the constitutional disturbances were very mild, or even
absent. In other instances, however, they were more or less pronounced, and
followed a course which may be regarded as characteristic of this form of injury.
In representing the course we have adhered to a classification, previously employed
by one of us, which differs slightly from the usual classification, and in which
the course is divided into five stages: (1) Initial shock; (2) Secondary shock;
(3) Acute toxæmia; (4) Septic toxæmia; and (5) Healing. It should be noted
that there are wide variations, in any group of comparable cases, in respect of the
severity and duration of each stage. The classification has been employed because
it is useful for description of the clinical course, and because it seems to give,
on the whole, the most accurate representation of the systemic disturbances.

1. INITIAL SHOCK

We have restricted the diagnosis of initial shock to the condition of low blood-
pressure in cases which were admitted to hospital within 2 hours of injury. The
criterion of blood-pressure level was essential for satisfactory diagnosis and analysis;
the period of 2 hours, though arbitrarily chosen, proved convenient for purposes of
classification.

Forty cases of the series were admitted within 2 hours of injury; in 35, and
amongst these were some of the most extensive and severe injuries, the systolic
level of blood-pressure was normal or, in a few, actually above normal. That is,
initial shock was present on admission in 5 cases only; in 2 it was severe, in 3
moderate or mild in degree.

The 2 cases of severe initial shock were associated with unusual circumstances.
Unfortunately in neither was investigation sufficiently complete to provide satis-
factory information. One was complicated by œdema of the glottis and pronounced
anoxæmia; following tracheotomy the blood-pressure regained a normal level, but
the circulation failed later and death occurred at 21 hours. The other had very
extensive and deep burns; initial shock, which was profound on admission at
1½ hours, gradually deepened till death at 7 hours. Here there was evidence,
from post-mortem examination, of unusual pathological features, namely infiltration
of the liver and spleen by eosinophil leucocytes, which will be referred to again.
In the cases of moderate or mild initial shock the maximum fall of systolic blood-
pressure was 24 mm. Hg; the other clinical features were pallid cold skin, sub-
normal rectal temperature, feeble radial pulse, which was usually little altered in
rate, and apathy or anxiety. Recovery to a normal pressure level occurred within
an hour of administration of sedatives and warmth.

In addition to the cases classified as initial shock, there were several which,
but for the necessary criterion of hypotension, would have been included as examples
of initial shock. Although the systolic level and pulse pressure were unaltered,
the condition otherwise was indistinguishable from initial shock, and was similarly
responsive to treatment.

During the first 2 hours, and irrespective of the presence of shock, there was
no noteworthy change in blood-chemistry or corpuscular sedimentation-rate. The
hemoglobin content of venous and capillary blood was also usually normal; excep-
tions are mentioned in the description of secondary shock. A leucocytosis in venous
and capillary blood was a frequent, though not invariable, occurrence. The count
was sometimes surprisingly high; 38,000 per cmm. at 45 minutes after injury, and 45,000 at 1 hour were recorded. The proportions of leucocytes were unchanged, and in no instance were eosinophils in excess. The leucocytosis was not merely a consequence of increased concentration, because in nearly all instances of high counts the haemoglobin content was normal. The mechanism has not yet been investigated. A number of agencies, such as reflex nervous action or increased secretion of adrenaline, which has been found after experimental burns, might be suspected.

Even in this series of severe injuries, therefore, initial shock was infrequent, usually of moderate severity, and transient. Profound initial shock was associated with unusual circumstances.

2. SECONDARY SHOCK

As examples of secondary shock we have included cases in which shock developed subsequent to admission and also those in which hypotension was already present at admission later than 2 hours after injury; in the majority of the second group the interval between injury and admission was considerably greater than 2 hours.

Development.—In most instances of secondary shock in the present series, the condition began during, or immediately after, local treatment, and the development was then rapid. The development of secondary shock before local treatment was usually gradual, though 2 cases of rapid development were observed. In cases of gradual development of shock, the pulse pressure decreased steadily over a period of 1 or 2 hours, the systolic level falling slightly while the diastolic level rose; after this period both levels fell rapidly and on occasion the fall was sudden and pronounced. In severe shock the systolic pressure fell below 60 mm. Hg. (adults), and we have in fact observed systolic levels of 25 and even 16 mm. Hg. Simultaneously the quality of the radial pulse deteriorated and the heart-rate increased.

Established Shock.—The well-known features of surgical shock always appeared once the main collapse of arterial pressure had begun; sometimes they preceded it by many minutes. In severe shock the chief complaint was thirst, which was often almost insupportable; pain, on the other hand, was rarely prominent unless the hands or face were injured. Adults were usually alert and distinctly anxious, while children tended to be apathetic except for the constant and intense desire to assuage thirst. The skin was cold, pale, and clammy; the lips, cheeks, and ears were ashen-grey in colour (the greyness being accentuated sometimes by impregnation of the skin with carbon particles); the rectal temperature was subnormal; respiration typically was shallow and rapid, though in the most profound shock the irregular exaggerated movements of ‘air-hunger’ appeared, together with great restlessness and distress. Vomiting was practically invariable; fluid drunk to relieve thirst was always vomited very shortly afterwards. Capillary blood from ear or finger-tip usually showed a distinct rise in haemoglobin content; an average figure was 115 per cent and a rise to 150 per cent has been found. Occasionally venous blood showed a similar rise, though usually of lesser degree, but more often the venous blood haemoglobin was normal. No constant change in blood-chemistry was observed, and even the carbon-dioxide combining power, a fall of which is generally regarded as characteristic of traumatic secondary shock, was rarely significantly lowered. In one recent case, however, a distinct fall in serum sodium has been recorded—a feature requiring further investigation.
In moderate or mild degrees of secondary shock the changes were correspondingly less pronounced; the systolic level remained above 60 mm. Hg, there was little change in concentration of capillary or venous blood, and no alteration in blood-chemistry.

Incidence and Consequences.—The incidence and degree of secondary shock were closely related to the extent of skin surface which had been injured; the greater the extent, the more rapid and severe the shock. Extent was not the only factor, however. In most, though not all, cases in which secondary shock became severe, the burns were deep as well as extensive. As already mentioned, the procedure of local treatment appeared to precipitate secondary shock, or to aggravate it if already present. Usually signs of shock were inconspicuous before local treatment, but if more than 20 per cent of the skin surface were injured, some degree of secondary shock invariably developed during or after the procedure. Treatment, of course, introduced factors liable to aggravate shock, such as anaesthesia, the production of painful nerve impulses, and some additional loss of plasma from the injured surface. Nevertheless the regularity of the development of secondary shock, even when every effort was made to mitigate the effect of these factors, was striking. It was possible also to demonstrate the specially deleterious actions during shock of open ether anaesthesia, of anoxaemia, and of the application to the injured surface of irritant cleansing agents such as ether and alcohol.

The capacity for spontaneous recovery was present, though uncertain, in moderate and mild degrees of secondary shock. On the other hand, in severe degrees the circulatory collapse was continuous and progressive, and the course, we are convinced, judging from our own experience and that of others, would invariably have terminated fatally in 12 to 24 hours after injury but for the active therapeutic measures employed. It may be noted that no patient treated by the methods previously outlined died from secondary shock.

3. ACUTE TOXÆMIA

Acute toxæmia, even in this selected series of dangerous burning injuries, was frequently absent, or was so mild as to amount to nothing more than an inconsiderable and unimportant malaise. In a number, however, it occurred in severe form, and at its worst it resembled the overwhelming intoxication produced by the most virulent bacteria. This fulminating form, which was most frequently observed in young children and infants, had very constant and characteristic features, which will now be described.

Severe Acute Toxæmia in Children.—The onset was as a rule insidious and the development gradual, and even when the condition appeared to make a late and abrupt entry, there were premonitory signs that all was not well. The onset was at any time between 6 and 50 hours after injury, in the majority at about 12 to 15 hours, and the first sign was usually vomiting, which was more continuous and persistent than could readily be attributed to the preceding anaesthetic. Altered blood in the vomit at an early stage presaged a serious illness. Simultaneously a highly characteristic disturbance of the mental state began. The child became apathetic and listless, and yet curiously, and sometimes intensely, irritable and restless, made repeated efforts every few seconds to change position, and evinced special resentment at finding the movement of the limbs restrained. Drowsiness was evident, yet sleep was fitful and was frequently interrupted by jerking movements.
of limbs and trunk. The restlessness was very little influenced by ordinary doses of sedatives, and gradually merged into delirium, stupor, and finally coma. In two infants recurring epileptiform convulsions preceded coma, which deepened after each convolution. The mental disturbances usually appeared before any serious failure of the circulation, and evidently some process was peculiarly noxious to the brain cells at this stage. Further evidence may be cited here. During the period of investigation, 6 children with small burns were admitted to hospital, between 14 and 50 hours after injury, solely on account of severe cerebral disturbance which overshadowed the other signs of acute toxæmia; 4 had recurring epileptiform convulsions and 2 wild delirium.

Hyperpyrexia.—This was a characteristic feature, and as a rule was persistent and progressive. It may be noted that the hyperpyrexia of acute toxæmia has been considerably modified in our series in which treatment by exposure of extensive skin surfaces has facilitated regulation of body temperature.

Circulatory Failure.—This was responsible for some of the most distinctive signs of acute toxæmia. The radial pulse became progressively more rapid and feeble. The skin of the trunk and limbs became pale, or mortled, and cold; pallor replaced the reactionary erythema surrounding the burned area, thus throwing into sharp relief the dark colour of the tanned surface, while the low temperature of the skin, particularly of nose, ears, fingers, and toes, was strikingly at variance with the high rectal temperature. The greyish-cyanotic hue of lips, cheeks, and ears, indicating stasis in the minute vessels, was further evidence of failure of the peripheral circulation, and at an advanced stage the eyes became sunken and dark-ringed and the pupils dilated. The blood-pressure changes were variable. Usually the systolic pressure remained at or near a normal level till within a few hours of death, while the pulse pressure was diminished by a rise of diastolic pressure; the diastolic level was often, however, very erratic. Less frequently there was a very slow and almost imperceptible decline in systolic and diastolic pressures, terminating in an abrupt fall as the circulation finally failed. In a few cases there were sudden falls in pressure at intervals, associated with signs of collapse. In the early stages recovery to a normal level occurred spontaneously or after intravenous infusion of a colloidal solution, such as gum saline or blood, but the response became steadily more evanescent and incomplete, and usually failed entirely at any time after 60 hours.

Respiration.—In the absence of pulmonary complications respiration was not specially affected. It was not as a rule shallow, and the rate was increased only in proportion to the degree of pyrexia.

During the earlier part of the investigation acute toxæmia of such severe degrees always pursued an inexorable course to a fatal termination between 50 and 100 hours after injury; the average time of death was 70 hours. Recent experience, however, has suggested\textsuperscript{32} that in a proportion of cases of severe toxæmia circulatory failure may be successfully treated and the course considerably modified.

Blood Changes.—Even in the most severe and fulminating acute toxæmia there was no constant change in blood concentration. Frequently the haemoglobin content of capillary blood remained unaltered, and it was unusual to find a significant rise in venous blood. In burns of more than moderate extent there was a tendency for the capillary blood to be concentrated during the first two or three days, but estimations in cases with and without toxic signs elicited no evidence of
any constant relation between increased blood concentration and acute toxæmia. These points are well illustrated in the cases quoted later.

The leucocytosis which often appeared immediately after injury persisted with a steadily diminishing count during the first four days and was unaffected by the advent of toxæmia. During fulminating toxæmia the leucocyte count might remain normal and the rate of corpuscular sedimentation unchanged.

Common changes in blood-chemistry were a diminution in chlorides, carbon-dioxide combining power, and plasma albumin, and a rise in non-protein and urea nitrogen. Such changes, however, were neither constant nor proportional to the severity of the systemic disturbances. Recent investigations suggest that serum sodium and potassium may prove a more reliable index of toxæmia, but only a few observations are at present available.

Urine.—Abnormal constituents were variable; acetone, albumin, and casts were occasional, and bile has been found as early as 48 hours.

Bacteriology.—The cultures, aerobic and anaerobic, of the burned tissues were taken from several points which seemed likely to be reasonably representative of the burned area. Cultures were also made from blisters, fissures, and any raw surfaces which might appear during the first few days. The latter contained various organisms such as streptococci, hämolytic or non-hämolytic, staphylococci, and coliform bacilli, but the cultures of ‘representative’ areas very frequently showed no growth up to 90 hours. If we accept the latter as a true indication of bacterial activity in the burned area, the evidence was against bacterial action as the cause of acute toxæmia. As it happened this evidence was most decisive in cases of severe and fatal toxæmia. Certainly there was rarely any suggestion that hämolytic streptococci were flourishing in the burned area and invading the bloodstream. Moreover, hämolytic streptococci were sometimes grown in pure culture from isolated portions when systemic disturbances were entirely absent. If the remarkably severe and rapidly fatal illness were to be explained by bacterial action, we should have suspected not the hämolytic streptococcus, but rather an organism capable of producing the most potent exotoxin, and probably growing anaerobically under the tanned layer. The local condition of the burned area during life and after death, and the results of cultures, gave not the slightest indication of such a process.

Milder Degrees of Acute Toxæmia in Children.—The features of milder degrees of acute toxæmia were occasional vomiting, slight cyanosis, and a moderate rise of pulse-rate and rectal temperature. They appeared at the usual time and subsided at 30 to 40 hours after injury. One sequel, however, was of special significance, namely jaundice, which was observed in 5 such cases. The results of examination of blood concentration, blood-chemistry, and bacterial growth were substantially the same as in the severe grade of toxæmia.

In 3 cases a variation in the clinical course was recorded. Acute toxæmia began at about 12 hours and remained mild, in 2 cases so mild as almost to escape detection, until between 40 and 60 hours, when suddenly it became severe and proved rapidly fatal.

Acute Toxæmia in Adults.—The condition in adults was on the whole less dramatic and distinctive than in children, and survival was more prolonged. The illness was less overwhelming, though several cases followed the course described above. Vomiting was again an early sign, and continuous hiccup, which rapidly
produced extreme exhaustion, was noted in more than one case. The mental state varied from apathy and stupor to anxiety and delirium, which was notably resistant to sedatives. Pyrexia and augmented pulse-rate were constant, but, except when the injuries were very extensive, circulatory failure was less prominent than in children. We have, however, observed several adults with very extensive burns—up to 75 per cent of the body surface—in whom the disturbances from an early stage were predominantly those of circulatory failure. In 2 secondary shock was very severe and the response to treatment was incomplete, so that the blood-pressure did not regain a normal level, though life was prolonged till between 55 and 90 hours—that is, well into the stage of acute toxæmia. No doubt the stages of secondary shock and acute toxæmia overlapped and both conditions contributed to the fatal issue. Naturally, when the circulatory failure was profound between 6 and 24 hours, it was often impossible to judge whether it were due to secondary shock or early acute toxæmia. Another variation of acute toxæmia in adults was fairly frequent. A state of low-grade intoxication, marked by pyrexia and tachycardia, but without serious circulatory failure, was continued beyond the first week till bacterial infection supervened and proved an insupportable additional burden. In 2 such cases jaundice appeared at the 4th or 5th day. Investigation in adults gave results in all respects similar to those in children.

Incidence of Acute Toxæmia.—Several points which were noted regarding the incidence of acute toxæmia are worthy of record. It was the sole or main cause of death in 13 cases of the series and occurred in severe form in 4 others. It was more common and more severe in infants and young children than in adults. The relation between the extent of skin surface involved and the severity of acute toxæmia was much less constant than in the case of secondary shock. We have seen fulminating toxæmia in a small burn and very mild toxæmia in a burn of 60 per cent of the body surface. On the other hand, there was evidence of an association of toxæmia with a certain depth of injury, such as that produced by steam, boiling water, or a momentary exposure to flame. Cases with more superficial or with deeper burns frequently escaped toxæmia. Generally, in burns of moderate extent, the incidence of toxæmia was so irregular as to render impossible at the commencement of the course any prediction of its occurrence. If, however, the specific toxic manifestations had not appeared by 90 hours after injury, the chances of their development were remote.

4. SEPTIC TOXÆMIA

In regard to the stage of septic toxæmia, we shall deal separately with superficial and deep burns, since the incidence of infection was very intimately related to the depth of injury. The burns were classified as superficial when they involved only the skin, and as deep when they destroyed the whole thickness of skin and penetrated to deeper tissues. Usually scalds by hot liquid or steam were superficial, although we have observed destruction of the whole thickness of the skin over a large extent of surface by boiling water. After a burn by fire, a considerable proportion of the total area affected had often been deeply injured; nevertheless mining explosion burns were largely superficial.

Superficial Burns.—When incisions were made through the coagulum during the first week it was found that the coagulated layer was firmly incorporated with the oedematous underlying tissue; rarely did a collection of fluid intervene,
and, as already mentioned, there was seldom evidence of bacterial growth up to 90 hours. Subsequently various organisms such as streptococci and staphyloccoci appeared in cultures taken from certain portions of the burned areas, although both local and general signs of inflammation were often absent. If blisters formed in untanned areas, or if the coagulum became fissured or separated at the edges, then organisms, usually haemolytic streptococci, could be grown from blister fluid or exposed raw surface; such conditions certainly provided an opportunity for bacterial growth. Infection was restricted to such points, and was denoted by reddening of the surrounding intact skin and exudation of fluid from the edge of the coagulum; the systemic disturbance, if any, was mild. Gross or dangerous infection of superficial burns was rare.

Deep Burns.—In the initial stages, and even during local treatment, it was often difficult to determine if the injury had destroyed the whole depth of skin. Sometimes deeply burned areas were indicated by the characters of the epidermis, which was scorched dark brown, toughened, firmly adherent, and therefore was unaffected by the application of tannic acid. If in deep areas the epidermis could be stripped off, a pale avascular tissue was exposed of which the surface layer was readily susceptible to the coagulating action of tannic acid, and the appearance subsequently was similar to that of superficial burns. Sometimes the main or only indication that the injury had penetrated deeply was the continued firm adherence of the coagulum for two or three weeks or longer. Separation of dead tissue, incorporated with the coagulated surface layer, was slow and was effected by the growth of granulation tissue, between which and the necrotic cells intervened a layer of yellow, inspissated serum containing leucocytes and cell debris. Bacterial invasion was heralded by local and general signs. The local signs were usually, though not invariably, obvious; the site of invasion was as a rule at the edge of the burn and, not infrequently, the inflammatory process was more extensive in the adjacent unburned tissues than in the burned area. Confirmation of this fact was obtained when attempts were made to remove the coagulum; a short distance from the inflamed area the coagulum was found everywhere firmly attached to healthy granulation tissue. Exceptionally a spreading cellulitic process invaded the tissues subjacent to the coagulum, by which the local inflammatory signs were obscured. The general systemic disturbance proved the more reliable index of bacterial activity. Even when the coagulum had become sodden and loose in parts, and large sloughs of necrotic tissue were being thrown off, revealing a thick purulent exudate of unpleasant aspect and odour, the general condition frequently remained satisfactory; in spite of some degree of pyrexia, the circulation was efficient and strength was unimpaired. Serious bacterial infection was usually caused by the haemolytic streptococcus, and was denoted by a swinging temperature, rapid pulse, and, in the worst cases, signs of pyæmia. The organism was then found in cultures from burned area and blood.

In our series local signs of bacterial infection of deep burns were rarely present before the 5th day, and usually were not obvious till after the 7th day. Even in fatal septæmia and pyæmia, haemolytic streptococci did not appear in the blood before the 9th day. As regards incidence, if we assess bacterial infection by the results of cultures from the exudate beneath the coagulum and dead tissue, then infection was always present in deep burns during some part of the course. To judge by the general disturbance produced, the degree of infection in the majority
of cases was mild; in some, however, it was severe or very severe and fatal. Sepsis was the predominant cause of death in 10 cases of the series.

It was by no means always easy to determine the role of bacterial infection in systemic disturbances during the second week. Great difficulty was encountered in adults in whom a low-grade acute toxæmia had continued from an earlier period with a steady deterioration of strength culminating in prostration, stupor, or delirium, and sometimes incontinence of urine and faæces. The local signs of inflammation were often no more, or even less, obvious than in other cases without serious upset. Even at the post-mortem examination, in the absence of cellulitis or pyæmia it was impossible to judge whether death had been caused mainly by bacterial intoxication or by the effects of preceding or coincident acute toxæmia. As we shall show, diffuse destruction of liver cells was a characteristic lesion of acute toxæmia, and in all probability liver insufficiency was the main or an important contributory cause of death. No doubt even the mildest form of bacterial activity would in such instances have sufficed to turn the scales adversely.

As a point of practical interest, it may be mentioned that in 2 cases haæmolytic streptococcal infection, ultimately fatal, began in a granulating surface many weeks after the coagulum had been removed.

As in the case of acute toxæmia, it may be said that recent experience suggests that our conception of the course may shortly require modification. Since haæmolytic streptococcal infections can now be in large part prevented or successfully treated in deep burns, the cause of the systemic disturbances at the time when sloughs are separating may demand reconsideration. Till now we have attributed them to absorption of products of bacterial activity.

5. HEALING

This stage, which follows that of infection, has not been specially studied. Its importance will in the future be enhanced as therapeutic improvements serve to diminish the mortality in the earlier stages. Many surgical problems of great interest await attention.

COMPLICATIONS

It is convenient to consider separately the common complications of burning injuries.

Lesions of the Respiratory Tract.—The association of such lesions with burns of the chest has long been recognized, and it has been implied that they were in some way produced by the action of heat on the skin and tissues of the chest wall; the same association of inflammatory lesions of viscera with burns of overlying tissues has been claimed for other regions, such as the abdomen and head. In our experience the association held for burns of the chest, but not for those of the abdomen, and only in very exceptional circumstances for burns of the head, when the lesions were produced apparently by the direct action of heat on the brain itself. For instance, we have seen very severe, though temporary, cerebral disturbance in an infant following prolonged application of flame to the head; subsequently a large portion of the vault of the skull was extruded as a sequestrum.

Consideration of the facts in our cases of thoracic visceral lesions suggested an explanation of the association which seemed more simple and probable than the above. They were common after burns by fire which involved the anterior
aspect of the upper part of the trunk and the face, and particularly after accidents in which clothing had caught fire and some minutes had elapsed before the flames were extinguished. The lesions were common also after mining explosion burns, when the victims had been momentarily enveloped in a wall of flame and had subsequently breathed air at a very high temperature. On the other hand, if the burns involved only the posterior aspect of the thorax, respiratory tract lesions were unusual, and the same was true for scalds of any part of the thorax unless hot fluid or steam had been inhaled—by no means a rare accident in infants. Lesions of the respiratory tract, we consider, were caused by direct injury to its lining membranes by inhalation of flame, hot air, or hot fluid. Admittedly the mucous membrane of nose and mouth usually escaped severe damage. Often the mucous membrane of pharynx, larynx, and trachea was also little affected, though we have observed in all these parts extensive sloughing lesions. The common respiratory lesions were, however, bronchitis, bronchopneumonia, and pulmonary oedema. They were particularly dangerous complications and an important contributory cause of death during the first and second weeks. Pulmonary oedema was a common lesion in cases of fatal acute toxæmia, and apparently was prone to develop when large quantities of fluid were administered intravenously, and particularly by the continuous-drip method.

**Duodenal Ulcer.**—Ulcers in the duodenum were found post mortem in 4 cases, one of which is quoted in detail among the illustrative cases. In only one instance was there any indication of the presence of ulceration during life, in this case haæmatemesis on the day before death. The victims were females, and the ages were 1 year 5 months, 7 years, 16 years, and 23 years. In all, the injuries were very extensive, and the time of death was between the 10th and the 12th day. In other respects, however, differences were present. In 3 the burns were deep, in 1 mainly superficial; 2 had haemolytic streptococcal septicaemia and pyæmia, in 2 sepsis was inconspicuous. The liver cells were extremely and diffusely necrotic in 1, severely damaged in 2, but only slightly affected in the last. In no case was there histological evidence of special injury to the suprarenal gland or to the hypothalamus. In other cases of extensive burns, though not in any in which duodenal ulcers were subsequently found, we examined gastric secretion by test-meal at intervals during the first two weeks; total acidity was always reduced, and little or no free hydrochloric acid was found.

As regards causation, it would be useless at present to speculate. The ulcers were recent and were evidently a result of the burn. Their situation, on the posterior wall of the first part of duodenum, excluded the possibility that the direct action of heat on the viscus was responsible. Evidently bacterial infection was not essential for the production of the lesion, and it would seem that hypochlorhidria, and not hyperchlorhidria, was the usual sequel of extensive burns. In spite of negative histopathological evidence we cannot ignore the possibility that damage to the suprarenal gland or to the hypothalamus may have been responsible; damage to either may be followed by peptic ulceration.

**Jaundice.**—With increasing experience we have come to regard jaundice as one of the signs of acute toxæmia rather than a complication. It was noted in 12 cases of the series, and would probably have been detected more frequently in the earlier part of the investigation had its import been more fully realized. Jaundice was usually of the 'toxic' type; skin pigmentation was difficult to detect,
only traces of bile were found in the urine, the Van den Bergh reaction was biphasic, and the icteric index about 20 to 30. In several the jaundice was more definite and the urine contained much bile. In two cases 'latent' jaundice was present. Jaundice was found during fulminating toxæmia even as early as 48 hours after injury, but the most pronounced jaundice occurred in the slowly progressive low-grade toxæmia of adults, appearing usually about the 4th day. It was certainly not related to any special therapeutic measure, since it appeared under many modifications of treatment and was found in one late admission in which the burns had received no treatment beyond application of oil. Nor was it dependent on sepsis, since in most instances the presence of sepsis in the burned area was excluded. Jaundice indicated the occurrence of degenerative and necrotic changes in the liver.

Other Complications.—During the past ten years we have noted a steady diminution in the incidence of complications such as scarlatina and gastro-enteritis, which at one time frequently supervened during the course of burns. No doubt scarlatina was an indication of streptococcal infection of the burned area, which can now be more effectively controlled. In our series these complications were almost entirely restricted to untreated or badly-treated cases, for which admission to hospital was sought solely on account of the complication. We have already mentioned the common cerebral manifestations of acute toxæmia, such as delirium and epileptiform convulsions. One unique sequel of a small burn, in a child previously healthy, was extensive intravascular clotting, which involved not only the intracranial venous sinuses and Rolandic veins, but also the arteries of the lower extremities from the level of the lower part of the abdominal aorta downwards.

RAPIDLY FATAL BURNS OF MODERATE OR SMALL EXTENT

Most surgeons of experience can recall one or more instances of unexpectedly rapid death after a small burn, and this feature alone has impressed many with the potential dangers of such injuries.

Two examples have been encountered in our series. One (Case 9) is described among the illustrative cases. The other, a male child aged 3 years 6 months, died 24 hours after an injury involving only 5 per cent of the total skin surface; no treatment of any kind had been carried out. Since both died immediately after admission to hospital, clinical investigation was impossible. There was in both a striking pathological change, namely, infiltration of the liver by eosinophil leucocytes, which will be described later. The association of such a change with a rapidly fatal outcome suggested the possibility of anaphylaxis, and it is of interest that the second child had sustained a burn one year previously. The possibility is a mere conjecture, and is mentioned here in order that others may be led to inquiry on the point.

PATHOLOGY

The pathological investigation was carried out on 33 fatal cases, in 20 of which a study of the clinical course had been made.

Death within 24 hours.—Six cases of death within 24 hours of injury were available for examination. Three of these were under our own care and have already been mentioned, 1 a very rapid death after burns of moderate extent, and 2 cases of severe initial shock. We have received sufficient clinical data for a rough
analysis of the others; 2 had sustained very extensive injuries and died from initial or secondary shock within a few hours; 1 is described later (Case 5).

The pathological feature of note in 2 cases of rapid death (see Table I) was infiltration of the liver and other organs with eosinophil leucocytes, which was evidence of some unusual process. In the remaining cases, those of fatal initial or secondary shock, the changes were neither conspicuous nor specially distinctive. Pallor was the outstanding feature in most organs, though some, such as the brain, lung, and spleen, were sometimes moderately congested. Pulmonary oedema was a common occurrence and was most pronounced when intravenous infusions had been given. Examination of the injured surface revealed some surprising features. In superficial lesions the surviving dermis frequently showed little or no cellular infiltration, hyperaemia, or even oedema. Oedema, if present, was more obvious in the subcutaneous tissues than in the dermis. On occasion injury by scalding produced lesions of unexpected depth; we have observed coagulative necrosis of the whole thickness of the skin by a scald. At 21 hours after injury there appeared the earliest signs of the characteristic change of liver degeneration.

Death between 24 and 100 hours.—Our material includes 14 cases which terminated fatally during this period. Eleven patients who were personally observed died solely or mainly from acute toxæmia; in 2 of the remainder secondary shock probably accounted for death. In general, therefore, this period may be regarded as that during which severe acute toxæmia proved fatal.

In only one case was there evidence of microbial infection of the burned area; the pathological changes were therefore characteristic of acute toxæmia of burns. The most striking features were found in the liver; apart from this, no organ showed any constant or remarkable change. Some degree of fatty degeneration was common in the kidney and occasional in the myocardium. Changes in the suprarenal glands were carefully looked for; they were, however, very inconstant, and consisted of varying degrees of congestion, which when pronounced was associated with slight haemorrhage, and of nuclear degeneration of the cortical cells. On occasion multiple erosions of the gastric mucosa were found, to which vomiting of altered blood during toxæmia was to be attributed. The other organs were affected in much the same way as in individuals dying before 24 hours. In most instances practically the whole of the burned area was free from any sign of bacterial growth.

Death after 100 hours.—Thirteen cases in which death occurred between 6 days and 6 weeks were examined. Five were examples of prolonged acute toxæmia without definite signs of severe bacterial infection; the presence of sepsis was doubtful or at most the degree of infection was very mild. In the remaining 8 cases sepsis was severe or very severe.

In prolonged acute toxæmia the changes were very similar to those described for rapidly fatal toxæmia: in 2 instances there were also duodenal ulcers. In cases of sepsis the changes were those of septæmia or pyæmia. Congestion and haemorrhage in the suprarenal gland, though inconstant, were more common in this group than in cases of earlier death.

Liver Necrosis and Degeneration.—This, the most striking and characteristic feature of the pathology of burns, has not, so far as we can find, received special attention in the past.

In its earliest form, at 21 hours after injury, it appeared as fatty degeneration of the epithelial cells surrounding the efferent veins in the central zone of the
BURNS UNDER MODERN TREATMENT

hepatic lobules; the fatty degeneration was accompanied by nuclear damage, especially karyolysis, which was constant and was more severe in proportion to

Fig. 606.—Microphotograph of liver showing degeneration and necrosis of cells of central zone of lobule. Death at 100 hours from acute toxaemia. (x 50.)

cytoplasmic changes than in most other conditions, such as anaemia and chronic venous congestion, which produce degeneration of cells of the central zone. Evidently even at this early stage the cells had suffered serious injury.

Fig. 607.—Microphotograph of liver showing extreme fatty degeneration of cells of central zone. Death at 68 hours from acute toxaemia. (x 160.)
At a more advanced stage, from 57 hours onwards, the characteristic severe form of damage was found. On naked-eye examination the liver was slightly enlarged, light yellow, soft, greasy, and friable. On the cut surface the lobular marking was conspicuous owing to greater pallor of the central zone; sometimes, however, haemorrhage in the central zones produced an appearance resembling 'nutmeg' liver. On microscopic examination necrosis of varying degree of the cells of the central parts of the lobules was seen (Figs. 606–608). In the most extreme examples only a narrow strip of liver substance surrounding each portal tract showed surviving liver cells; the remainder were completely necrotic. Sections suitably stained showed much free fat in the dead cells, but the most completely necrotic cells of the central zones might contain less fat than those less severely damaged nearer the periphery of the lobules. The disorganization of liver structure was such that with collapse of the walls of the sinusoids haemorrhage occurred in the central zones, thus producing, as already mentioned, a condition simulating the 'nutmeg' liver of chronic venous congestion. It was clear, however, from consideration of the earlier changes, that the process was primarily a degeneration leading to necrosis of the parenchyma cells. In the extent and completeness of destruction of liver tissue, the microscopic picture was comparable with that of acute liver atrophy, but differed in the zonal distribution, which was constant and characteristic. It differed also from the majority of bacterial toxemias both in affecting the central instead of the peripheral zone and in the more pronounced severity of the injury to the liver cells.

In Table I the relation of the liver lesion to the incidence and severity of acute toxemia is shown. Cases not personally observed by us and cases admitted late with grossly infected burns have been marked as yielding insufficient data; in one
Table I.—The Relation of Acute Toxæmia and Sepsis to Liver Changes in 33 Fatal Cases

<table>
<thead>
<tr>
<th>INITIALS</th>
<th>SEX</th>
<th>AGE IN YEARS</th>
<th>TIME OF DEATH</th>
<th>ACUTE TOXÆMIA</th>
<th>SEPSIS</th>
<th>LIVER Degeneration</th>
<th>Eosinophil Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>G. B.</td>
<td>M.</td>
<td>1 yr. 7 mth.</td>
<td>5 ½ hr.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Numerous</td>
</tr>
<tr>
<td>M. P.</td>
<td>F.</td>
<td>2 yr. 10 mth.</td>
<td>7 ½ hr.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Numerous</td>
</tr>
<tr>
<td>T. W.</td>
<td>M.</td>
<td>57 yr.</td>
<td>9 hr.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>J. F.</td>
<td>F.</td>
<td>50 yr.</td>
<td>11 hr.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>A. McL.</td>
<td>F.</td>
<td>2 yr. 10 mth.</td>
<td>21 hr.</td>
<td>—</td>
<td>—</td>
<td>Slight</td>
<td>—</td>
</tr>
<tr>
<td>G. M.</td>
<td>M.</td>
<td>7 yr.</td>
<td>23 hr.</td>
<td>?</td>
<td>—</td>
<td>Slight</td>
<td>—</td>
</tr>
<tr>
<td>R. B.</td>
<td>M.</td>
<td>3 yr. 6 mth.</td>
<td>24 hr.</td>
<td>I. D.*</td>
<td>—</td>
<td>—</td>
<td>Slight Present</td>
</tr>
<tr>
<td>C. M.</td>
<td>F.</td>
<td>2 yr.</td>
<td>24 hr.</td>
<td>I. D.</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>G. H.</td>
<td>M.</td>
<td>1 yr. 7 mth.</td>
<td>36 hr.</td>
<td>I. D.</td>
<td>—</td>
<td>—</td>
<td>Present</td>
</tr>
<tr>
<td>E. T.</td>
<td>F.</td>
<td>8 yr.</td>
<td>57 hr.</td>
<td>Severe</td>
<td>—</td>
<td>Severe</td>
<td>Present</td>
</tr>
<tr>
<td>N. T.</td>
<td>F.</td>
<td>20 yr.</td>
<td>60 hr.</td>
<td>Severe</td>
<td>—</td>
<td>Slight</td>
<td>—</td>
</tr>
<tr>
<td>A. R.</td>
<td>F.</td>
<td>10 yr.</td>
<td>63 hr.</td>
<td>Severe</td>
<td>—</td>
<td>Very severe</td>
<td>—</td>
</tr>
<tr>
<td>F. G.</td>
<td>F.</td>
<td>5 yr. 6 mth.</td>
<td>68 hr.</td>
<td>Severe</td>
<td>—</td>
<td>Severe</td>
<td>—</td>
</tr>
<tr>
<td>R. O'D.</td>
<td>M.</td>
<td>9 mth.</td>
<td>68 hr.</td>
<td>Severe</td>
<td>—</td>
<td>Severe</td>
<td>—</td>
</tr>
<tr>
<td>J. R.</td>
<td>F.</td>
<td>1 yr. 10 mth.</td>
<td>68 hr.</td>
<td>Severe</td>
<td>—</td>
<td>Severe</td>
<td>—</td>
</tr>
<tr>
<td>R. G.</td>
<td>M.</td>
<td>9 mth.</td>
<td>71 hr.</td>
<td>Severe</td>
<td>Present</td>
<td>Very severe</td>
<td>—</td>
</tr>
<tr>
<td>J. B.</td>
<td>M.</td>
<td>8 mth.</td>
<td>78 hr.</td>
<td>Severe</td>
<td>—</td>
<td>Severe</td>
<td>—</td>
</tr>
<tr>
<td>J. M.</td>
<td>F.</td>
<td>50 yr.</td>
<td>80 hr.</td>
<td>Severe</td>
<td>—</td>
<td>Slight</td>
<td>—</td>
</tr>
<tr>
<td>E. S.</td>
<td>F.</td>
<td>9 yr.</td>
<td>93 hr.</td>
<td>Severe</td>
<td>—</td>
<td>Fairly severe</td>
<td>—</td>
</tr>
<tr>
<td>M. A.</td>
<td>M.</td>
<td>30 yr.</td>
<td>100 hr.</td>
<td>Severe</td>
<td>—</td>
<td>Very severe</td>
<td>—</td>
</tr>
<tr>
<td>T. S.</td>
<td>M.</td>
<td>6 yr.</td>
<td>6 d.</td>
<td>I. D.</td>
<td>Severe</td>
<td>—</td>
<td>Present</td>
</tr>
<tr>
<td>A. O.</td>
<td>M.</td>
<td>1 yr.</td>
<td>7 d.</td>
<td>I. D.</td>
<td>Severe</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>G. McL.</td>
<td>F.</td>
<td>2 yr. 3 mth.</td>
<td>8 d.</td>
<td>Severe</td>
<td>Present</td>
<td>Severe</td>
<td>—</td>
</tr>
<tr>
<td>P. A.</td>
<td>M.</td>
<td>3 yr.</td>
<td>8 d.</td>
<td>Prolonged</td>
<td>Severe</td>
<td>Severe</td>
<td>—</td>
</tr>
<tr>
<td>G. G.</td>
<td>F.</td>
<td>1 yr. 11 mth.</td>
<td>9 d.</td>
<td>I. D.</td>
<td>Severe</td>
<td>Slight</td>
<td>Present</td>
</tr>
<tr>
<td>A. J.</td>
<td>F.</td>
<td>7 yr.</td>
<td>10 d.</td>
<td>Severe</td>
<td>—</td>
<td>Severe</td>
<td>—</td>
</tr>
<tr>
<td>C. S.</td>
<td>F.</td>
<td>1 yr. 5 mth.</td>
<td>11 d.</td>
<td>Mild</td>
<td>Very severe</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>B. R.</td>
<td>F.</td>
<td>23 yr.</td>
<td>11 d.</td>
<td>Prolonged</td>
<td>Very mild</td>
<td>Very severe</td>
<td>—</td>
</tr>
<tr>
<td>J. W.</td>
<td>F.</td>
<td>16 yr.</td>
<td>12 d.</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
<td>—</td>
</tr>
<tr>
<td>M. C.</td>
<td>F.</td>
<td>3 yr. 6 mth.</td>
<td>14 d.</td>
<td>Fairly severe</td>
<td>—</td>
<td>Recovering</td>
<td>—</td>
</tr>
<tr>
<td>C. McG.</td>
<td>M.</td>
<td>1 yr. 10 mth.</td>
<td>15 d.</td>
<td>I. D.</td>
<td>Very severe</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>G. W.</td>
<td>M.</td>
<td>2 yr. 5 mth.</td>
<td>20 d.</td>
<td>Moderate</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>B. M.</td>
<td>F.</td>
<td>12 yr.</td>
<td>6 w.</td>
<td>Mild</td>
<td>Severe</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* I.D. = Insufficient data. Cases not specially investigated.
other case the diagnosis of toxaemia was doubtful. Omitting these from consideration, it will be seen that the relationship of the liver lesion to acute toxaemia was in every respect very close. Of 16 cases of severe or prolonged acute toxaemia, the liver suffered intense damage in 14. In cases of toxaemia without severe liver damage, treatment had included continuous intravenous dextrose saline from an early stage, a point to which we shall refer in discussing treatment.

Evidently, also, bacterial infection was not responsible for the liver lesions. In the majority of cases with liver damage there was no definite evidence of infection. Moreover, the typical lesion was not produced by sepsis even in its worst form; in sepsis the changes in the liver were those usual after grave bacterial infections, but were incomparably less serious than the changes we have described as characteristic for burns. Lastly, when liver lesion and sepsis coexisted, the severity of one bore no relation to the severity of the other.

That some degree of liver damage was sustained in a number of patients who survived was indicated by the occurrence of jaundice. Pathological confirmation was afforded by a case of accidental death on the 14th day after extensive and deep burns. The main features of the course had been profound secondary shock, moderately severe acute toxaemia, and jaundice between the 3rd and 9th days; there was no obvious bacterial infection and the outlook had been favourable. In the liver (Fig. 609) the cells in the centre of each lobule had disappeared more or less completely, leaving only a reticulum with a few remnants of necrotic cells, and the surrounding liver cells were healthy. The obvious interpretation was that an injurious agent which had destroyed many cells had ceased to be active at the time of death and that such cells as had survived had returned to normal.

![Fig. 609.—Microphotograph of liver showing mild injury with recovery of surviving cells. Accidental death on 14th day. (X 65.)](image-url)
In summarizing we may affirm that after death from burns a lesion of the liver cells was found in many cases which was characteristic of this form of injury. Its relation to acute toxæmia was so remarkably close as to leave little doubt that liver lesion and acute toxæmia were produced by the same mechanism. The responsible agency was certainly not bacterial infection, and, in our view, the liver lesion furnished the strongest indication of a non-bacterial toxin circulating during the first few days after a burn.

**Eosinophil Cell Infiltration.**—This feature has not to our knowledge been mentioned previously in pathological descriptions. We found it in 7 fatal cases (*Table I*). The most striking examples were in 2 cases of early death (5½ and 7½ hours after injury). In these the accumulations of eosinophil leucocytes were large enough to be visible to the naked eye as bright yellow spots of pin-head size under the capsule of the liver and on the cut surface; microscopically they presented a remarkable appearance (*Fig. 61o*) of dense masses of leucocytes crowding the tissue, especially the fibrous tissue of certain portal tracts, and associated in one instance with small foci of necrosis. In the remainder the infiltration was much less massive and was found only on microscopic examination; there was also some excess of eosinophils in other situations, particularly the spleen and lymph-glands. The infiltration was found as late as 9 days after injury, and evidently was not always associated with a rapidly fatal issue. As mentioned previously, we have found no eosinophilia in the blood in our series. At present we are unable to express an opinion as to the significance of the observation.

**DESCRIPTION OF ILLUSTRATIVE CASES**

The following cases have been selected to illustrate important clinical and pathological features on which our main conclusions in the foregoing sections have been based.
Case 1.—Extensive scalds. No initial or secondary shock; mild acute toxæmia; very mild sepsis; recovery.

E. H., male, aged 11 years, admitted 2 hours after injury. Lesions healed by 30th day. Extent shown in Fig. 611. Clinical course during first 12 days illustrated by Chart 1.

POINTS.—(1) High leucocyte count on admission. (2) During mild acute toxæmia circulatory efficiency was unimpaired, there was no change in blood concentration or sedimentation rate, and no evidence of bacterial infection; changes in blood chemistry were insignificant. (3) Jaundice from 4th to 9th day following toxæmia. (4) Very mild sepsis from 8th to 12th day.

Comment.—A fairly typical example of mild acute toxæmia and mild sepsis.

Figs. 612, 613.—Case 2. Photographs showing extent of scalds.
Case 2.—Moderately extensive scalds. No initial or secondary shock; early fulminating acute toxæmia; death at 78 hours.

J. B., male, aged 8 months, admitted at 1½ hours after injury. Extent shown in Figs. 612, 613. Clinical course illustrated by Chart 2.

Chart 2. Case 2.

Points: (1) No initial or secondary shock. (2) Onset of acute toxæmia at 8 hours; early progressive pyrexia; severe cerebral disturbance with restlessness, apathy, stupor, and terminal coma punctuated by repeated convulsions. (3) No serious fall in systolic blood pressure till a few hours before death; erratic diastolic level. (4) No conspicuous increase in blood concentration; very evanescent improvement after each intravenous infusion. (5) No evidence of bacterial infection. (6) Moderate fall in blood-chlorides at 9 hours before death.


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<tbody>
<tr>
<td>5½</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
</tr>
<tr>
<td>7½</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
</tr>
<tr>
<td>Post-</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
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</table>

Post-mortem Examination.—Liver.—Large, pale, 'nutmeg' appearance. Severe degeneration and necrosis of cells in central zones of lobules; hemorrhagic congestion in parts.

Lungs.—Congestion, some edema.

Injured Area.—Coagulative necrosis of whole thickness of skin, no cellular infiltration, no hyperæmia; edema of subcutaneous tissues.

Other Organs.—Nothing of importance.

Comment.—A typical example of early fulminating acute toxæmia. Anhydremia, hypochloraemia, and bacterial infection were excluded as aetiological factors. Some other agency was responsible for the overwhelming illness and for the destruction of liver cells.

Case 3.—Very extensive burns. No initial shock; secondary shock; severe acute toxæmia; bronchopneumonia; death at 93 hours.

E. S., female, aged 9 years, admitted 1 hour after injury. Extent was about 65 per cent of total body surface, including face and front of chest. Clinical course illustrated by Chart 3.
BURNS UNDER MODERN TREATMENT

Points: (1) No initial shock even after very severe and extensive burns. (2) Secondary shock after local treatment; tendency for blood-pressure to fall remained for 24 hours. Probably overlapping of secondary shock and onset of acute toxæmia. (3) During acute toxæmia there were periods of collapse with sudden falls of blood-pressure. (4) The capillary blood became concentrated, evidently as a result of local circulatory stasis; the venous blood was unaltered. (5) No evidence of bacterial infection; no leucocytosis. (6) No evidence of acidosis and no fall of blood-chlorides.

Post-mortem Examination.—
Trachea and Bronchi.—Acutely inflamed.
Lungs.—Extensive acute broncho-pneumonia. These respiratory tract lesions were associated with burns of face and front of chest.
Liver.—Severe degenerative changes in central zones of all lobules; many necrotic cells.
Kidney.—Degeneration of epithelium of tubules.
Burned Area.—A narrow band of dense leucocytic infiltration deep to the coagulum. In deepest part of cutis vera and subcutaneous tissues no cellular infiltration or oedema and little hyperæmia.

Other Organs.—Nothing of importance.

Comment.—Another example of early severe acute toxæmia which was not due to anhydremia, bacterial infection, or changes in blood chemistry. Respiratory tract lesions were a contributory cause of death.
Case 4.—Scalds of small extent. Severe acute toxæmia on admission; death at 68 hours.

J. R., female, aged 1 year 10 months, admitted at 20 hours after injury. Toxæmia had begun at 8 hours after injury. Extent shown in Fig. 614. Clinical course illustrated by Chart 4.
POINTS: (1) Gravely ill on admission. Toxaemia not controlled by tannic acid treatment. Apparent temporary benefit from intravenous sodium bicarbonate. (2) Steady slow fall in blood-pressure during the last 16 hours. (3) No increased blood concentration, no evidence of bacterial infection, and, apart from some fall of blood-chlorides, no change in blood chemistry.

POST-MORTEM EXAMINATION.—

Liver.—Pale, yellow, greasy. Extreme fatty degeneration of all parts of the lobules, early necrosis of cells in central zones.

Kidney.—Widespread fatty degeneration of the cells of all tubules.

Heart.—Fatty degeneration of inner part of myocardium.

Lungs, Spleen, Suprarenals.—Congestion.

Other Organs.—Nothing of importance.

Comment.—An example of early, severe, and fatal acute toxaemia following a small injury. Degenerative changes in the organs were widely distributed, the liver being most affected. Anhydremia, bacterial infection, and significant changes in blood chemistry were absent. The failure to respond to tannic acid treatment was unusual in such a small injury.

Case 5.*—Scalds of moderate extent. Treatment by a weak tannic acid preparation; death at 23 hours from persistent secondary shock or fulminating acute toxaemia or both.

G. M., 7 years, admitted at 1 hour after scalds of both legs. Local treatment was the application of jelly containing 5 per cent tannic acid and a mercurial antiseptic. Clinical course illustrated by Chart 5.

* The investigation and treatment of this case were carried out by Dr. G. D. Rowley, to whom we are indebted for details and for permission to publish.
POINTS.—(1) No initial shock. (2) Persistent tendency to fall in blood-pressure after 4½ hours. The response to intravenous gum saline was only evanescent at 8 hours and failed altogether at 18 hours. (3) Pyrexia and other features of the clinical course were strongly reminiscent of acute toxæmia. (4) No change in blood concentration or chemistry; no bacterial infection.

CASE 5.

BACTEROLOGY: CULTURES.

<table>
<thead>
<tr>
<th>Hours</th>
<th>Burned Area</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sterile</td>
<td>Sterile</td>
</tr>
<tr>
<td>8</td>
<td>Sterile</td>
<td>Sterile</td>
</tr>
<tr>
<td>17</td>
<td>Sterile</td>
<td>Sterile</td>
</tr>
<tr>
<td>20+</td>
<td>Sterile</td>
<td>Sterile</td>
</tr>
<tr>
<td>22+</td>
<td>Sterile</td>
<td>Sterile</td>
</tr>
</tbody>
</table>

BLOOD CHEMISTRY.

<table>
<thead>
<tr>
<th>Hours</th>
<th>% CO2</th>
<th>% HCO₂</th>
<th>Alk. Phos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>68</td>
<td>1.9</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>640</td>
<td>1.7</td>
</tr>
<tr>
<td>17</td>
<td>61</td>
<td>600</td>
<td>1.7</td>
</tr>
<tr>
<td>22+</td>
<td>61</td>
<td>600</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Differential blood film (4 hours): slight increase in eosinophils.

POST-MORTEM EXAMINATION.—Beyond slight degeneration of the cells of the central zones of the liver lobules, there was no change of note. There was nothing to suggest mercurial poisoning.

Comment.—This case is included here because the clinical course, though resembling that frequently described for fatal burns, has been outwith our experience in the present series. It is possible that the unusual course was the result of the use of a preparation with a slow coagulating action. The balance of evidence would appear to favour the view that death was due mainly to fulminating toxæmia. Anhydræmia, bacterial infection, and changes in blood chemistry certainly played no part.

Case 6.—Scalds of moderate extent. No initial or secondary shock; fulminating acute toxæmia which steadily regressed when extract of suprarenal cortex was administered; no sepsis; recovery.

D. M., male, 3 years 2 months, admitted 2 hours after injury. Extent shown in Fig. 615. Clinical course up to 120 hours illustrated by Chart 6.

![Fig. 615.—Case 6. Photograph showing moderate extent of lesions.](image)

POINTS.—(1) No initial or secondary shock. (2) Acute toxæmia of fulminating type; diminished pulse pressure, increased heart-rate, pyrexia. By 45 hours pronounced circulatory failure and coma. (3) Toxic signs receded steadily when administration of extract of suprarenal

"This case has been mentioned briefly in a previous publication."
cortex was begun. (4) During development and also regression of toxæmia there was no significant change in blood concentration or blood chemistry; no evidence of bacterial infection up to 90 hours. (5) Diminution of early leucocytosis irrespective of toxæmia.

**Chart 6. Case 6.**

<table>
<thead>
<tr>
<th>BACTERIOLOGY: CULTURES</th>
<th>BLOOD CHEMISTRY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hours</strong></td>
<td><strong>Burned Area.</strong></td>
</tr>
<tr>
<td>3</td>
<td>Sterile, Sterile.</td>
</tr>
<tr>
<td>24</td>
<td>Sterile, Sterile.</td>
</tr>
<tr>
<td>40</td>
<td>Sterile, Sterile.</td>
</tr>
<tr>
<td>67</td>
<td>Sterile, Sterile.</td>
</tr>
<tr>
<td>90</td>
<td>Sterile, Sterile.</td>
</tr>
</tbody>
</table>

**COMMENT.**—The action of extract of suprarenal cortex, which was exerted apparently mainly on the circulatory mechanism, was in this case dramatic. Apparently the liver and other important organs escaped irreparable damage.
Figs. 616, 617.—Case 7. Photographs, taken post mortem, showing very extensive area of lesions.

Chart 7. Case 7.

**Temperature**

**Pulse Rate**

**Haemoglobin, Venous Blood**

**Haemoglobin, Capillary Blood**

**Systolic B.P.**

**Diastolic B.P.**

**Hours after Injury**

- Admission
- Very severe
- Shock
- Vomited once
- Condition Satisfactory
- Sudden onset severe haemorrhage
- Bluish altered blood
- Pulse impossible

Intravenous Continuous Drip Infusion 6% Dextrose Saline, Total 2000 cc.
BURNS UNDER MODERN TREATMENT

Case 7.—Very extensive scalds. No initial shock. Severe secondary shock. Late onset of rapidly fatal acute toxæmia.

A. R., female, 10 years, admitted at 1½ hours after injury. Extent shown in Figs. 616, 617. Clinical course illustrated by Chart 7.

Points: (1) No initial shock even after very extensive scalds. (2) Very severe secondary shock developed during local treatment; rapid response to treatment. (3) Intravenous continuous-drip infusion of dextrose-saline throughout. (4) Sudden and unexpected onset of toxic signs at 56 hours; extract of suprarenal cortex then given intravenously was without benefit. Rapidly fatal toxæmia. (5) Early appearance, at 48 hours, of jaundice. (6) Serum sodium low before shock and again during toxæmia; chlorides and urea-nitrogen unaltered. (7) Blood concentration moderately raised throughout.

POST-MORTEM EXAMINATION.—

Liver.—Intense diffuse necrotic and degenerative changes.

Stomach.—Numerous erosions of mucosa—the cause of hæmatemesis.

Lungs.—Edema pronounced.

Kidney.—Widespread degeneration of tubular epithelium.

Other Organs.—Nothing of importance.

Comment.—One of the latest cases of the series. Intravenous dextrose-saline was given throughout in the hope of mitigating liver damage, and extract of suprarenal cortex was given when circulatory failure appeared; both measures failed to achieve their objective. The fall of serum sodium at 3½ hours indicated the need for further investigation; the later fall during toxæmia suggested that functional impairment of the suprarenal cortex might be present without histopathological changes. Liver insufficiency was probably the main cause of death. In view of the extreme degree of liver damage, the long period of apparent well-being and the late onset of toxic signs were noteworthy.

<table>
<thead>
<tr>
<th>Case 7</th>
<th>Blood Chemistry</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Serum Na, mg. %</td>
</tr>
<tr>
<td>3½</td>
<td>115</td>
</tr>
<tr>
<td>23</td>
<td>147</td>
</tr>
<tr>
<td>60</td>
<td>141</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Case 7</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours</td>
<td>Chlorides</td>
</tr>
<tr>
<td>18</td>
<td>+</td>
</tr>
<tr>
<td>48</td>
<td>+</td>
</tr>
<tr>
<td>57</td>
<td>+</td>
</tr>
</tbody>
</table>

Case 8.—Very extensive and deep burns. Very severe shock; mild acute toxæmia; severe sepsis and pyæmia; duodenal ulcers; death on 11th day.

E. S., female, 1 year 5 months, admitted 1½ hours after injury. Extent comparable with that in Cases 3 and 7. Clinical course illustrated by Chart 8.

POINTS.—(1) Very severe shock, probably initial merging into secondary. Capillary blood concentrated during low pressure. (2) Acute toxæmia of mild degree on 3rd and 4th days. (3) Severe bacterial infection from 7th day; hemolytic streptococci in blood-cultures on 9th day.

Post-mortem Examination.—Hemolytic streptococci in burned area and blood. Pyemic abscesses in lungs. In all organs the usual changes found in pyæmia.

Liver.—No change beyond those usual in bacterial infection.

Duodenum.—Two acute ulcers on posterior wall of first part.

Hypothalamus.—Toxic changes, but no greater than in other parts of brain.

Comment.—One of the earliest cases of the series, and incompletely investigated. It illustrated the association of very deep burns with severe shock, but with only mild acute toxæmia, and also with severe sepsis. This was a typical example of the results of hemolytic streptococcal infection and pyæmia. There were no special histopathological changes in suprarenal glands or hypothalamus to suggest a cause for the duodenal ulcers.

Case 9.—Scalds of moderate extent. Early onset of cerebral disturbance; death at 5½ hours; infiltration of liver with eosinophil cells.

G. B., male, 1 year 7 months, previously healthy, sustained scalds of about 15 per cent of body surface. Picric acid was applied. At 2 hours he became apathetic and stuporous, epileptiform convulsions began and recurred at short intervals. On admission to hospital at 5½ hours he was deeply comatose and died in a few minutes.

Post-mortem Examination.—

Meninges and Brain, Lungs, Thoracic Lymph-glands.—All greatly congested.

Liver.—Eosinophil leucocyte aggregations, which have already been described.

Injured Area.—Hyperæmia of cutis vera, but no cellular reaction. Extreme hyperæmia and œdema of subcutaneous tissues.

Other Organs.—Nothing of importance.

Blood-culture.—No growth.

Portions of brain, lungs, and liver were tested for picric acid with negative results.

Comment.—A case with very unusual features, especially the rapidly fatal illness and the eosinophil-cell infiltration of the liver. The absence of picric acid in the organs examined did not support, though it did not exclude, the possibility of picric acid poisoning in a susceptible individual. Explanations such as local loss of plasma need scarcely be considered in view of the moderate extent of injury, and bacterial infection can be excluded.

Case 10.—Extensive scalds. Treatment at first by application of gentian violet alone; acute toxæmia developed, controlled by tannic acid.

E. K., male, 4 years 6 months, admitted thirty minutes after scalds of 20 per cent of body surface; 1 per cent gentian violet applied at intervals. At 8 hours vomiting of altered blood began and the blood-pressure fell. At 11 hours 20 per cent tannic acid applied. Toxic signs receded and had disappeared by 20 hours.

Capillary blood concentration and blood-chlorides remained unaltered throughout.

Case 11.—Extensive scalds. Increased blood concentration without systemic disturbance.

J. W., male, 6 years 9 months, admitted at 2 hours after scalds of 20 per cent of body surface. Secondary shock developed during local treatment, but disappeared after intravenous gum saline. Afterwards no systemic upset. Yet the capillary blood hemoglobin remained between 112 per cent and 130 per cent up to 67 hours.
Case 12.—Extensive burns. Haemolytic streptococci in cultures from burned area without systemic disturbance.

T. W., male, 4 years 10 months, admitted at 8 hours after burns of 20 per cent of body surface. Secondary shock following local treatment disappeared by 18 hours. Afterwards there was no systemic upset. Yet haemolytic streptococci were grown in all cultures from two areas between 24 hours and 7 days.

Case 13.—Extensive burns. Mild secondary shock. Severe acute toxemia with recovery on administration of extract of suprarenal cortex.

E. F., male, 49 years, admitted at 1½ hours after burns of 25 per cent of body surface. Severe acute toxemia between 32 and 93 hours. Blood examination is shown in Table 2.

Table II. Case 13.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>CO₂, 10 per cent</th>
<th>Na⁺, mEq/l</th>
<th>Urea Nitrogen</th>
<th>Plasma Sodium, 10 per cent</th>
<th>Van den Bergh Reaction</th>
<th>Hb, per cent</th>
<th>Htc,</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>55 55 487 87</td>
<td>63 10</td>
<td>-</td>
<td>-</td>
<td>60 17-2</td>
<td>After</td>
<td></td>
<td></td>
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<tr>
<td>31+</td>
<td>58 40 444 60</td>
<td>63 10</td>
<td>-</td>
<td>-</td>
<td>67 19-1</td>
<td>Before</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>66 38 450 84</td>
<td>74 10</td>
<td>-</td>
<td>-</td>
<td>83 17-9</td>
<td>During</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>69 39 452 86</td>
<td>70 10</td>
<td>-</td>
<td>-</td>
<td>51 14-7</td>
<td>Toxaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>101+</td>
<td>68 37 440 84</td>
<td>40 10</td>
<td>-</td>
<td>51 14-7</td>
<td>50 14-3</td>
<td>After</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35h+</td>
<td>70 38 450 87</td>
<td>38 10</td>
<td>-</td>
<td>-</td>
<td>38 10-9</td>
<td>Toxaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48h+</td>
<td>69 36 452 83</td>
<td>37 10</td>
<td>-</td>
<td>38 10-9</td>
<td>29 8-3</td>
<td>Toxaemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comment.—This case is quoted to illustrate a detailed examination of blood chemistry before, during, and after acute toxemia. It was one of the few cases in which the venous blood became concentrated (see values of iron and haemoglobin). There was also a moderate rise of urea-nitrogen during acute toxemia. The indirect van den Bergh reaction, indicating latent jaundice, was present as early as 37 hours. Otherwise there was no change of note.

DISCUSSION

The points which seem to call for consideration are the nature of shock, the classification of the clinical course, the causation of acute toxemia, and the therapy of burns. To avoid discursive and speculative discussion, we shall direct attention mainly to features on which evidence can be offered.

SHOCK

On the first point—that is, the nature, causation, and classification of shock—we have no evidence that is at all decisive, and the most that can be said for our views is that they are favoured by clinical experience in the present and also previous studies. We shall consider first the occurrence, incidence, and aetiology of initial shock. One great difficulty in deciding this question arises from the fact that very few burned individuals can be examined immediately or very shortly after injury; few arrive at hospital within an hour of injury. It is, however, reasonably certain that a shocked condition, of nervous origin, may arise very shortly after injury; it is a highly probable mechanism of causing death, for example, in those who succumb very rapidly after burns involving almost the entire body surface. In burns of lesser extent, shock at an early stage is infrequent, rarely serious, and responds rapidly to administration of warmth and sedatives; these features it shares with known neurogenic shock arising under other circumstances—for example, during
operations on the upper abdomen.28 Though initial shock, assuming its occurrence and nervous origin, is usually transient, there is good reason to infer that it may, for lack of adequate and timely therapeutic measures, be so prolonged and aggravated as to merge into secondary shock.

To distinguish between initial and secondary shock would also seem justifiable. Secondary shock is delayed; the fall of arterial pressure may not begin till 3 or 4 hours have elapsed. It may appear after initial shock has passed off, and it develops and progresses under conditions of warmth and relief from pain to which initial shock readily responds. The high incidence, indeed the almost invariable occurrence, of secondary shock in extensive lesions, the progressive nature of the circulatory collapse, and the absence of capacity for spontaneous recovery are other broad distinguishing features. Secondary shock, in fact, is the common and dangerous form of shock after burns. Investigation of the condition of secondary shock and of its response to treatment, to which further reference is made, does not yet permit of any decision as to its etiology. Each of the suggested causes of secondary shock, viz., local loss of fluid, nociceptive nerve-impulses, and toxin absorption, can find support in some observations; none of them can at present be excluded. To argue in favour of, or against, one or more, or to assume that all three are operative, would be profitless.

CLASSIFICATION OF THE CLINICAL COURSE

The stages of shock having been dealt with, we pass to acute toxämia. It has been classified, as in previous publications,29,31 as a condition separate from secondary shock on the one hand, and from septic or bacteriogenic toxämia on the other. The separation can be amply justified. Though certain features, such as those associated with circulatory failure, are common to both secondary shock and acute toxämia, and though on rare occasions differentiation may be difficult or impossible (see Case 5), yet in most respects the distinction is clear. Acute toxämia is of later onset; it never begins before 6 hours, usually not till 12 hours, and occasionally serious symptoms are delayed till 48 or even 56 hours after injury. The rectal temperature is usually high in acute toxämia, subnormal in secondary shock. A fall in blood-pressure is the central feature of shock, but is only occasional during most of the toxic phase; commonly the normal systolic level is maintained till a very late stage. The occurrence of toxämia is much more erratic and uncertain than that of secondary shock; it may follow lesions of small or moderate extent after which secondary shock is rarely seen. There seems little justification, too, for regarding acute toxämia as secondary shock which has been delayed or modified by treatment; the characteristic toxämic signs may appear, and at the usual time, when local treatment has been of a primitive type or omitted altogether. In all these facts, however, there is nothing to exclude the possibility that both conditions may be produced by a similar mechanism—for example, absorption of toxic principles from damaged tissues.

There is little doubt that acute toxämia is a condition distinct from septic or bacteriogenic toxämia. This fact is in no way affected by the difficulty of differentiating between the conditions in certain individual cases; the difficulty arises particularly in the low-grade forms of acute toxämia, and is partly due to the fact that we do not yet know how long non-fatal acute toxämia or its sequelae, such as liver damage, may continue to exert their effects.
CAUSATION OF ACUTE TOXÆMIA

We have been able with reasonable certainty to rule out all the suggested causes of acute toxæmia except one. Evidence from purely clinical sources could scarcely be more emphatic. Under the conditions of treatment, increased concentration of the blood, haemolytic streptococcal infection of the burned area, hypochloræmia, and acidosis were inconstant features, even during the most intense toxæmia, and were evidently of no aetiological significance. Moreover, one or more might be present in cases without obvious toxæmia. Investigation is still too limited to permit of conclusions regarding changes in serum sodium and potassium, which may yield evidence of functional impairment of the suprarenal cortex. Apart from these there is no important change in blood chemistry during toxæmia, and certainly none which in itself could produce the striking toxic manifestations.

We do not, however, ignore the possibility that, under other conditions of treatment, one or more of these factors may play an important part in producing symptoms; for example, treatment which permits of continued exudation of fluid at the site of injury may be followed by serious anhydæmia, and haemolytic streptococcal infection of the burned area may occur at an early stage. Nevertheless, neither can be regarded as a real cause of acute toxæmia. It seems to us that recently the importance of these factors has been unduly stressed, and to the exclusion of the essential cause of acute toxæmia.

It is necessary in considering the causation of acute toxæmia to take into account not only the clinical picture of overwhelming poisoning, but also the almost invariable and entirely characteristic pathological changes. The damage to the liver cells is incomparably more severe and extensive than that produced by anoxæmia, by circulatory failure, or by any of the common bacterial toxins; it is in fact an easily recognizable and specific lesion of the toxæmia of burns. In view of this lesion, it is extremely doubtful whether the hypotheses of anhydæmia, streptococcal infection, and hypochloræmia could be considered, even had we not already excluded them with certainty. The only remaining suggested hypothesis—that of the action of a toxic principle which has been absorbed from the burned area—is, on the contrary, adequate to explain both clinical and pathological features. Indeed it is difficult to suggest any mechanism other than the action of a toxin which could produce the extreme degree of liver damage. Such grounds nevertheless would be insufficient for acceptance of the toxin hypothesis were it not that evidence from animal experiment is also favourable. It has recently been shown⁶⁹ that toxin formation occurs in burned areas, and that it is the result, probably, not of bacterial action, but of autolysis of injured tissue. Admittedly the final link in the chain of evidence is still missing, namely, the demonstration of the toxin in the circulating blood during acute toxæmia. At present the available evidence is strongly in favour of the view that acute toxæmia of burns is caused by the action of a specific toxin, of non-bacterial origin, which has been absorbed from the burned area.

A few final points relating to acute toxæmia deserve mention. Measured by histopathological standards, the lesions in the liver are usually much more intense than those in other organs. There is here a suggestion either that the action of the toxin is selective or that it becomes concentrated in the liver; the latter possibility must be considered in any attempt to demonstrate the toxin in the circulating blood. Secondly, it is obvious that the liver lesion is of serious prognostic import.
Since, as is well known, extreme degrees of liver damage can be incurred before signs of insufficiency are apparent, acute toxæmia may be masked and the onset of serious symptoms delayed if other mechanisms, such as the circulation, are not especially incapacitated or are maintained by therapy. Liver function tests may therefore prove of diagnostic and prognostic value.

Lastly, acute toxæmia is clearly a complex condition, involving grave disarrangement of many vital functions. Although investigation of blood chemistry, so far as it has gone, has revealed surprisingly few changes, and those of minor degree only, it is not permissible to assume that tissue chemistry is similarly unaffected. The disturbance of gastric secretion, which occurs even in favourably progressing cases, suggests the possibility of other alterations as yet unsuspected.

**TREATMENT**

In our opinion the treatment of an extensive burn is a problem which constitutes a challenge to the best therapeutic capacity and resources at present available. Knowledge and interest, as well as energy and care, are essential if lives are to be saved. The present results of treatment would probably be improved if these injuries were universally regarded as emergency conditions which yield to none in urgency and in their demands for the highest surgical skill and judgement.

The methods of treatment, already described, are directed at the three main dangers, namely, secondary shock, acute toxæmia, and bacterial infection. In practice they have proved on the whole adequate, and at present we know of no substantial alteration which promises better results. They give a reasonable chance of recovery to the victims of burns which involve less than 50 per cent of the body surface, and a possible chance even to some with burns of greater extent. The advantages and limitations of the present treatment can best be described in respect of stages.

**Initial Shock.**—Our experience of severe initial shock, for reasons already stated, has been very limited, and no opportunities have arisen, for example, in cases with enormously extensive injuries for the trial of methods employed for severe secondary shock, or, in fact, of any active treatment. It is virtually certain, however, that there is a limit to the capacity for recovery; the victims of burns which implicate almost the total skin surface will inevitably die at some stage, and it is questionable whether survival to a later stage is desirable.

**Secondary Shock.**—Treatment by immediate coagulation of the burned area combined with intravenous gum-saline or blood has been used in a large number of cases during the past five years and has proved uniformly efficacious in controlling secondary shock—a pleasing contrast to the treatment of traumatic secondary shock. Evidently the combination of immediate coagulation and intravenous therapy is necessary, as has been repeatedly demonstrated when one or other has been omitted. Apparently similar effects are obtained when rapid coagulation is induced by the silver-nitrate-tannic-acid combination. In only 2 of our patients did the blood-pressure fail to regain a normal level, and yet both lived till long after the time when secondary shock usually proves fatal. Both had injuries of 70 per cent or more of the body surface, and in lesions of such extent we are probably approaching the limits for successful treatment of secondary shock.

Secondary shock is certainly a common cause of death after burns in methods of treatment other than those we have described. Our inquiries on this point
allow no other conclusion. Immediate coagulation of the burned area may therefore be claimed as a life-saving measure at this stage, and we regard its use as imperative. The question will be referred to again in discussing acute toxæmia.

**Acute Toxæmia.**—The practical points to be discussed are the efficacy of tannic acid treatment, its mode of action, the methods of its application, and the effects of adjuvant measures. It may be accepted that the coagulation treatment of burns is still the method of choice; its many advantages enormously outweigh any disadvantages. Most observers are agreed also that it has effected a considerable reduction in mortality. On this account we felt that the use of control cases, in which tannic acid was omitted, would have been unjustifiable, although some information might have been gained. The reduction in mortality is not, however, a universal experience even when the method is efficiently employed. Seeger\(^24\) reported no significant difference in total mortality between a series treated by tannic acid and a comparable series treated by other methods. There was, however, evidence that with tannic acid treatment the death-rate was lower during the first 5 days, thus suggesting that the tannic acid method was superior to others in combating secondary shock and acute toxæmia. In our experience\(^20\) tannic acid undoubtedly minimizes acute toxæmia.

Davidson\(^9\) introduced tannic acid because of its property of precipitating protein, with the object of fixing any toxic agent which might be formed in burned tissues. It has since been suggested that the benefits of tannic acid treatment are to be referred rather to the action of the protective coagulum in diminishing exudation of fluid at the injured surface, in relieving pain, or in preventing bacterial growth. If, however, our views as to the aetiology of acute toxæmia are correct, it is reasonable to assume that precipitation of the proteins of damaged cells by tannic acid minimizes autolytic changes, and thus lessens the chances of toxin formation and absorption. Davidson's original assumption as to the action of tannic acid would therefore seem to be justified.

It is quite evident, however, that tannic acid does not always control acute toxæmia, and the reason is difficult to find. The most suggestive fact in this connection is the association of acute toxæmia with certain types of injury, and therefore, presumably, with lesions of a certain depth, and, up to certain limits, irrespective of extent. As has been mentioned, very deep or very superficial injuries are often associated with mild or no toxæmia. On the other hand very extensive burns, whatever the depth, are always followed by toxæmia. We may be permitted some speculation on these observations. In deep burns, which penetrate to subcutaneous tissues, the opportunities for absorption during the first few days are probably small compared with those in burns which do not destroy the vascular dermis; it is possible, however, that in deep burns the opportunities are enhanced at a later stage by the growth of new vessels when dead tissues are becoming separated. It is at least conceivable that the depth of injury which is optimum for the development of acute toxæmia is that which is too deep to allow penetration of tannic acid to many damaged cells and yet permits of absorption from numerous intact vessels. In very extensive injuries, whatever the depth, the total mass of damaged tissue which is in relation to intact vessels and which escapes coagulation by tannic acid is bound to be great, and is probably always sufficient to produce severe toxæmia.
On the above reasoning it would seem important to secure penetration of the tannic acid. It has been asserted\(^2\) that strong solutions—for example, stronger than 5 per cent—do not penetrate so well as weaker solutions, and are therefore less effective in controlling toxæmia. This view is not in accord with our experience. Certainly the incidence of severe acute toxæmia would seem to be no higher with 20 per cent tannic acid than with 2·5 per cent. In the last 100 consecutive cases in children treated by one of us from an early stage with 20 per cent tannic acid, there were 4 cases of severe toxæmia, of which 2 proved fatal. In a previous investigation\(^3\) 98 consecutive cases in children, admitted before the toxic phase, were treated with 2·5 per cent tannic acid. Again, there were 4 cases of severe toxæmia, of which 1 proved fatal. There is no evidence here of a significant failure to control toxæmia on the part of 20 per cent tannic acid in comparison with the weaker solution. We have felt impelled to continue its employment in preference to weaker solutions because of its undoubted life-saving properties in the treatment of secondary shock.

As adjuvant measures to the treatment of acute toxæmia we have tried intravenous administration of normal saline, gum saline, and dextrose saline, and, recently, extract of suprarenal cortex. We have seen little benefit from intravenous administration of large quantities of normal saline during toxæmia. 'Forcing' fluids is neither necessary nor advisable except in the case of frequent vomiting. Attention may also be drawn to the danger of pulmonary òedema, especially in lesions of the respiratory tract, and this risk is considerably enhanced by intravenous infusions, especially prolonged continuous-drip infusions. On general principles it would seem advisable to use a colloidal solution, such as gum saline, during the circulatory failure of acute toxæmia, when, presumably, capillary permeability is abnormally increased; particularly in the late stages the effects are, however, very evanescent. Dextrose saline has been given in the hope of mitigating liver damage, and in 2 cases in which a continuous-drip infusion of dextrose saline was used throughout the course, the liver lesion was found to be slight, though the progress of circulatory failure had been unaffected. In another (Case 7), however, in spite of dextrose the liver damage was extreme and was probably the immediate cause of death. Sodium bicarbonate was used in 1 case only, without special benefit.

A short report of the use of extract of suprarenal cortex in acute toxæmia has already been published\(^4\); 3 cases, one an example of dramatic benefit (Case 6), another in which given at a very late stage the extract was without effect (Case 7), and a third (Case 13) are recorded in this paper. Other personal experience is limited to 3 further cases. In 2, of low-grade slowly developing toxæmia in adults, it was without obvious action. In the other, a child with the typical circulatory failure of acute toxæmia at 23 hours, the benefit was certain. From other sources we have learned of 3 cases of 'collapse' between 6 and 30 hours after injury which responded satisfactorily to extract therapy. Our conclusions, necessarily guarded at present, are that in a proportion of cases of acute toxæmia, notably in children with circulatory failure, suprarenal cortical extract confers definite or even striking benefit. It produces no obvious change in septic burns or other severe bacterial infections. Until more information is forthcoming, we prefer not to speculate as to its action.

The necessity for continued administration of the extract over a long period has been demonstrated. Apparently, in the form of watery extract at present
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available, it is very rapidly destroyed or eliminated. Our present practice in extensive burns is to institute continuous-drip intravenous infusion of dextrose saline from the time of local treatment up to about 60 hours after injury. If circulatory failure develops, suprarenal cortex extract is introduced into the infusion fluid; a constant supply of extract together with sodium chloride is thus maintained. At present the only hope of mitigating liver damage seems to lie in dextrose, though success is far from assured. An agent, such as an antitoxic serum, which will neutralize the toxic principle is the obvious need of the future.

Septic Toxaemia.—The main problems relating to sepsis arise in deep burns which provide conditions exceptionally favourable to the growth of organisms—for instance, a mass of dead and damaged tissue, and impairment or abrogation of the protective bactericidal functions of the skin.

Fig. 618.—Cage used in treatment of burns. Heat supplied by morganite elements; thermostatic control; ventilation by electric fan.

The question has often been raised whether tannic acid is a suitable treatment for deep burns, on account of the frequency with which suppuration occurs under the tanned layer. The introduction of gentian violet by Aldrich as a substitute for tannic acid was an attempt to reduce the incidence of infection, especially by the common invader, the hemolytic streptococcus, on which the dye was believed to exert a selective action. Our view is that the incidence of gross infection after tannic acid has been exaggerated, owing partly to a common misapprehension—the thick inspissated yellow exudate which ultimately intervenes between living and necrotic tissues is often erroneously accepted as evidence of active suppuration. We would conclude also that the method is not in itself conducive to sepsis in deep burns. The aim is to provide a dry impermeable protective covering and so to produce and preserve conditions which are unfavourable to bacterial growth and activity, and the aim can often be achieved if the treatment is well conducted. The
alternative method of combating infection, by antiseptic wet dressings and baths from an early stage, has obvious disadvantages. The methods must be judged from considerations other than infection alone.

The additional application of antiseptics such as gentian violet and acriflavine is of great value in tannic acid treatment. Infection most commonly arises from failure to keep the coagulum dry by exposure to the air. Exposure involves the use of a heating cage, with facilities for regulating temperature and ventilation. Small cages are seldom, if ever, satisfactory. The cage illustrated encloses the cot or bed (Fig. 618); heat is supplied by morganite elements thermostatically controlled, and ventilation is regulated by an electric fan.

The future outlook for the prevention and treatment of haemolytic streptococcal infection in deep burns has been rendered promising by the advent of an effective chemotherapeutic agent. We have used prontosil or other sulphonamide preparation during the past year; it has been administered by mouth from the third day as a prophylactic measure, and supplementary doses have been given intramuscularly at the first sign of infection. The results have been distinctly encouraging, though experience is still too limited to permit of analysis.

Healing.—Since this stage has not entered the scope of the investigation in any particular respect, its treatment needs no discussion here.

Complications.—Lesions of the respiratory tract are likely to remain a difficult problem. The possibility of infection, particularly streptococcal, of such lesions should be borne in mind and appropriate chemotherapeutics adopted. A moist, warm atmosphere gives relief to the discomfort associated with scorching of the upper air-passage, and pulmonary lesions require the prompt and continued administration of oxygen. The prevention of other complications, such as jaundice and duodenal ulcer, probably depends upon the eradication of acute toxæmia.

Although our knowledge of the clinical course and pathology of burns is still incomplete, and the development of effective methods of treatment slow, yet progress in both respects has been steady during the past 12 years. It seems to us that the most urgent need at present, and towards which future investigation should be directed, is the complete prevention or control of acute toxæmia.

SUMMARY

1. An investigation of the clinical course of burns has been carried out in a specially selected series of 65 cases of severe and extensive injuries. The pathology of burns has been studied in 33 fatal cases, in 20 of which the clinical course had also been investigated.

2. The clinical course has been classified in respect of stages; the changes in each stage have been described in detail.

3. The important feature of the investigation relates to the causation of the stage of acute toxæmia. Such factors as anhydremia, changes in blood chemistry, and bacterial infection have been excluded as primary or essential aetiological agencies. The older hypothesis of a specific toxin, which is formed in burned tissue and absorbed into the blood-stream, receives support from this investigation. The important and characteristic pathological lesion of acute toxæmia is degeneration and necrosis of the liver cells. An occasional, and apparently hitherto unrecognized, change is infiltration of the liver, and sometimes of other organs, by eosinophil leucocytes.
4. Evidence for the main conclusions is detailed in a description of illustrative cases.

5. The application of the results to the treatment of burns is discussed.

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