STUDIES
IN
PERINATAL PATHOLOGY

based on
1,947 consecutive autopsies
1952-56

by
# CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREFACE</td>
<td>1</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>3</td>
</tr>
<tr>
<td>COLLECTION OF CLINICAL DATA</td>
<td>8</td>
</tr>
<tr>
<td><strong>INFECTIONS</strong></td>
<td></td>
</tr>
<tr>
<td>General review</td>
<td>11</td>
</tr>
<tr>
<td>Inclusion-body giant cell pneumonia</td>
<td>17</td>
</tr>
<tr>
<td>Thrush (Monilia albicans)</td>
<td>27</td>
</tr>
<tr>
<td>Cytomegalic Inclusion Disease</td>
<td>37</td>
</tr>
<tr>
<td>Congenital toxoplasmosis</td>
<td>56</td>
</tr>
<tr>
<td><strong>CONGENITAL DEFECTS</strong></td>
<td></td>
</tr>
<tr>
<td>General review</td>
<td>97</td>
</tr>
<tr>
<td>Congenital bowing of long bones</td>
<td>113</td>
</tr>
<tr>
<td>Congenital laryngeal atresia</td>
<td>144</td>
</tr>
<tr>
<td>Arterial calcification in infancy</td>
<td>154</td>
</tr>
<tr>
<td>Renal non-function</td>
<td>170</td>
</tr>
<tr>
<td><strong>ANOXIA</strong></td>
<td></td>
</tr>
<tr>
<td>General review</td>
<td>292</td>
</tr>
<tr>
<td>Electronic recording of foetal heart</td>
<td>301</td>
</tr>
<tr>
<td><strong>FOETAL EXSANGUINATION</strong></td>
<td>312</td>
</tr>
<tr>
<td><strong>INTERSTITIAL EMPHYSEMA: PNEUMOTHORAX</strong></td>
<td>334</td>
</tr>
<tr>
<td><strong>SUBDURAL HAEMORRHAGE</strong></td>
<td>354</td>
</tr>
</tbody>
</table>
CONTENTS

MISCELLANEOUS CONDITIONS

The macerated foetus ............... 373

Prematurity

Pulmonary hyaline membrane ....... 374

Intraventricular cerebral haemorrhage 375

Kernicterus ......................... 379

Adrenal cytomegaly .................. 387

Tumours in the Newborn

Cystic hygroma ..................... 395

Congenital neuroblastoma ........... 400

Congenital leukaemia ............... 406

HOSPITAL FIGURES .................. 416

ACKNOWLEDGEMENTS ................. 426
PREFACE

Perinatal Pathology is the science embracing the study of disease processes in the newborn. The perinatal mortality rate has over the last four years failed to maintain the downward trend so evident in the previous decade. To that extent it provides not only a continuing cause for concern, but a challenge to paediatric pathology - a comparatively new and hitherto much neglected medical science.

This thesis is based on a series of 1947 consecutive autopsies performed over a period of 4½ years - 1st January, 1952 to 30th June, 1956 - whilst on the staff of the Department of Pathology, University of Edinburgh, and seconded to the Royal Hospital for Sick Children, Edinburgh.

Personal gain in experience and knowledge has amply rewarded the many often arduous miles travelled, and the many evenings and weekends spent in outlying hospitals. Little benefit would have been derived from this experience without the training, guidance and continual encouragement of Dr. Agnes Macgregor, Consultant Pathologist to the Royal Hospital for Sick Children, Edinburgh. Professor G.L. Montgomery, Professor of Pathology of the University of
Edinburgh has also shown the greatest interest in my work and spared of his time with unfailing support and advice to my ultimate gain.

To Dr. R.F. Ogilvie I will always remain indebted for a basic pathological training, characterised by that so meticulous attention to histological detail - the foundations upon which the experience of ensuing years has been built.

In the words of Michael Scot, one of our earliest (13th century) Scottish scholars ... "with such maistres aye ahint me, there gaed strength to me, sae that the task was aye lichtsome ..........."
This thesis is an account of pathological conditions in the newborn which merit description either on account of their relative importance, or extreme rarity, or because of further advances contributed to existing knowledge. In no way has this thesis been intended as a statistical survey of perinatal mortality.

In the consecutive series of autopsies on which this thesis is based, the still births are those stated by the obstetrician to be of 28 weeks gestation or over. The neonatal deaths include a small proportion of infants under 28 weeks gestation. The survival of numbers of these tiny infants provides at obstetrical hospital meetings a frequent source of spirited, though good humoured verbal exchange. As one paediatrician, in a lighter vein, rather pointedly declared, he "..... now encounters abortions walking in the streets." The pathologist cannot afford to neglect this group of infants and for this reason they have been included in the present series.

This work has been completed at a time when the scope of paediatric pathology in this region has been widening to suit conditions altered as
the result of regional hospital development - consequently the inception of a regional paediatric pathology service - unique in this country. The appendix includes figures supplied by the six main maternity hospitals in the region. The neonatal, stillbirth and perinatal mortality rates have been calculated, and added to these figures are the numbers of autopsies performed at each hospital. These autopsies have risen steadily in number and this year (1956) it has become evident that a death rate-autopsy ratio of considerably over 90% is a practical and feasible proposition. The enthusiasm of obstetricians at the various hospitals has been limited only by their consideration of the physical strain imposed on the pathologist by the natural barriers of distance and a narrow (so far unbridged!) strip of water. For this reason, autopsies have not always been performed on a few severely macerated or obvious anencephalic foetuses. In certain of the hospitals the number of autopsies on neonatal deaths is consequently relatively greater in comparison with the number on still births.

Unfortunately, no uniform system of recording of maternity hospital figures has been
Scale Map: To show centres (black circles) at which the routine perinatal autopsies have been performed.
employed. Figures for the Simpson Maternity Pavilion are given on a weight basis only, whereas in the other hospitals the figures are based on gestational age.

Where babies have been transferred from one hospital to another and subsequently died, allowance has, as far as possible, been made in the respective hospital figures. The strict accuracy of this is only reliable in relation to the Simpson Maternity Pavilion. With a regional paediatric pathology service, however, it is a reasonable assumption that where post-mortems have been performed on any of these babies they have been included in the autopsy figures for their respective hospital of birth.

To this extent the autopsies on which this thesis has been based may be regarded as a reasonable survey of the majority of perinatal deaths occurring in children born in hospital within this region.

It has been a practical impossibility to relate pathological figures as a whole to maternity hospital figures - a fact essential were this to be a review of perinatal mortality. The conduct of such a review must of necessity
be carried out in prospect, the obtaining of information in retrospect being always open to difficulty, with doubt in some cases as to its authenticity.

If the knowledge available to others from this review of 1,947 autopsies is limited, personal gain has been immeasurable. Means for utilisation of the data available from such a vast source of pathological material are now becoming clarified. The keeping of a register of still births and neonatal deaths at each individual hospital is one of the first essentials.

The very utmost obstetrical and paediatric co-operation has been assured and one can envisage in the coming years the rapid collection of thoroughly documented and systematically filed information which, perhaps not to this, but to future generations, might prove of fundamental importance. In this present so-called "atomic" age, it is more important than ever that as a base line, accurate pathological data be available in regard to perinatal mortality.
COLLECTION OF CLINICAL DATA

The collection of clinical information in relation to autopsy work will always present many problems. The completion of forms is always tedious and this may appear even more so to a sleepless obstetrical resident. Information required must be cut to a minimum. To expect a detailed memorandum to be completed in respect of every autopsy case has never proved a practical proposition. The form originally intended for the collection of clinical data for this thesis has, after several modifications, proved entirely satisfactory. After the adoption of this form experimentally in five of the six maternity hospitals, it has been decided to use it throughout this region for routine perinatal autopsies.

The information which can subsequently be card indexed from this form, obviates many of the inaccuracies frequently encountered in reviewing peri-natal autopsies.

The age can be estimated precisely. To be supplied with the information that a baby is one day old is of no value in statistical work, one day meaning anything from 22-28 hours.
The birth weight is available along with the autopsy weight.

The date of the L.M.P. is specifically asked for.

For obstetrical information not specifically sought, a large space has been set aside.

Whilst the information on this form may appear inadequate to an obstetrician, for any survey of pathological conditions in the newborn it will generally prove adequate.
<table>
<thead>
<tr>
<th>NAME</th>
<th>MOTHER'S</th>
<th>HOSPITAL</th>
<th>OBSTETRICIAN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>WARD</td>
<td>PAEDIATRICIAN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autopsy Ref. No.</td>
<td>Hospital Case No.</td>
<td>Booked No.</td>
<td>Date of last Menstrual Period</td>
</tr>
<tr>
<td>Yes/No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Parity</td>
<td>No. of Pregnancy</td>
<td>Previous Pregnancies</td>
<td>Complications of Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Toxaemia (severity)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placenta Praevia (degree)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antepartum Haemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hydramnios</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Premature Rupture of Membranes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any other illnesses</td>
</tr>
</tbody>
</table>

Placenta
Size
Weight
Abnormalities

Cord
Length
Placental Insertion
Round neck 1/2/3
Abnormalities

Method of Delivery
- Labour induced: medical, surgical
- Vertex: with or without forceps
- Breech: with or without forceps
- Caesarean Section

Duration of Labour .......... hours

Complications of Labour
Maternal Distress
Foetal Distress
Heart Rate
Meconium staining
F. H. last heard (precise time)
Prolapse of cord
Haemorrhage: intra, post, partum

Any other relevant information
INFECTIONS
The most striking feature of the present decade in relation to infant mortality has been the pronounced fall in the number of deaths attributable to infection. Macgregor (1946) in a review of 618 neonatal deaths found that 30.7% of these were the direct result of infection. In a corresponding series of 401 neonatal deaths (1949-53) she found the incidence of deaths from infection had fallen to 13.7%.

In the present series of entirely unrelated autopsies, there were 509 deaths from the 2nd - 28th day of life. Of these, 90 (17.6%) were attributable to infection. A figure such as this tends to give an erroneous impression.

The bulk of the number of deaths from infection falls into the period 2 - 7 days. If this period was further broken down into individual days it would be found that the majority of these deaths occurred within the 2nd or 3rd day. As will be seen from Table II, of the 59 deaths (2 - 7 days) 53 were diagnosed pneumonia, and pneumonia within the first few days of life is generally associated with conditions relating to labour. As such these 59 deaths have been regarded as post anoxial; they are directly
related to conditions of labour and are better classified as anoxic deaths, on account of the fact, that it is frequently impossible to decide whether anoxia or pneumonia was the chief cause of death.

**TABLE A.**

<table>
<thead>
<tr>
<th>Days</th>
<th>Total no. of deaths</th>
<th>No. of deaths attributable to infection</th>
<th>Infective deaths as a percentage of total deaths</th>
<th>No. of deaths from infection in premature babies</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 7</td>
<td>378</td>
<td>59</td>
<td>15.6</td>
<td>34</td>
</tr>
<tr>
<td>8 - 14</td>
<td>75</td>
<td>16</td>
<td>21.3</td>
<td>9</td>
</tr>
<tr>
<td>15 - 21</td>
<td>31</td>
<td>9</td>
<td>29.0</td>
<td>4</td>
</tr>
<tr>
<td>22 - 28</td>
<td>25</td>
<td>6</td>
<td>24.0</td>
<td>-</td>
</tr>
</tbody>
</table>

Several noteworthy features are evident even from this totally inadequate survey. Most striking of these is the fact that not one single case of congenital syphilis has been encountered. Thrush (monilia albicans) as a cause of infant mortality in this region has been almost entirely eradicated. The so-called septic aspiration pneumonia has not once been encountered.

Infection with Staphylococcus aureus has been responsible for only 5 deaths - a remarkably
low figure in view of the incidence of staphylo-
coccal infections which have been rated by
various authors (Nelson, 1952, Barber et al, 1953,
Edmunds et al, 1955) as between 10 - 15% of
infants born in large maternity units. Only
two of the cases of staphylococcal infection
encountered were born within the group of 6
maternity hospitals. One infant was born at home.

Sensitivity tests were performed on the
strains of staphylococcus aureus isolated at
autopsy from these 5 cases. All the staphylo-
cocci were penicillin resistant, but all were
sensitive to aureomycin, chloromycetin and
streptomycin.

It is of considerable interest that no
case in an infant or child has yet been encount-
ered at autopsy in this region where the staphylo-
cocci have been resistant to erythromycin.

Meningitis, in every case due to infection
with Esch. coli, accounted for 9 deaths, and it is
of significance that 8 of these occurred in babies
by birth weight premature. Evidence of
phagocytosis of the Esch. coli excluded any
possibility of this organism as a contaminant.

The Esch. coli isolated at autopsy from
the meninges were all tested for type specificity,
but in only one instance was an agglutinable strain isolated - 0126. In this case an Esch.Coli of the same type was isolated from the mother.

Pneumonia: Excluding the period 2 - 7 days, pneumonia accounted for 10 deaths. Post-mortem bacteriological examination was carried out on all of these, but no specific organism was identified. From a retrospective review of these cases, there seems no reason to suspect any other than a pyogenic infection. As in many of these cases an antibiotic had been administered shortly before death, failure to isolate an organism post-mortem might be explained.

Miscellaneous infections: Both on account of their rarity and their pathological interest, the following infections are being considered in greater detail; inclusion body giant cell pneumonia of infancy, thrush enteritis, cytomegalic inclusion disease and toxoplasmosis.
## DEATHS FROM INFECTIONS

### 2-7 days

<table>
<thead>
<tr>
<th>Infection</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis (Esch.Coli)</td>
<td>3</td>
</tr>
<tr>
<td>agglutinable stain 0126</td>
<td></td>
</tr>
<tr>
<td>Pyaemia (staphylococcus aureus)</td>
<td>1</td>
</tr>
<tr>
<td>Dysentery (Sh. Flexner)</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>53</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>59</td>
</tr>
</tbody>
</table>

### 8-14 days

<table>
<thead>
<tr>
<th>Infection</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis (Esch.Coli)</td>
<td>4</td>
</tr>
<tr>
<td>Infections, staphylococcus aureus</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia (no specific organisms found)</td>
<td>7</td>
</tr>
<tr>
<td>Pneumonia (inclusion body)</td>
<td>1</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16</td>
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</tbody>
</table>

### 15-21 days

<table>
<thead>
<tr>
<th>Infection</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis (Esch.Coli)</td>
<td>1</td>
</tr>
<tr>
<td>Empyema (Strep. pyogenes)</td>
<td>1</td>
</tr>
<tr>
<td>Pyaemia (staphylococcus aureus)</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>9</td>
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### 22-28 days

<table>
<thead>
<tr>
<th>Infection</th>
<th>Deaths</th>
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</thead>
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<tr>
<td>Gastro-enteritis (no agglutinable strains)</td>
<td>2</td>
</tr>
<tr>
<td>Peritonitis (strep. pyogenes)</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Purulent bronchitis</td>
<td>1</td>
</tr>
<tr>
<td>Enterocolitis (monilia albicans)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6</td>
</tr>
</tbody>
</table>
REFERENCES


INCLUSION BODY GIANT CELL PNEUMONIA

The British literature contains no references to cytoplasmic inclusion giant cell pneumonia of the newborn. From America, Adams (1941), in the study of an epidemic of pneumonia in the newborn, reported the occurrence of typical cytoplasmic inclusion bodies in the alveolar, bronchiolar and bronchial epithelium of the lungs of patients who died of primary virus pneumonitis. In 1948 the same author described six cases of generalised pneumonitis in the newborn, characterised by giant cells containing cytoplasmic inclusion bodies.

The following case, the only one of its kind in this entire series of autopsies, is described, firstly on account of the apparent rarity of the condition in this country, and secondly on account of the confusion which has arisen between the histological picture in inclusion body giant cell pneumonia and that in infectious diseases such as whooping cough and measles.

Case Report:

The baby, birth weight 6 lbs., was born at home - a full-time spontaneous delivery. It was admitted to hospital aged 6 days, having vomited a small quantity of blood. On examination the baby
was cold and cyanosed, with scattered moist sounds throughout the chest. X-ray of the chest showed collapse of the upper lobe. The baby's condition gradually deteriorated, and death took place at the age of 11 days.

Post-mortem Report:

The body was that of a male infant weighing 2465 gms.

Head: The brain and meninges were healthy.

Thorax: Pharynx and oesophagus were healthy and the trachea did not contain any foreign material. The serous sacs were healthy. The right lung, in the upper, middle and lower lobes, was firm and dark purple. Section showed a consolidated parenchyma, from the cut surface of which thick, greyish pus could be expressed. The left lung showed extensive consolidation of the lower lobe with patchy consolidation of the upper lobe. The heart was of expected size and developmentally normal.

Abdomen: No abnormality was noted in any of the abdominal organs.

Bacteriological Report:

Blood culture: Contaminants only.
Lung culture: Streptococcus non-haemolyticus ++.  
B. coli ++.

Subculture: Staphylococcus aureus coagulase positive, strongly sensitive to aureomycin, sensitive to streptomycin, poorly sensitive to penicillin and chloromycetin.

Microscopical Report:

Lungs: Sections of both lungs confirmed the presence of an extensive bronchopneumonia, the alveoli and bronchioles being packed with masses of polymorph leucocytes, with a varying admixture of histiocytes. The bronchial epithelium was in parts desquamated with giant cell formation evident in the remaining portion. Giant cell formation was a rather striking feature throughout all sections, these giant cells being present also in many of the alveoli. The giant cells were obviously of epithelial type and sections stained phloxin-tartrazine revealed within many of the giant cells well-defined intracytoplasmic inclusions 4-6 microns in diameter.

Subsequent Investigation:

At this time, unfortunately, no deep freeze was available and consequently only "fixed material"
was examined.

Copy of letter later obtained from child's own doctor:

While this baby was ill at home a sister was coughing, and shortly after the baby died, this girl began to whoop, so the baby must have been exposed to whooping cough. There was no history of contact with any other infectious disease, although there was measles in the camp where the child was born.
Section of Lung showing numerous large multinucleated giant cells. Bronchial epithelium can still be distinguished (top right). Polymorph leucocyte infiltration is also evident. x 160. Haematoxylin & eosin.

Section of Lung: Giant cells with intracytoplasmic inclusion bodies 4-5 microns in diameter. x 470. Phloxin-tratrazine.
DISCUSSION

Giant cell pneumonia has previously been described by many observers. Hecht (1910) reported a large number of cases of giant cell pneumonia in children dying with measles. He also found giant cells present in pneumonia associated with diphtheria and whooping cough, and considered that the giant cell reaction could be produced in the lungs by bacterial, chemical or mechanical irritation. None of these cases showed inclusion bodies in the giant cells. Freyter (1925) reported 14 cases of giant cell pneumonia in children who died after infection with measles. Whereas some of the children died during the prodromal period, the majority died some time after the rash appeared. Although numerous authors, McCallum (1919), Denton (1925) and Kreider (1943), have carried out large surveys of the bronchopneumonia associated with measles, none of the authors noted giant cells, probably because in all cases death took place after the development of suppurative bronchopneumonia.

Pinkerton, Suntey and Anderson (1925) reviewed giant cell pneumonia and observed that whereas it was sometimes associated with measles,
it could be found in other diseases. They examined the pulmonary lesion in distemper in minks and found that it was similar to that in measles.

Goodpasture (1939) and his co-workers reported several cases of pneumonia in infants where the lungs contained large acidophilic intranuclear inclusions following measles or whooping cough. They included the case of a two week old infant who had no other known disease. As has already been mentioned, Adams (1941) reported several cases of generalised pneumonitis characterised by giant cells containing cytoplasmic inclusion bodies, and the same author later reported inclusion pneumonia occurring both sporadically and in epidemic form in premature and also full-term infants.

In my experience, giant cell pneumonia with cytoplasmic inclusion bodies has been found on two occasions, firstly in association with measles pneumonitis in a child aged 14 months, who died shortly after the appearance of the rash, and secondly in the case of inclusion body giant cell pneumonia which has just been described.

Although there was a possible exposure to
measles infection in the present case, any association between the giant cells and measles is unlikely. In cases of measles epithelial giant cells in the lungs are not found prior to the appearance of the rash (Roberts & Bain).

The history of exposure to whooping cough in the present case is interesting, but any discussion on this subject would be merely speculative.

There was in this case no evidence of infection by pneumocystis carinii - a now more frequently reported causative agent of atypical pneumonia in infancy.

The present case is histologically similar to the primary virus pneumonitis described by Adams (1941). It is interesting that this author suspected a relationship between infections of the upper respiratory tract in the mother and primary virus pneumonitis in the infant.
Child aged 14 months. Koplick's spots and lympho-reticular giant cells present at time of autopsy. Rash had not appeared.

Section of Lung: shows numerous epithelial giant cells. x 90. Haematoxylin & eosin.

Section of Lung: Large epithelial giant cells containing cytoplasmic inclusion bodies. x 500. Phloxin-tartrazine.
REFERENCES

ROBERTS & BAIN. The Pathology of Measles - awaiting publication.
THRUSH INFECTION (MONILIA ALBICANS)

The most striking feature of this entire series of autopsies was that only one death was attributable to thrush infection. There is little doubt that this is due to the greatly improved hygiene in the hospitals throughout this region. Ludham and Henderson (1942) reported that of 163 infants who clinically showed evidence of moniliasis, this infection appeared to be the cause of death in 13. Morison (1952) records the autopsy incidence of thrush infection as 48% (out of 352 newborn infants). This infection and the resulting complications were the cause of death in just under 60% of those in whom the infection was found. The possibility has long been recognized that alteration of microfloral balance in one of the body tracts during antibiotic therapy might permit either the emergence of dominant or resistant potential pathogens already present, or the introduction of a fresh infecting agent resistant to the antibiotic. With the widespread use of antibiotics, the mortality from thrush might have been expected to have been higher.

It is indeed of great interest that this
mortality from thrush infection in this present series has been so very low. It might, however, be suggested that in the neonatal period there was insufficient time for prolonged antibiotic therapy to alter the flora, but in respect of thrush one cannot recall any death from this infection between the age of one month and one year.

The one fatal instance of monilial infection encountered was rather unusual in its presentation but not unique, Macgregor and Henderson (1943) having reported two previous cases of intestinal thrush.

Clinical History:

The baby, birth weight 4 lbs. 9 1/2 oxs., was born in hospital at what was estimated to be fullterm. It was slow in sucking and tube feeding was commenced on the second day. At the age of seven days oral thrush was diagnosed, but this responded to treatment. Vomiting commenced and the abdomen became distended. X-ray of the chest showed a patch of pneumonia in the right upper lobe. A flatus tube was passed and the distended bowel was partially deflated. Surgical advice was sought and it was considered that
conservative treatment should be continued. At the age of seventeen days the baby became very limp and severely ill. Four days later the baby passed a large stool along with what appeared to be blood-stained tissue. Oral thrush reappeared about this time, but responded rapidly to gentian violet. In spite of blood transfusion the infant's condition deteriorated and death ensued at the twenty-eighth day.

Autopsy Report:

The body was that of a small, emaciated male infant weighing 1610 gms. There was considerable distension of the abdomen.

Head: The brain and meninges showed no abnormality.

Thorax: Mouth, pharynx and oesophagus showed no evidence of thrush infection. Trachea showed slight congestion of the mucosa. Serous sacs were healthy. Right lung was bulky, firm and nodular - a pneumonia; this pneumonia extended throughout upper, middle and lower lobes. Pneumonic foci were present in the left lower lobe, but the upper lobe was comparatively well aerated.

Abdomen: Peritoneal sac was healthy. Stomach
and duodenum were normal. There was no evidence of thrush infection. The jejunum and ileum were both distended. The mucosa of the jejunum was healthy. In the upper part of the ileum the mucosa was merely congested, but in the lower part there were several small, circumscribed areas of ulceration. The large intestine was grossly distended, the mucosa being largely necrotic with areas in which it had completely sloughed away. The remaining mucosa was intensely congested, with on the surface diffuse whitish plaques, which were almost certainly due to a thrush infection. No obstructive lesion was found throughout small or large intestine. Liver was of natural size; it possessed a uniform brown colour, suggestive of a toxic state. Gall bladder, bile ducts, spleen, kidneys, urogenital tract, pancreas and adrenals showed no abnormality.

Bacteriological report:

**Intestine:** Direct films - Monilia albicans ++.  
Cultures - B. coli +. Monilia albicans +++.

Microscopical report:

**Intestine:** Sections of the colon showed
considerable ulceration of the mucosa, which not infrequently extended right down to the muscle coat. There was infiltration of the ulcerated areas by polymorphs, lymphocytes and plasma cells. Numerous filaments and spores of monilia were present in the ulcerated areas, throughout the adjacent submucosa and occasionally actually within the muscle coat.

**Lungs:** Microscopy confirmed the presence of an extensive bronchopneumonia. No filaments or spores were evident.

**Liver:** There was a widespread fatty change, mainly in the periportal regions.

**Spleen, Pancreas, Kidneys, Adrenals:** No abnormality was noted in any of these tissues.
Section of Colon

There is extensive ulceration. The mucosa is no longer evident, and the inflammatory reaction extends downwards into the muscle coat. x 90. Haematoxylin & eosin.

Section of Colon

Thrush filaments extending deep into the muscle. x 320. Gram.
DISCUSSION

Thrush infection is generally confined to the mouth and alimentary tract, but where associated with antibiotics, it may be found in other sites or even as a generalised blood dissemination (Morison, 1952). Thrush infection involving the intestine is comparatively rare and the only two previous cases reported are those of Macgregor and Henderson. In the first of their cases about two feet of the middle of the small intestine was involved with absence of lesions in the stomach, but with involvement of the oesophagus and mouth. In the other case, the thrush lesion consisted of a solitary ulcer about the ileo-caecal junction, with complete absence of thrush elsewhere in the body.

In the present case oral thrush was found at the age of one week and later at the age of seventeen days, but in both instances the infection responded to treatment, and at autopsy no evidence of thrush infection could be found in the upper alimentary tract. No antibiotics had been administered.

The lesion in the present case was predominantly that of an acute ulcerative colitis, with
a less severe ulcerative enteritis. Whilst certainly uncommon in infancy, ulcerative colitis is known to occur in this period. In view of the striking appearance of the lesions found in the large intestine in the present case it would appear imperative to exclude an infection such as thrush before finally accepting a diagnosis such as acute ulcerative colitis of infancy. The capricious involvement of the colon and terminal ileum without any pathological evidence of lesions in the upper alimentary tract is certainly a noteworthy feature demonstrated in this case.
a less severe ulcerative enteritis. Whilst certainly uncommon in infancy, ulcerative colitis is known to occur in this period. In view of the striking appearance of the lesions found in the large intestine in the present case it would appear imperative to exclude an infection such as thrush before finally accepting a diagnosis such as acute ulcerative colitis of infancy. The capricious involvement of the colon and terminal ileum without any pathological evidence of lesions in the upper alimentary tract is certainly a noteworthy feature demonstrated in this case.
SUMMARY

In the present series only one death attributable to thrush infection has been encountered.

The most outstanding feature of this case was the intestinal involvement with absence of lesions in the upper alimentary tract. Also noteworthy has been the appearance of the large intestine, where the lesion was that of a severe and extensive ulcerative colitis.

Before finally arriving at a diagnosis of acute ulcerative colitis in the newborn, it is suggested that an infective agent such as monilia albicans must be excluded.
REFERENCES

LUDLAM, G.B. & HENDERSON, J.L. 1942. Lancet, 1, 64.
Generalised cytomegalic inclusion disease in the newborn is an oft suspected but rarely proven condition. The rarity of this condition in relation to perinatal mortality is emphasised by the incidence in the present series of only one instance in the course of 1,947 consecutive perinatal autopsies. Inclusions in various organs, particularly in the salivary gland, are encountered as an incidental finding in children. Generalised cytomegalic inclusion disease, however, as it affects the newborn commonly presents a picture clinically resembling haemolytic disease with jaundice, hepatosplenomegaly and occasionally a purpuric rash. Clinically also the condition may be indistinguishable from toxoplasmosis and some of the reported cases of cytomegalic inclusion disease have indeed possessed cerebral lesions, the description of which is highly suggestive of a toxoplasma infection. With all these factors in mind there presented the case of an infant, Baby F., 16 hours old, jaundiced and with severe hepatosplenomegaly.

Maternal History

The mother, Mrs F., a primapara, aged 20 years, was noticed to have on routine examination
at the fifth month fairly severe molluscum contagiosum, which had been present for at least 10 days. She was referred to the skin department at the Royal Infirmary of Edinburgh where the diagnosis was confirmed. A certain amount of vaginal bleeding occurred at the 24th week but this subsequently settled. External version for breech presentation was attempted at the 36th week but was unsuccessful. Two days later she was delivered of a live male child.

Infant's History.

The infant, birth weight 3 lbs 15 ozs. was limp and cyanosed at birth but responded to resuscitation. At the age of 12 hours blood was found to be oozing from the rectum, the mouth and injection sites in the cord and the arm. Synkavit was given and subsequently repeated. Jaundice, followed soon after by petechiae, appeared 9 hours after delivery. The jaundice rapidly deepened and the liver and spleen were found to be grossly enlarged. At the age of 10 hours the respirations began to be irregular with commencing apnoeic attacks.

Investigations: Cord blood; Coombs test negative. (Mother A, Rh.positive). Serum bilirubin 13 mgm.%. Capillary blood: Hb.73%;
R.B.C. 3.3 million; platelets 42,500. **Film:** 3-4 normoblasts per high power field.

Exchange transfusion was attempted but the baby died shortly after commencement, aged 16 hours.

**Autopsy.** *(performed 12 hours after death)*

The body was that of a male infant weighing 3 lbs 12 ozs. A pronounced degree of jaundice was present and the numerous petechiae noted clinically were still evident.

**Head:** There was a severe subdural haemorrhage with a large quantity of flattened and compressed blood clot overlying almost the entire aspect of the right cerebral hemisphere. A lesser quantity of blood clot was present, overlying the left cerebral hemisphere. There was no tearing of the tentorium or falx, and the great cerebral veins were intact. The brain on section showed a rather diffuse yellowing of the actual cerebral substance, but no kernicterus was present. No cerebral haemorrhage was present, nor were there any areas of necrosis in the brain substance.

**Thorax:** The pharynx, oesophagus and trachea did not show any abnormality. The serous sacs were healthy. The lungs were moderately
aerated in the upper lobes but rather poorly expanded in the lower lobes. There was no increase in bulk and the consistence did not suggest pneumonia. There were no subpleural haemorrhages. The heart was of the appropriate size and developmentally normal.

Abdomen: The peritoneal sac was healthy. The gastro-intestinal tract showed nothing to note. The liver was within the upper limits of normality as regards size. It was firm and on the surface, especially towards the bare area, showed a whitish mottling which was even more pronounced when a section was made into the liver parenchyma in this region. The liver parenchyma did not present the homogeneous brownish appearance usual in haemolytic disease, there being in general a whitish speckling of the surface. The gall-bladder and bile ducts were normal. The pancreas appeared healthy. The spleen was grossly enlarged to about five or six times the usual size; it weighed 39 gms. It was remarkably firm and showed on section a homogeneous parenchyma in which the Malpighian bodies could not be discerned. The kidneys were of the expected size. Both the cortex and medulla were deep yellow but they showed no other pathological condition. The ureters,
bladder and suprarenals showed no abnormality.

**Microscopical Report:**

**Salivary gland:** Sections of the parotid showed generalised distension of the ducts. Many of the lining epithelial cells were enlarged. They contained large, basophilic intranuclear inclusions and numerous intracytoplasmic basophilic particles, presumably of virus origin. The inclusions were in various stages of development, and occasionally basophilic virus particles were seen discharged into the lumina of the ducts.

**Kidney:** Groups of proximal convoluted tubules were enlarged and their lining epithelial cells swollen. These cells contained large basophilic inclusions.

**Liver:** Sections showed abundant haemopoiesis, much of which was of primitive type. In addition, there was a cirrhosis with considerable fibrous thickening extending well beyond the portal tracts. No inclusions were evident in the bile duct epithelium.

**Gall-bladder, Urinary bladder, Ureter:** No inclusions were seen. No abnormality was present.

**Pancreas:** There was no cytomegaly or inclusion disease. No pathological change was present.
Fig. 3. Salivary gland, Baby F.
Dilated ducts with swollen epithelial cells and large intranuclear inclusions.
Haematoxylin and eosin. x 140.

Fig. 4. Salivary gland, Baby F.
Epithelial cells with intranuclear inclusions.
Phloxin-tartrazine. x 550.
Fig. 1. Kidney, Baby F.
Enlarged proximal tubules with swollen epithelial cells and numerous intranuclear inclusions. Haematoxylin and eosin. x 165.

Fig. 2. Kidney, Baby F.
Tubular epithelium with large intranuclear inclusions and numerous intracytoplasmic basophilic particles. Haematoxylin and eosin. x 1200.
Fig. 5. Liver, Baby F.

Cirrhosis with excessive erythropoiesis. No inclusions present. Haematoxylin and eosin. x 130.
Spleen: There was abundant haemopoiesis, a considerable proportion of primitive type.

Lung: Sections showed patchy areas of intra-alveolar haemorrhage with the remainder of the lung parenchyma poorly aerated. No pneumonia was present, and there was no evidence of any inclusions.

Suprarenal, Skin, Lymph glands, Submandibular salivary gland: There was no evidence of any inclusions in these tissues.

Bone marrow: No abnormality was present.

As haemolytic disease of the newborn was most unlikely on account of the serological investigations already performed, the suspected diagnosis appeared to lie between toxoplasmosis or cytomegalic inclusion disease. Accordingly, the autopsy had been performed with sterilised instruments and with as much asepsis as could possibly be obtained. During the autopsy sections had been taken from the kidney and on the frozen sections a diagnosis of generalised cytomegalic inclusion disease made. Consequently, tissues were available for direct animal inoculation and for storage in deep freeze.
Animal inoculation

A fine suspension of kidney, to which streptomycin and penicillin had been added, was inoculated into animals and also on to blood agar plates. The plates showed no growth after 48 hours. A wide variety of animals, excluding monkeys which were unobtainable, was used.

Mice: Thirty-six young mice were inoculated with the kidney suspension, eighteen by the intraperitoneal and eighteen by the intracerebral route. Half of each group were killed on the 11th day. Smears were made of the spleens and a suspension of splenic tissue was passaged into a further six mice. These were killed eleven days after inoculation and a splenic suspension was passaged once more. The remainder of the mice that received the primary inoculum were killed at intervals over 3 weeks. No macroscopic pathological condition could be found in any of the mice, and histological sections of various organs and splenic smears were all negative.

Guinea pigs: Six guinea pigs were inoculated with kidney suspension; two by intracutaneous inoculation into the pad; two by scarification of the skin and two intraperitoneally. Two of the guinea pigs died of an
incidental tuberculous infection within five days. Histological examination of the various organs, of the skin and of the pads of these and the remaining guinea pigs failed to reveal any pathological condition.

**Rabbits:** Two rabbits were inoculated by scarification of both the skin and the conjunctiva. No change was ever found.

**Hamsters:** Two hamsters were inoculated, one by scarification of the skin, the other intraperitoneally. These animals were killed after fourteen days and no pathological condition found.

**Eggs:** Chorio-allantoic inoculation of twelve eggs with kidney suspension was carried out. Attempts to isolate a virus thus or to demonstrate any pathological change were unsuccessful.

**Tissue culture:** HeLa cells from squamous epithelium of cervix (originally isolated in 1951 by Grey) were set up in roller tubes. The medium contained 10% horse serum, lactalbumin hydrolysate and Hank's basic salt solution. 1 ml of the kidney emulsion was added to each tube containing 1.9 ml of medium. The tubes
were incubated at 37°C. for 14 plus days. No cytopathogenic effect whatsoever was found.

Further attempts using tissue culture by slide techniques are still in progress.
DISCUSSION

There is no mention in the literature of any previous attempt to isolate a virus from generalised cytomegalic inclusion disease. As the tissue was fresh, the present case afforded an excellent opportunity for such an attempt. The assumption, most probably correct, has been that the inclusions in this condition are of virus origin and of the same nature, if not identical with, the salivary gland virus.

The salivary gland virus is found widely and frequently in the animal kingdom, infected animals apparently showing no signs of disease. Kuttner and Wang (1934) reported the presence as an incidental finding of the virus in the salivary gland of numbers of Chinese children. After preserving the tissues in glycerol they attempted to isolate the virus in animals, including monkeys, but were unsuccessful. At the same time attempts to transfer infection from one species of animal to another failed. It would appear, therefore, that the virus is species specific. Certainly in the present case animal and even chorio-allantoic egg
inoculation produced negative results. While in the present instance tissue culture inoculation was negative in producing no cytopathogenic effect, this line of investigation at present being pursued by different modes is the more likely to prove of value. Tissue culture appears in fact to be the only procedure likely ever to be successful.

Cytomegalic inclusions limited to the salivary glands have only rarely been found in the salivary glands of children in Edinburgh and district, despite routine search. In London, on the other hand, salivary gland inclusions have been found much more frequently (Bodian, personal communications). I have examined routinely over a period of one year, the parotid glands (and also submaxillary) of all stillbirths and neonatal deaths in the Edinburgh region. Salivary gland inclusions have never been found. The conclusion appears to be therefore that whereas in older children infection with the salivary gland virus is certainly not a fatal condition, when such an infection occurs in intra-uterine life it is responsible for infantile morbidity, if not
fatality. Cappell and McFarlane (1947) provide a classical description, excellently illustrated, of a case of generalised cytomegalic inclusion disease simulating haemolytic disease. France (1951) has reviewed the literature on the subject and after including four cases of his own, found in all a total of twenty-seven cases. Of his own cases, one showed an area of necrosis and cellular infiltration in the brain, the description of which could well be that of toxoplasmosis. As the latter condition is an important differential diagnosis, dye tests and complement fixation tests for toxoplasma antibodies were carried out in the present instance but all proved negative. Extreme caution must be employed in attaching to any case a diagnosis of generalised cytomegalic inclusion disease, and of the twenty-seven cases in the literature the diagnosis in some must be regarded with an element of doubt. The findings in the lungs of cytomegaly and inclusions, especially in older infants, is far from specific and may be related to a number of conditions, including even whooping cough and measles (Roberts and Bain).
No satisfactory explanation can be afforded for the excessive extramedullary erythropoiesis in the perinatal cases of generalised cytomegalic inclusion disease. For the present at least it must be regarded, like toxoplasmosis, as being related to a generalised infection. That death results from damage to the haemopoietic system and not directly from any viraemia seems most probable. It would appear, therefore, that exchange transfusion may sometimes be indicated in this disease. Kinny (1942) in fact describes an instance in which kernicterus subsequently developed.

Evidence of cirrhosis of the liver has already been noted in 3 previous cases of cytomegalic inclusion disease (Wyatt et al, 1950. France, 1951), the maximum age at death being seven weeks. It has been generally assumed that the liver damage was an obstructive effect secondary to the swelling of the bile duct epithelium as a result of the inclusions. No inclusions were found in the biliary tract of Baby F. Cirrhosis of the liver is occasionally found in haemolytic disease per se, and it would therefore be injudicious to attribute the
cirrhosis in all cases directly to the infection.

Maternal histories have largely been lacking in reported cases (France 1951). The presence of molluscum contagiosum in the mother of Baby F is probably of doubtful significance. Smears from the cervix and from the urinary deposit in Mrs. F failed to show any inclusions. Serum from mother and baby were kept in deep freeze and will be stored indefinitely should any virus ever be isolated.
A case of generalised cytomegalic inclusion disease has been described. The simulation of haemolytic disease and the differential diagnosis involving toxoplasmosis has been discussed. Attention has also been drawn to the care required in interpreting inclusions, particularly in the lungs, and also in attributing death to cytomegalic inclusion disease.

In the newborn it would appear that the most common fatal factor is damage to the haemopoietic system, although at a later stage liver damage is liable to be manifest.

An attempt to isolate the virus from fresh tissue has been detailed. Animal inoculation by various routes was unsuccessful. Chorio-allantoic inoculation of eggs also failed. Inoculation of tissue culture using the roller tube technique produced no cytopathogenic effect. Attempts using other methods of tissue culture are continuing.
REFERENCES


CONGENITAL TOXOPLASMOSIS

A Report on Four Cases

Congenital toxoplasmosis was first described by Janku in 1923, since when its features have become well recognized. Diagnosis has usually rested on clinical, radiological or histological grounds. Out of a series of 1,947 consecutive perinatal autopsies in Edinburgh and district, there have been four cases in which a confident diagnosis of congenital toxoplasmosis has been made. The diagnosis of toxoplasmosis resting predominantly on the actual isolation of the parasite, this was attempted in all four cases, but in only two instances was it successful. It was also felt that at this stage when only one conclusively proved congenital case had so far been reported in this country, correlation of serological and pathological evidence was required.

Case 1. Baby M.

Baby M was born in district on 1.1.54. The mother had three previous children all alive and healthy. During her fourth pregnancy she had a threatened abortion at twelve weeks, but no other illness whatsoever. Her membranes
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Case 1. Baby M.

Baby M was born in district on 1.1.54. The mother had three previous children all alive and healthy. During her fourth pregnancy she had a threatened abortion at twelve weeks, but no other illness whatsoever. Her membranes
ruptured spontaneously when she was reputed to be seven and a half months pregnant. Labour was normal, lasting a total of four hours. The baby was admitted to hospital, cyanosed and showing signs of cerebral irritation. Its condition deteriorated and the baby died aged 24 hours.

At autopsy the infant, a female, weighed 2230 gms. (The placenta was not available). A slight degree of jaundice was present but the subcutaneous tissues were not oedematous. Over the meningeal surfaces of both cerebral hemispheres were small, yellowish, non-gritty patches, which were distinct, firm and not adherent to the underlying cerebral tissue. In the floor of each lateral ventricle was a fairly large area composed of soft yellowish material which projected slightly into the ventricular cavity. There was no evidence of hydrocephalus and no cerebral haemorrhage was present. The lungs and the heart were both congested but showed no other abnormality. For an infant of this weight the liver was larger than usual, whilst the spleen was fully twice the normal size.

Microscopically, the lesion in the brain
was composed of necrotic tissue, throughout which was abundant granular calcium deposition. Around the margins of this area was a dense inflammatory cell infiltration made up predominantly of histiocytes, lymphocytes and plasma cells, with a sprinkling of polymorphonuclear leucocytes. No toxoplasms were found in direct smears. Sections of the liver showed haemopoiesis more abundant than usual for an infant of this maturity. The splenic pulp contained numerous islands of erythropoietic cells. Erythropoiesis was also present in the adrenals and kidneys.

**Attempted isolation of the toxoplasma.**

An emulsion of brain tissue was inoculated peritoneally into four mice. These were alive and healthy fourteen days after inoculation. Two of the mice were then killed and smears made from the peritoneal fluid. No toxoplasms were found. Brain emulsion from these two mice was passaged into further mice. Both the passaged and the primary inoculated mice remained healthy. In the light of subsequent experience, primary inoculation should have been both intracerebral and intraperitoneal simultaneously in the same mice. In this case, also, although only
intraperitoneal inoculation was carried out, further passage should have been attempted.

Serology.

Various approaches were made to obtain serum from the mother, but owing to the fact that she was delivered in district, none of these proved successful. A sample of her plasma finally obtained two years after delivery of the infant produced a Dye Test of 1/18 with the Complement Factor Test negative.

Subsequent maternal history.

It was later reported that the mother had been seen by a gynaecologist and her name added to the waiting list for hysterectomy, but no further information was forthcoming.

Case 2. Baby D.

Baby D, a first pregnancy, was born on 8.7.54. During the mother's pregnancy there was an excessive gain in weight, hydramnios and profuse vaginal discharge. Labour was normal lasting sixteen hours. The foetal heart ceased ten minutes before delivery. The baby was still-born, severely hydropic and weighed 4 lbs. 13½ ozs. The
placenta was unduly large, pale and soft.

At autopsy when the skull was opened, numerous small, whitish-yellow, necrotic areas were seen beneath the pia-arachnoid on the surfaces of both cerebral hemispheres. During removal of the brain a large quantity of yellowish fluid escaped, suggesting hydrocephalus. Multiple soft, yellowish, necrotic areas were found throughout both cerebral hemispheres, particularly around the lateral ventricles. The hind brain showed no apparent lesion, but its softness precluded detailed examination. The serous sacs contained a considerable excess of free fluid. Heart, lungs, kidneys and suprarenals showed no abnormality. The liver and spleen were enlarged, the latter being four times the usual size.

Microscopical examination of the sections from the brain showed multiple areas of necrosis and calcification. These were particularly abundant in the superficial cortical zone and in the subependymal region. The areas of calcium deposition were generally surrounded by an intense inflammatory reaction, predominantly histiocytic, but with varying numbers of lymphocytes, plasma
cells and a sprinkling of polymorphonuclear leucocytes. Some of the blood vessels in relation to necrotic foci were surrounded by inflammatory cells. The choroid plexus was heavily infiltrated with acute and chronic inflammatory cells. Typical toxoplasma pseudocysts were found, not in the necrotic areas, but in the adjacent apparently healthy tissue, 1 - 2 mm. away. Among the necrotic debris were aggregations of granular material which had some resemblance to both pseudocysts and terminal colonies, but had no surrounding membrane. In the heart, the subepicardial region and, to a lesser extent, the myocardium, were infiltrated by lymphocytes, histiocytes and plasma cells. No necrosis of the muscle fibres was present. No toxoplasms could be found. Haemopoiesis in the liver was excessive, even allowing for prematurity, and much of it was of primitive type. The Prussian blue reaction was also negative. In the kidneys a narrow neogenic zone remained, indicative of prematurity. As in the liver, haemopoiesis was excessive. Many of the red cells in the renal vessels were of primitive type. In the eye posterior uveitis was present. There was no evidence of involvement of the optic nerve.
Aggregations of bodies resembling toxoplasma were found in the disorganized retina. Pancreas and suprarenals showed no abnormality. In the placenta the villi were swollen and oedematous, as in haemolytic disease.

Blood Grouping.

Mother: Group A. Rh. positive.

Mother's serum and baby's cells: Indirect Coombs' test negative. No abnormal anti-bodies found.

Father: Group B. Rh. positive.

Baby: Group A. Rh. positive. Direct Coombs' test negative.

Wasserman: Mother negative.
<table>
<thead>
<tr>
<th>Toxoplasma Antibodies</th>
<th>Dye Test</th>
<th>C.F.T.</th>
</tr>
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<tbody>
<tr>
<td><strong>Baby:</strong> 12.7.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord blood</td>
<td>1/2,500</td>
<td>1/32</td>
</tr>
<tr>
<td>Heart blood</td>
<td>1/5,750</td>
<td>1/32</td>
</tr>
<tr>
<td><strong>Mother:</strong> 12.7.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/12,500</td>
<td>1/32</td>
</tr>
<tr>
<td>27.7.54</td>
<td>1/18,000</td>
<td>1/640</td>
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<td>25.1.55</td>
<td>1/7,000</td>
<td>1/64</td>
</tr>
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<td>21.4.55</td>
<td>1/220</td>
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<td>1/275</td>
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<td>1/800</td>
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</tr>
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<td>11.8.55</td>
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<td>1/64</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>1/4</td>
<td>1/4</td>
</tr>
<tr>
<td><strong>After birth of succeeding healthy baby 31.8.55</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mother:</strong> 31.8.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/1,000</td>
<td>1/32</td>
</tr>
<tr>
<td><strong>Baby:</strong> 31.8.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/1,250</td>
<td>1/64</td>
</tr>
<tr>
<td><strong>Cat belonging to Mrs. D.</strong></td>
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</tr>
<tr>
<td><strong>Cat:</strong> 25.4.55</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>TISSUES USED</td>
<td>ANIMAL</td>
<td>DOSE AND ROUTE</td>
</tr>
<tr>
<td>--------------</td>
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<td>----------------</td>
</tr>
<tr>
<td>Brain</td>
<td>G.P. 97</td>
<td>2 ml. I.P.</td>
</tr>
<tr>
<td>&quot;</td>
<td>G.P. 98</td>
<td>2 ml. I.P.</td>
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<tr>
<td>&quot;</td>
<td>Mice</td>
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<tr>
<td>95</td>
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<tr>
<td>100</td>
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<td>1 ml. I.P.</td>
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G.P. = Guinea pig
I.P. = Intraperitoneal inoculation
I.C. = Intracerebral inoculation

+ = Toxoplasms isolated
0 = Isolation not attempted
- = Attempts to isolate toxoplasms failed.
Isolation of Toxoplasma

At first it was thought that attempts to isolate the parasite would fail. A suspension of the brain was inoculated on 8.7.54 in Edinburgh into two guinea pigs intraperitoneally, two mice by the same route, and two mice intracerebrally. One of the guinea pigs (97) was killed on 16.7.54, but no toxoplasms were found in smears of peritoneum, spleen, liver or brain. Nevertheless, a suspension of these tissues was inoculated into the peritoneal cavity of two guinea pigs (111 and 112) and two mice.

Apart from one passage mouse which died of ante-partum haemorrhage nineteen days after inoculation, and the guinea pig which was killed, all the original and passage animals were still alive on 17.9.54. All the mice had been sent to Sheffield, and on that date one of the original mice (Group D.3.) and the surviving passage mouse were killed. No toxoplasms were found, but a suspension of their brains, livers, and spleens was inoculated intracerebrally and intraperitoneally into two mice. In ten days these looked ill, were killed and toxoplasms were found in their peritoneal fluids. The rest of
the original mice (Group D.3.) were killed on 27.9.54. Again no toxoplasms were found, but combined intracerebral and intraperitoneal inoculation of a suspension of their organs into further mice produced toxoplasmosis.

Group D.1. In Edinburgh the two guinea pigs (111 and 112) were heart punctured on the 74th day (29.9.54) after inoculation, and the dye test proved positive on each serum. Pooled sera from the animal house stock in Edinburgh were negative. G.P. 111 was killed on the 84th day; no toxoplasms were seen in smears of peritoneum, liver and spleen. A suspension of these tissues (brain not used) was transferred to mice through uncombined intracerebral and intraperitoneal inoculations. Three successive blind intraperitoneal passages at six day intervals failed to demonstrate toxoplasms and attempts to isolate the organisms in this series were then abandoned. The second guinea pig (112) was killed on the 280th day (18.3.55) and toxoplasms were isolated without difficulty in the first set of mice inoculated with brain suspension by the combined intracerebral/intraperitoneal technique. The line was passaged
thus on three occasions at four day intervals, final inoculation being into two guinea pigs in order to maintain a reservoir.

It is of interest that this second guinea pig (112) was a virgin female at the time of inoculation on 16.7.54. She was caged with a boar for the last two weeks of October, 1954 and gave birth to two healthy females on 9.1.55. These are alive and well to date.

Group D.2. Blood taken from guinea pig (98), in Edinburgh, on the 83rd day after inoculation, gave a positive dye test; sera from stock animals were negative. The animal was killed on the 95th day. No toxoplasms were found in smears from the peritoneum, spleen or liver. The brain was not examined. Saline washings from the peritoneum, spleen and liver were transferred by uncombined intraperitoneal and intracerebral inoculations to mice. Four blind intraperitoneal passages in mice failed to demonstrate toxoplasms.
BRAIN (BABY DYE)

- INTRAPERITONEAL

GUINEA PIG (97)

- INTRAPERITONEAL

(8 DAYS)

VIRGIN

GUINEA PIG (112)

- DYE TEST POSITIVE

CAGED WITH BOAR

2 OFFSPRING

ALIVE AND WELL

(250 DAYS)

MICE

- INTRAPERITONEAL

INTRACEREBRAL

TOXOPLASMS

BRAIN

- INTRAPERITONEAL

EDINBURGH LAB. ANIMALS

2 GUINEA PIGS

MOUSE PASSAGE

TOXOPLASMS

4 MICE

MOUSE PASSAGE IN SHEFFIELD
Fig. 1. Brain, Baby D.
Numerous areas of necrosis and calcification are visible on the surface.

Fig. 2. Brain, Baby T. Longitudinal section. Distension of lateral ventricle with area of necrosis on lateral wall.
Fig. 3. Brain, Baby D. Section of cortex.
This low power field shows an area of necrosis affecting the superficial part of the cortex. Haematoxylin and eosin. x 25.

Fig. 4. Brain, Baby D. Section through wall of lateral ventricle.
This shows necrosis and inflammatory cell infiltration of the subependymal region. There is also an acute inflammatory reaction involving the choroid. Haematoxylin and eosin. x 40.
Fig. 5. Brain, Baby D. Section through an area of calcification (left).
The calcium is in the form of fine deposits. In the surrounding brain substance there is a mixed inflammatory cell infiltration - a few polymorphs but mainly histiocytes and lymphocytes. Haematoxylin and eosin. x 250.

Fig. 6. Heart, Baby D.
Inflammatory cell infiltration of myocardium and subepicardial region. The infiltration is mainly lymphocytic with a sprinkling of histiocytes. Haematoxylin and eosin. x 150.
Section of retina.
Inflammatory exudate on surface of retina.
Haematoxylin and eosin. x 150.

Excessive erythropoiesis, much of this being of primitive type. Haematoxylin and eosin. x 250.
Fig. 9. Spleen, Baby T.
Conspicuous islands of erythropoiesis throughout the pulp. Haematoxylin and eosin. x 160.

Fig. 10. Smear from mouse. Peritoneal cavity second passage.
The organisms are distinctly crescent-shaped. Leishman, x 575.
Fig. 11. Smear from mouse. Peritoneal cavity; after repeated passage. Organisms tend to be more ovoid. Leishman. x 1300.

Fig. 12. Smear from mouse. Peritoneal cavity. Large cell (centre) showing undoubted intracellular toxoplasms. The nucleus of the cell is pushed to one side. Leishman. x 800.
Fig. 13. Placenta, Baby D.
The villi are swollen and oedematous.
Haematoxylin and eosin. x 40.
Case 3. Baby T.

Baby T, a first pregnancy, was born on 6.12.54. The mother had been subject to epileptic fits, but the last was eight years before this pregnancy, during which she was well. The membranes ruptured prematurely and she was admitted to hospital in labour at thirty five and a half weeks, labour lasting eleven hours. The presentation was breech and forceps were applied to the after-coming head. In spite of endotracheal oxygen the baby gasped only a few times and died.

At autopsy, apart from emphysematous swelling of the neck, no external abnormality was noted; in particular there was no external evidence of hydrocephalus nor of oedema. The placenta was large, pale and soft, as in haemolytic disease. When the skull was opened, deep yellow fluid escaped, probably from the lateral ventricles. There was considerable subdural haemorrhage with large amounts of blood clot lying on the superior surface of each half of the tentorium cerebelli and extending around the midbrain. The pia arachnoid was healthy and no necrosis or calcification was obvious on the
surface of the brain. Section, however, showed numerous areas of necrosis and calcification, most pronounced in the walls of the greatly dilated lateral ventricles. Bilateral pneumothorax was present, the lungs lying far back in the pleural cavities. The heart showed no abnormality. Both liver and spleen were enlarged, the latter being approximately three times the usual size. The Prussian blue reaction on both organs was negative. The kidneys and suprarenals showed no pathological changes. After fixation the eyes showed on section a small, whitish, opaque lesion on the surface of the retina, immediately posterior to the ciliary body.

The histological features were exactly similar to Case 2, Baby D. The cerebral lesions were alike. Toxoplasma pseudocysts, terminal colonies, and aggregations of granular material, similar to those in Case 2 were found. Microscopy showed chorio-retinitis and myocarditis. The liver and spleen both showed excessive haemopoiesis, much of this, in the liver, being of primitive type.
Serology.

Blood Grouping

Mother: Group O. Rh. positive. No abnormal antibodies found.

Baby: Coombs' test negative.

Toxoplasma Antibodies

<table>
<thead>
<tr>
<th></th>
<th>Dye Test</th>
<th>C.F.T.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baby: 9.12.54</td>
<td>1/1,300</td>
<td>1/240</td>
</tr>
<tr>
<td>Mother: 16.12.54</td>
<td>1/1,050</td>
<td>1/64</td>
</tr>
<tr>
<td>14.11.55</td>
<td>1/280</td>
<td>1/20</td>
</tr>
<tr>
<td>19.1.56</td>
<td>1/54</td>
<td>1/20</td>
</tr>
<tr>
<td>Father: 19.5.55</td>
<td>1/8</td>
<td>1/8</td>
</tr>
</tbody>
</table>

A subsequent healthy baby was born in February, 1956.

Isolation of Toxoplasma

Suspension of brain was inoculated in Sheffield by combined intracerebral and intraperitoneal routes into six mice on 9.12.54. Toxoplasms were found in five of these mice killed between the eighth and thirteenth day after infection.

Suspension of brain, liver and spleen was inoculated intraperitoneally into eight mice
in Edinburgh on 8.12.54. Four (M 183-186) were taken to Sheffield. These were killed after twelve, forty-two, eighty-two and eighty-three days. Toxoplasms were isolated from three in first intracerebral and intraperitoneal passage. Second passage mice were inoculated and left for 102 days. Third passage from one of these resulted in death from toxoplasmosis in ten days.

One of the original mice had a litter of four, forty-four days after inoculation. These were alive and apparently well twenty-eight days later. They were then killed and one was observed to have an enlarged spleen and increased peritoneal fluid. Neither from this mouse nor its litter mates were toxoplasms obtained.

Passage was made by the intraperitoneal route alone from the four mice retained in Edinburgh. Scanty toxoplasms were found in the passage mice, but two further passages were unsuccessful.

A further three mice (207-209) were inoculated in Edinburgh on 8.12.54 with a suspension of the baby's brain, liver and spleen. Scanty toxoplasms were found in the peritoneal
MAIN PATHOLOGICAL FINDINGS

NECROTIC AREAS IN BRAIN
HYDROCEPHALUS
GROSS HEPATO–Splenomegaly
RETINITIS
MYOCARDITIS (MICROSCOPICAL)
<table>
<thead>
<tr>
<th>TISSUE USED</th>
<th>ANIMAL</th>
<th>DOSE AND ROUTE</th>
<th>DATE INOCULATED</th>
<th>LABORATORY IN WHICH INOCULATED</th>
<th>TOXOPLASMS ISOLATED IN</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain*</td>
<td></td>
<td>combined I.C.O.02ml I.P.O.5ml.</td>
<td></td>
<td>Sheffield</td>
<td></td>
<td>0 +</td>
</tr>
<tr>
<td>Brain, Liver &amp; Spleen</td>
<td>G.P.193</td>
<td>2 ml. I.P.</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0 0</td>
<td>G.P. 193 killed; not examined.</td>
</tr>
<tr>
<td>Brain, Liver &amp; Spleen</td>
<td>MICE 183, 184, 185, 186</td>
<td>0.5 ml. I.P.</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0 +</td>
<td>M.183-186 sent to Sheffield 8.12.54. Brain passaged combined I.C./I.P. to mice. Toxoplasma isolated large numbers first attempt in 3 out of the 4.</td>
</tr>
<tr>
<td>Brain, Liver &amp; Spleen</td>
<td>MICE 187, 188, 189, 190</td>
<td>0.5 ml. I.P.</td>
<td>&quot;</td>
<td>&quot;</td>
<td>+ 0</td>
<td>Passaged I.P. only. Scanty toxoplasma seen second passage mice. Two further passages negative.</td>
</tr>
<tr>
<td>Brain</td>
<td>MICE 207, 208, 209</td>
<td>0,02 ml. I.C.</td>
<td>24.12.54</td>
<td>&quot;</td>
<td>+ 0</td>
<td>Primary inoculation from Baby T. brain which had been kept at 40°C for 16 days. Large numbers toxoplasma 1st passage I.C./I.P. mice. Became established I.P. passage strain and passaged 19 times. In 2 G-pigs as reservoir.</td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Poorly staining, scanty toxoplasma-like structures seen in fresh smears of brain from Baby T.
fluid of one, and in three subsequent passages. The other guinea pig was not examined.

Unsuccessful attempts were made to isolate toxoplasms by inoculating a suspension of the baby's brain on the chorio-allantoic membrane of fertile eggs.

Case 4. Baby G.

Baby G was born on 23.8.55. The mother's first pregnancy was in August, 1952 and resulted in abortion at twelve weeks. The second pregnancy went to term and a normal live baby was born in February, 1954. This, her third pregnancy, resulted in the birth of a still-born macerated male foetus at thirty weeks. Except for a slight dysuria the mother's health was good during this pregnancy.

At autopsy, the body was severely macerated, with widespread epidermal desquamation. The remaining epidermis was deep yellow, but this may have been the result of meconium staining. The foetus weighed 1,600 gms. When the skull was removed, the underlying brain, although extremely soft and macerated, showed what appeared to be ill-defined, yellowish-white areas, probably either on the surface of the brain or related
to the pia arachnoid. Nothing could be distinguished when the brain was sectioned, as it was almost entirely mush. All the serous sacs contained blood-stained fluid. No abnormality was noted in the heart or lungs. The spleen, however, was found to be approximately twice the usual size. The liver was of normal size. Neither the liver nor spleen gave a positive Prussian blue reaction. No pathological changes were found in any other organs and the placenta was not unusual in appearance.

Microscopically, advanced maceration made it difficult to detect any changes in the organs. No calcification was found in the brain.

Serology:

**Blood Grouping**
- Mother: Group A. Rh. negative.
- Father: Group O. Rh. positive.
  (probable Rh. genotype CDe/cde.
- Previous pregnancy (1954) Baby Group O. Rh. unknown. Coombs' test negative.

**Toxoplasma antibodies.**

<table>
<thead>
<tr>
<th></th>
<th>Dye Test</th>
<th>C.F.T.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother:</td>
<td>25.8.55</td>
<td>1/10,000</td>
</tr>
<tr>
<td>Father:</td>
<td>2.9.55</td>
<td>1/46</td>
</tr>
</tbody>
</table>
Attempted Isolation of Toxoplasma

In both Edinburgh and Sheffield suspensions of placenta, brain, spleen and liver were inoculated into mice and guinea pigs. Some of those inoculated with brain died a few days later of bacterial infection. The rest survived for two months. Their sera were then tested for toxoplasma antibodies without significant result. Failure to isolate toxoplasms is attributed to the advanced decomposition of the brain.

DISCUSSION

The investigations which have been described present many points of interest from the histo-pathological, serological and parasitological points of view.

In comparison with Baby D (Case 2) and Baby T (Case 3), the cerebral lesion in Baby M (Case 1) was relatively limited and it is probable that this was in fact an earlier stage of the disease process. The histological picture was similar to that in the other two cases, and on the basis of this similarity, together with the
fact that no other lesion of a similar nature has ever been encountered in all the perinatal autopsies in Edinburgh, there would appear to be little doubt about the diagnosis of toxoplasmosis. The abundant calcium deposition enhances the extreme difficulty of identifying toxoplasms, even in pseudocyst form. In smears of fresh brain, scanty toxoplasms were identified in the case of Baby T (Case 3), and then only after the most careful search.

In the liver and spleen both the macroscopical and microscopical appearance is indistinguishable from haemolytic disease. The absence of a positive Prussian blue reaction is probably of little significance. Even in haemolytic disease of the newborn the presence of this reaction is variable and capricious. Microscopical evidence of haemopoiesis in other organs, the kidney and adrenal, can also be found in haemolytic disease of the newborn. Not found, however, is either myocarditis or chorioretinitis.

In the case of Baby G (Case 4), the only really positive findings were an enlarged spleen with microscopical evidence of excess nucleated
red cells in the pulmonary vessels. This suggests haemolytic disease. In all probability the diagnosis would have remained thus, had not high toxoplasma antibodies been found. Such strong serological evidence of toxoplasmosis in such a case opens up a much wider field, especially as in Baby G (Case 4) no definite cerebral lesion was found. Gross toxoplasmosis should not be misdiagnosed, but there must perforce be cases analogous to Baby G, to which there has been attached a diagnosis of haemolytic disease and the possibility of toxoplasmosis overlooked. Such cases have been encountered here in Edinburgh, the autopsy findings having been those of haemolytic disease, but serological proof of blood incompatibility never obtained. The subsequent birth of normal children has, moreover, provided a certain amount of circumstantial evidence. A detailed investigation of these cases was considered but, owing to the low toxoplasma antibody titres likely to be found at the present time, any such retrospective review would most probably have been inconclusive.

Toxoplasma antibody tests have been carried out on the mothers of several unselected macerated babies, but these tests all proved
negative.

Several authors have noted a resemblance to haemolytic disease of the newborn (Callahan et al, 1946; Magnusson and Wahlgren, 1948; Harwin and Angrist, 1948; Neiditsch, 1951; Beckett and Flynn, 1953; Hall et al, 1953).

Toxoplasma can affect the vascular and haemopoietic system, but the nature of the damage is obscure.

Among the earliest cases reported were the two in adults described by Pinkerton and Henderson (1941). In these there was a rash stated to resemble that of typhus. More recently Giroud and his co-workers (1951) have produced evidence that some cases of exanthematic fever in the Congo are due to toxoplasma. In these cases, as in typhus, it is possible that toxoplasma invades the endothelial cells lining the walls of the capillaries and so produces thromboses (Henderson and Pinkerton, 1941). Pericapillary lesions resembling those of typhus have, in fact, been reported in the brain.

In congenital cases rashes have been frequently reported, Zuelzer (1944), Callahan et
al (1946), Wylie, Fisher and Cathie (1950), Riley and Arneil (1950), Sabin et al (1952), Hall et al (1953), Magnusson and Wahlgren (1948), Beckett and Flynn (1955), Morris, Levin and France (1955). The rash has been described as purpuric, maculo-haemorrhagic or maculo-papular. Here again there may have been capillary damage or a reduction in platelets, or prothrombin deficiency. The last has been recorded by Magnusson and Wahlgren (1948) and by Gard, Magnusson, Wahlgren and Gilles (1949).

Bleeding has also been reported into the skin (Smitt and Winblad, 1948), from the umbilical cord and lip (Silver and Dixon, 1954), in the stomach, intestine and lung (Callahan et al, 1946).

In conclusion, as regards the simulation of haemolytic disease it would be satisfactory to be able to relate this to specific damage caused by toxoplasma to the blood forming organs. The frequency of jaundice might suggest liver damage, but only rarely can evidence of this be found histologically. Nor in spite of observations of the presence of toxoplasma in bone marrow (Pinkerton and Weinman, 1940; Kabelitz,
1952; Finckh, 1954) does damage to this tissue appear to be the cause. For the present at least it must be left as an instance (cytomegalic inclusion disease is another (Colebatch, 1955)) of excessive extramedullary erythropoiesis resulting from a generalised infection.

Mrs. D's serum dye test antibodies rose to a high titre in the last month of her subsequent pregnancy, and Buhn (1953) claims that in 10 - 15% of instances, pregnancy raises an already existing titre. The second Baby D was found to have passively transferred antibodies to even higher titre than its mother, yet it was well and remained so. High antibody titres alone, even if found both in mother and baby, do not necessarily indicate current toxoplasma infection.

Interesting, but not novel, is the prolonged survival of some of the inoculated animals and their giving birth to healthy offspring. One guinea pig, subsequently proved to be infected, survived for 250 days and produced a healthy litter. One of the mice had a healthy litter 44 days after inoculation, and was found to have toxoplasmosis 39 days later. As has been
shown by many workers, among them Lepine (1929), and Weinman (1943), toxoplasms may persist in mice for long periods, even for the duration of their lives, without any ill effect. Still more often they do so in the more resistant rat and guinea pig, hence the use of guinea pigs as a reservoir in the present cases.

Surveys for antibody suggest that toxoplasma infection is not uncommon in the population of this country, (Beverley, Beattie and Roseman, 1954). It is also likely, that as in animals, the parasite may in some cases persist for long periods. Jacobs, Fair and Bickerton (1954), isolated it from the eye of a man who gave a history of recurrent chorio-retinitis for eight and a half years. Stanton and Pinkerton (1953) found it in an enlarged cervical lymph node of a 26 year old woman who had an illness resembling toxoplasmic lymphadenopathy five years before. She gave birth to a healthy infant 36 weeks after the excision of the lymph node.

It would seem reasonable to expect that for a woman to infect her foetus she must have a parasitaemia while the foetus is susceptible. Generally it is assumed that this parasitaemia
will be due to recent infection. Very rarely will this infection produce clinical signs in the mother. The only known instance of proven clinical toxoplasmosis in both mother and baby is reported by Alexander and Callister (1955). The mother had toxoplastic lymphadenopathy, and the baby typical congenital toxoplasmosis with hydrocephalus, enlarged spleen and liver and chorio-retinitis. Marked extramedullary haemopoiesis and generalised oedema were also noted. Almost invariably the mother's infection is latent. That parasitaemia can occur in latent infection has been shown by Prior, Cole, Beeton, Saslaw and Chamberlain (1953) who isolated the parasite from the blood of a healthy young woman. It is, however, possible that transfer of infection to the foetus may be due not to the parasitaemia of acute infection, but to rupture of pseudocysts of chronic infection as suggested by Weinman (1952) and by Mellgren et al (1952). The difficulty in accepting the latter suggestion is that subsequent children do not have congenital toxoplasmosis.

The period during which the foetus is susceptible is probably long. It is unlikely
to be in the first few weeks when the parasite would be dissolved by the enzymatic action of the trophoplast. In the case reported by Gard and Magnusson (1951) infection immediately prior to or shortly after the onset of pregnancy was followed by the birth of a healthy infant.

It would seem worth while to examine for toxoplasma infection cases which appear to be haemolytic disease, but in which no blood group incompatibility between mother and child is found. The mother's and baby's sera should be examined for toxoplasma antibodies by the dye test of Sabin and Feldman and by the complement fixation test. Post-mortem blood has proved satisfactory. If the baby has died, a suspension of its brain should be inoculated into mice. This should not be dismissed as impracticable because mice are not immediately available since toxoplasmas survive for sixteen days in brain tissue kept at 4°C. Mice should be inoculated by the intracerebral and intraperitoneal routes, preferably the double inoculation in the same animal. In macerated babies it has been the practice here of late to inoculate guinea pigs and "dye test" these several weeks later.
It would be of interest and perhaps of importance to take note of any illness, however mild, suffered by the mother during pregnancy.

**SUMMARY**

Four cases of congenital toxoplasmosis are described. In all four instances there was a remarkable simulation of haemolytic disease. Two of the mothers subsequently gave birth to healthy infants. The prognosis for toxoplasmosis is unquestionably excellent in further pregnancies. The importance to the mother of establishing such a diagnosis where confusion with haemolytic disease might arise cannot be too strongly emphasised.
REFERENCES
Quart. J. Med. 12, 57.
CONGENITAL DEFECTS
At the present day considerable attention is being focused on the subject of congenital defects. Advances in the knowledge of the underlying influence of genetics, viruses and radiation will inevitably arouse interest in this cause of perinatal mortality.

Figures for the incidence of congenital defects as a principle cause of perinatal mortality have shown no relative increase over the last 15 years. In the series of neonatal deaths reported by Macgregor (1946, 1956) the incidence of congenital defects has remained constant at 10.5%. The report of the Registrar General for Scotland (1954) (abstracted below) has shown over the years 1936-1954 no apparent increase in the deaths from congenital defects in children under 1 year.

<table>
<thead>
<tr>
<th>Congenital Malformations under 1 year</th>
<th>1936-40</th>
<th>1952</th>
<th>1953</th>
<th>1954</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate per 1,000 live births</td>
<td>6.2</td>
<td>5.31</td>
<td>5.05</td>
<td>5.62</td>
</tr>
</tbody>
</table>

In Morison's series of unrelated autopsies on live born children under 28 days, the percentage of fatal congenital malformations in relation to total deaths was 13.0%.
In the present series of autopsies the incidence of fatal congenital malformations in live born children in relation to total neonatal deaths under 28 days was 18.2%.

Table A shows the number of fatal congenital defects in relation to total deaths.

Table B shows the percentage of infants dying from congenital defects in relation to age periods.

Table C shows the numbers and percentages of total malformations, together with age period at death of the more common congenital defects, some of those likely to be of surgical importance, and some of those comparatively rare, but of pathological interest.
The number of congenital defects in relation to stillbirths can only be an arbitrary figure owing to the fact that foetal congenital defects are seldom in themselves responsible for intra-uterine death in later pregnancy.

**TABLE A.**

<table>
<thead>
<tr>
<th>Total number of fatal congenital defects</th>
<th>Total Deaths</th>
<th>% of Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirths</td>
<td>199</td>
<td>991</td>
</tr>
<tr>
<td>Neonatal deaths</td>
<td>174</td>
<td>956</td>
</tr>
</tbody>
</table>

**TABLE B.**

<table>
<thead>
<tr>
<th></th>
<th>Fatal Congenital Defects as a Percentage of Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day</td>
<td>57</td>
</tr>
<tr>
<td>2-7 days</td>
<td>59</td>
</tr>
<tr>
<td>8-14 days</td>
<td>39</td>
</tr>
<tr>
<td>15-21 days</td>
<td>11</td>
</tr>
<tr>
<td>22-28 days</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>174</td>
</tr>
<tr>
<td>Defect</td>
<td>Total</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Anencephaly and variants</td>
<td>101</td>
</tr>
<tr>
<td>Spina bifida hydrocephalus</td>
<td>71</td>
</tr>
<tr>
<td>Congenital cardiac defects</td>
<td>53</td>
</tr>
<tr>
<td>Encephalocele</td>
<td>20</td>
</tr>
<tr>
<td>Multiple skeletal defects (not classified)</td>
<td>30</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>10</td>
</tr>
<tr>
<td>Defects of urinary system</td>
<td>26</td>
</tr>
<tr>
<td>Intestinal atresia (of these, 3 were mongols)</td>
<td>7</td>
</tr>
<tr>
<td>Cesophageal atresia</td>
<td>8</td>
</tr>
<tr>
<td>Exompholos</td>
<td>5</td>
</tr>
<tr>
<td>Hydranencephaly</td>
<td>3</td>
</tr>
<tr>
<td>Fibrocytic disease</td>
<td>5</td>
</tr>
<tr>
<td>Deformities of cervical spine</td>
<td>3</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td>2</td>
</tr>
<tr>
<td>Achondroplasia</td>
<td>4</td>
</tr>
<tr>
<td>Cyclops</td>
<td>5</td>
</tr>
</tbody>
</table>
DISCUSSION

By far the commonest fatal defect encountered was anencephaly and its variants.

The spina-bifida hydrocephalus complex was the defect encountered second in order of frequency. This deformity accounted for a not inconsiderable proportion of the total deaths in the periods 2-7 days and 8-14 days.

Congenital cardiac defects are a subject for study in themselves. The highest incidence of these defects was found in the periods 2-7 days and 8-14 days. The type and variety of defects encountered was so great that in this limited survey no useful purpose would be served by detailed descriptions.

Encephaloceles have accounted for a surprising number of defects.

Multiple skeletal defects which would not otherwise fall into this necessarily brief classification are numerous, although, if the individual defects were considered separately, the numbers of each defect would not be great.
Diaphragmatic hernia

Ten cases of diaphragmatic hernia were encountered in the present series. All of these were so-called false hernias, no peritoneal sac preceding the abdominal contents into the thoracic cavity. Most commonly the defect was in the postero-lateral segment of the left half of the diaphragm, although occasionally it was found involving the right half of the diaphragm. The size of the defect varied considerably. The extent of viscera in the thoracic cavity also varied, frequently including intestine, stomach and a portion of spleen or liver. In the Royal Hospital for Sick Children, Edinburgh, over the last 4 years, three newborn infants with diaphragmatic hernia have been subjected to operation. All of these infants failed to survive, difficulty being encountered with expansion of the lung on the affected side. It is obvious that many newborn infants with diaphragmatic hernia are not as yet reaching the surgeons. Diagnosis of diaphragmatic hernia will frequently depend on the obstetrician and until such time as the existence of this condition is recognized in maternity hospitals, it will be impossible to assess the results of surgical
The diaphragm is defective on the left side. Intestines have herniated into left thorax and the mediastinum is displaced to the right.

The diaphragm is defective on the right. The liver has herniated into the right thorax and displaced the mediastinum to the left.
intervention at this early age.

Oesophageal atresia - primarily a surgical problem, is important on account of the relative simplicity of diagnosis and also because of recent surgical success in treating this condition. The type of atresia and the generally associated tracheo-oesophageal fistula are varied. Morison (1952) (Foetal and Neonatal Pathology) illustrates the various types according to the classifications of Ladd (1944) and Vogt (1939).

The following figures for cases subjected to operation over the period 1952 to 1956 have been supplied through the courtesy of Mr. Mason Brown, Surgeon in charge, Royal Hospital for Sick Children, Edinburgh.

<table>
<thead>
<tr>
<th>Cases under 28 days</th>
<th>Infants surviving at present time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal atresia with tracheo-oesophageal fistula</td>
<td>13</td>
</tr>
<tr>
<td>Oesophageal atresia without tracheo-oesophageal fistula</td>
<td>5</td>
</tr>
</tbody>
</table>

No allowance is made in these figures for other concomitant congenital defects, not infrequently the actual cause of death.
Achondroplasia and Osteogenesis Imperfecta

In this series no familial history could be obtained in any of the cases of these malformations.

There are three pathological conditions in the newborn in which the limbs are shortened, and as these are frequently seen only by the obstetrician, considerable difficulty has often been experienced in differentiating between them. Diagnosis is, in fact, relatively simple, the achondroplasic having a characteristic facies. In congenital bowing of the long bones the degree of shortening of the limbs is not so pronounced and a dimple will be found overlying the site of angulation. Osteogenesis imperfecta has no characteristic facies and defects in the skull can frequently be palpated.
This condition is easily recognised on account of the facial appearance. Note the depression of the glabella and the protuberance of the frontal bones.

OSTEOSTROPLASIA

The limbs are similar in external appearance to those in achondroplasia. Note the difference in facial appearance when compared with achondroplasia.
This view of the opened thorax shows the multiple fractures of the ribs.
Bulldog, Dexter Calf. The hereditary aspect of achondroplasia is utilised in breeding Dexter-Kerry cattle which are relatively short limbed. Breeding of the pure Dexter may yield the severe achondroplastic calf. By courtesy of Mr. Beattie, Royal (Dick) Veterinary College, Edinburgh.

Cyclops Deformity

Piglet showing cyclops with hydranencephaly. This piglet was the last born of the litter. Mating with the same boar and the same sow was repeated but no deformed piglets were born. By courtesy of Mr. Head, Royal (Dick) Veterinary College, Edinburgh.
HYDRANENCEPHALY AND CYCLOPS.

There have been five cases of cyclops deformity in all of which the brain showed the abnormality usually referred to as hydranencephaly.

Hydranencephaly without any other malformation was found in three instances.

Hydranencephaly

The terminology of this defect is unfortunate as there is a tendency to confuse this condition with hydrocephalus. Hydranencephaly is compatible with life, affected infants having been known to survive for weeks or months. At birth the head is generally not enlarged. In brief, the cerebral hemispheres are small, about the size of the normal frontal lobe or less. Occasionally they may be completely absent. The space normally occupied by the cerebral hemispheres is filled with fluid surrounded by leptomeninges and dura. The corpus callosum is completely absent. The basal ganglia and the hind brain are apparently normally developed. The question arises in some, but not all, instances of hydranencephaly as to whether the deformity may be not a primary cerebral agenesis, but, forward displacement of the cerebral hemispheres by fluid. Further
detailed neuro-pathological examination is necessary.
Brain. The covering membranes of the brain have been reflected. Anteriorly can be seen the two small portions of cerebral cortex. There is a single common ventricle with well formed basal ganglia.
HIRSCHSPRUNG'S DISEASE

There were no deaths from this condition in this series of perinatal autopsies. This is a remarkable fact in view of the considerable number of operative specimens received for biopsy during the period under review. In spite of the fact that in the newborn Hirschsprung's disease is usually of the "long aganglionic segment" type, surgical skill would appear to be responsible for the survival of these infants.
CONGENITAL BOWING OF THE LONG BONES

Multiple involvement of the long bones as a result of congenital bowing is comparatively rare, and Angle (1954) in a review of the English literature found only eight previously reported cases. On the other hand, bowing of individual long bones occurs with greater frequency, the same author reviewing twelve cases of anterior and fourteen cases of posterior tibial angulation, together with an additional three involving only the femurs. In Edinburgh multiple congenital bowing has been encountered only once, and this in the course of the present series of consecutive autopsies. It may be that both types of lesions have in many, but not necessarily all instances, a common pathogenesis. The present case is that of a stillborn child which showed at autopsy congenital bowing of the long bones. In order to ascertain the presence or absence of accompanying abnormalities, prolonged anatomical dissection, together with detailed X-ray examination, was undertaken. It was hoped that at the end of the many months of labour such an examination might at least afford some clue as regards the pathogenesis. None of the previous
reported cases contained a thoroughly detailed dissection of the entire skeleton.

The diagnosis in this case made at autopsy was based on the presence of the deformities in the lower limbs, the associated cutaneous dimpling and the correlation of post-mortem radiographs.

Case Report

HISTORY: The mother aged 23, para 1 + 1, was first seen one month prior to the estimated date of delivery, when she was found to have an acute hydramnios. As a result of X-ray examination foetal malformation was not suspected, but foetal ascites or hydrops foetalis was queried. Pregnancy continued to term and the mother was delivered of a mature female foetus weighing 3175 gms. The mother's blood group was O, Rh. positive, W.R. negative.

Previous maternal history: The only history was that of pneumonia contracted at the age of 3 and 4 years, but since then she had experienced no trouble with her chest. She had been pregnant on two occasions prior to this
present delivery. In 1948 the pregnancy went to full term and she had a spontaneous delivery of a healthy living male infant weighing 8 lbs.12 ozs. This child is now 6 years old and very well. In 1951 she became pregnant again, but this ended in spontaneous abortion at the 6th week.

The family history is clear. She has two brothers and one sister, none married and all in good health. There is no history of any babies born suffering from congenital abnormalities, either on her or her husband's side.

EXTERNAL APPEARANCE:

The body was that of a female foetus weighing 3175 gms. The lower limbs appeared relatively short in comparison with the trunk and the arms. There was pronounced anterior angulation of the legs immediately above the ankles. At the apex of the protuberance there was a clearly defined cutaneous dimple. The feet showed a bilateral talipes equino-varus. No definite abnormality was noted in the upper limbs. The head was a peculiar shape with considerable protuberance of the frontal bones and a widely patent frontal suture. The base of the skull appeared relatively narrow in comparison with the breadth of the vault. In view of these
abnormalities the baby was X-rayed prior to the commencement of autopsy.

The baby was slightly hydropic, the subcutaneous tissues being slightly oedematous.

Head: The brain was injected with formalin in order to leave the skull intact for detailed anatomical dissection. Removal of the brain at a later stage failed to reveal any pathological condition.

Thorax: Pleural and pericardial sacs all contained an excess of free fluid.

Pharynx and oesophagus were healthy.

Trachea did not contain any foreign material.

Lungs were completely atelectatic. They were slightly compressed as a result of the excess free fluid in the pleural sacs. No subpleural haemorrhages were present.

Heart was of expected size and showed no developmental abnormalities.

Thyroid and thymus showed nothing to note.

Abdomen: Peritoneal sac contained a moderate excess of free fluid.

Alimentary tract showed nothing of interest.

Liver was slightly enlarged, paler than normal but showed no other abnormality. The Prussian blue reaction was negative. Gall bladder and bile
ducts were normal.

Pancreas appeared healthy.

Spleen was of normal size and consistence.

Right kidney was enlarged to about 1½ times the usual size on account of a hydronephrosis. Right ureter was moderately dilated, but no obstruction either at the pelvi-ureteric or vesico-ureteric junctions could be found to explain the hydronephrosis. Left kidney and left ureter were normal. No abnormality was noted in the bladder or urethra.

Adrenals showed nothing to note.

Ovaries, tubes and uterus showed no abnormality.

FURTHER EXAMINATION:

Immediately after dissection of the viscera, the body was fixed in formaldehyde. Curiously, after fixation the lower limbs became folded over to assume the so-called "Buddha" position. Certain bones were subsequently removed for histological examination, and the remainder of the skeleton subjected to strictly controlled maceration with dilute potassium hydroxide.

HISTOLOGICAL EXAMINATION:

Lungs: The lung parenchyma was mature. The alveoli contained an excess of amniotic debris
in keeping with an anoxial state.

Liver: There was a considerable excess of erythropoiesis, much of this of primitive type.

Spleen: Throughout the pulp were groups of normoblasts - excessive erythropoiesis for a mature foetus.

Pancreas, Suprarenals, Heart: No abnormality was present in these tissues.

Kidneys: Microscopy confirmed the renal parenchyma to be mature.

Bones: Sections were taken from rib, sternum, tibia and femur. In all of these there was a normal alignment of cartilage cells at the epiphyseal junction and normal ossification.

Tibia and femur: Sections through the sites of angulation showed the marrow cavity to be completely replaced by bone trabeculae arranged in a fan-like radiation towards the apex of the angulation.

Dimple: A section through the dimple present at the site of angulation showed the dermis to be directly contiguous with the underlying periosteum.

Placenta: Sections of placenta failed to reveal any pathological condition.
RADIOGRAPHIC EXAMINATION:

Lower limbs: X-rays showed bowing of both femora and tibiae, the convexity being anterolaterally, with localised embossing at the junction of the upper and middle third of the femora, and the middle and lower third of the tibiae.

Pelvis: There was dislocation of both hips with splaying of the ischia. The sacrum was narrow with absence of the ossification centres of the lateral masses. Three out of five of these centres should have been present at birth.

Humerus: X-rays showed slight bowing of the humeri.

Thorax: The clavicle was normal but the scapula, particularly the blade was abnormal. There were two heads in the first right rib, but no other abnormality.

Spine: There was flexion of the cervical column with a spina bifida in the lumbar region.

Skull: There was prominence of the frontal bones with the base of the skull relatively short in comparison with the vault.

ANATOMICAL DISSECTION:

Head: There was a cleft soft palate which extended into the posterior part of the hard palate.
The frontal bones were bulging and the interfrontal suture widely open. The chondro-cranium was small and the foramen magnum oval, its largest diameter being antero-posterior.

Vertebrae: The cervical vertebrae showed a considerable degree of flexion. The laminae were widely separated behind and directed caudally - this direction probably associated with the cervical flexion. The laminae of the second and third cervical vertebrae were fused suggesting incomplete segmentation. In the embryological development of vertebrae there are three primary centres of ossification, one for the centrum and one for each half of the neural arch. At birth the cartilage should persist at the neuro-central joints and in the regions of the spine. In the present case, C.6., on one side only the neuro-central joint was ossified, and the anterior end of the neural arch attached by bone to the centrum, the laminae being attached by membrane to the anterior end of the neural arch. The accompanying illustration shows the neurocentral region of C.6. In all the cervical vertebrae the pedicles were composed of membrane. Cervical 7 and thoracic 1 have a premature synostosis of their laminae. In the thoracic vertebrae, the
anterior ends of the neural arches, i.e. the pedicles, were as in the case of the cervical vertebrae membranous. The most anterior part of the bony arch was the transverse process. Thoracic 12 has a bony pedicle on the right but not on the left. In other words it was more normal. Neuro-central joints were absent except on the right side of thoracic 12.

The lumbar vertebrae were six in number, this probably of no significance. These vertebrae were the most reasonably normal, there being only a gross spina bifida. The pedicles were bony, and the neuro-central joints all present and normal.

The sacral vertebrae showed the centra and the pedicles to be normal. There was a gross spina bifida. The lateral masses showed no centres of ossification, which should in a normal course of events have been present at birth. The cartilage in which the centra should have been was also deficient, producing a very narrow sacrum.

Pelvis: The transverse inlet was very narrow and the antero-posterior diameter very long. The outlet by contra distinction was extremely wide because of the splaying of the conjoint rami. See X-ray. Moreover, the conjoint rami should
have been cartilage, while they were in fact membrane with no apparent chondrification. There was a bilateral congenital dislocation of the hip, the false joint being above the triradiate cartilage.

Shoulder Girdle: The scapulae were very small, especially the blades which were virtually absent below the level of the spines. There was no excess of cartilage in these regions and therefore the conclusion that might be reached is that there had been a primary cartilagenous defect.

The clavicles were normal.

Ribs: There were twelve pairs of ribs, the first and second right ribs having two heads. No other anomaly was found in the ribs.

Long Bones: Dissection confirmed the angulation noted in the femora, tibiae and humeri. The nutrient artery of the femur was directed downwards instead of upwards.

Summary and Conclusions:

In addition to the bowing of the long bones, the points of outstanding and significant interest were (1) the defect in the vertebrae, (2) the defect in the scapulae, and (3) the defect in the pelvis. (The pelvis was remarkably similar
to the "Roberts" pelvis described in adults but never before reported in a child. The "Roberts"
type of pelvis is associated with synostosis of the sacro-iliac joint and maldevelopment of the lateral masses.

All of these three defects were not primarily bony defects; they must have occurred in the cartilaginous phase or earlier.
This photograph shows the relative shortness of the lower limbs, the angulation of the right tibia and the peculiar shape of the head.
FIG. 2.
Position in which found after fixation. An approximation to the so-called "Buddha" position.

FIG. 3.
Close-up view taken to show dimple at site of angulation.
FIG. 4. Ante-natal X-ray: In the radiograph no bony abnormality of the foetus is apparent.

FIG. 5. Ante-natal X-ray: Lateral view shows the bowing of the femur.
FIG. 6.

Skull X-ray: This lateral view shows the relatively short base of the skull in comparison with the vault. The frontal bones are protuberant. There is flexion of the cervical spine.

FIG. 7.

Skull After Maceration: The base is short in comparison with the vault and the protuberance of the frontal bones is clearly demonstrated.
After Maceration: The anterior view shows the relative shortness of the base of the skull.

Vault of Skull: There is widening of the interfrontal suture.
FIG. 10.

X-ray of Body: This radiograph demonstrates the bowing of the femora.
FIG. 11.

X-ray of Pelvis & Lower Limbs: There is bowing of both femur and tibia, with convexity anterolaterally. The localised embossing is evident at the junction of the upper and middle thirds of the femur and the middle and lower third of the tibia. In the pelvis there is dislocation of both hips with splaying of the ischia.
FIG. 12.
Pelvis & Lower Limb After Controlled Maceration:
In the pubis the transverse diameter of the inlet is narrow and the antero-posterior diameter is long. There is splaying of the conjoint rami. There is bowing of both femur and tibia.

FIG. 13.
Section of Femur: The centre of the shaft is obliterated by dense bone with the trabeculae showing a fan-like arrangement radiating from the point of angulation. x 2. Haematoxylin & Eosin.
CONGENITAL BOWING OF THE LONG BONES

FIG. 14.
Section of Tibia: The section shows the pronounced fan-like arrangement of the bony trabeculae. x 8. Haematoxylin & Eosin.

FIG. 15.
Section Through Cutaneous Dimple: The dermis is continuous with the periosteum. x 50. Haematoxylin & Eosin.
FIG. 18.
X-ray of Thorax & Right Arm: There is absence of any bowing in the radius or ulna, and in this x-ray there is only a suggestion of bowing of the humerus.
The clavicle is extremely small.

FIG. 19.
X-rays of Sacrum: These radiographs confirm the absence of centres of ossification for the lateral masses.
FIG. 16.
Humerus after Maceration: This shows the localised embossing which is not so pronounced as that in the femur or tibia.

FIG. 17.
X-ray of Humerus (Specimen after Maceration): Slight localised embossing in the midshaft.
A typical vertebra is ossified from three primary centres, one in the body and one in each half of the vertebral arch (also called neural arch).

At birth the vertebra is in three pieces - the median, larger part (the centrum) of the body, and the two parts ossified from the centres for the arch.

The median part (the centrum) of the body is joined to each postero-lateral part by a plate of cartilage; the joint is called the neuro-central joint.
Neuro-Central Region of 6th Cervical Vertebra.

On one side only the neuro-central joint is ossified and the anterior end of the neural arch attached by bone to the centrum.


**DISCUSSION**

Multiple bowing of the long bones is not necessarily a fatal condition. Caffey (1947) records three cases in living children, and Bound, Finlay and Rose (1952) reported this condition in a child aged five months, in whom they noted the easy assumption at this age of the presumed foetal position, in which each foot compresses the opposite thigh. Abnormalities accompanying the bowing have been noted by Williams (1943). In a case involving bowing of the femora and anterior angulation of the tibia, he noted incomplete ossification of the body, and hypoplasia of the neural arch and spinous processes of the 5th cervical vertebra. In one of the cases of multiple bowing reported by Bound, Finlay and Rose there was micrognathia,
cleft palate, plagiocephaly and marked pidgeon breast deformity. Caffey, on the other hand, found, in his living cases, no evidence of other deformities or other skeletal disease. Angle (1954) found in a newly born premature infant, no radiological evidence of other skeletal deformity except multiple bowing. In the present case the deformities other than the bowing of particular interest are those related to the scapula, the vertebrae and the pelvis. These defects are not primarily bony defects and they must have occurred at the cartilage phase or earlier. The bowing of the long bones also need not necessarily be a primary bony defect. In the present case it might be reasonable to assume the existence of an association between the other defects and the bowing. Such other defects, incidentally, were only really manifest after meticulous dissection.

As regards the pathogenesis of this condition, analysis of the present case leads to the assumption of a defect at the cartilagenous stage of development or earlier. Angle (1954) stated that the most widely accepted hypothesis was the mechanical theory. This held that the curvatures in the bones were mechanical in
origin resulting from the moulding of long bones over other parts by centripetal forces. Murray (1936), in offering what was then an alternative theory to that of pure mechanical origin, considered that the diaphysis had been buckled during its cartilagenous stage. He postulated that the subsequent ossification of the cartilage concentrated in the region of the angulation would result in a fan-like radiation of the trabeculae. Two theories as to the mode of production of this fan-like trabecular arrangement have therefore been propounded - (1) that postulated by Murray in which there is a primary cartilagenous defect, and (2) that illustrated by Angle in which he suggests that it may be the result of sheering stresses which would develop as the angulation increases, by virtue of the nonorthogonal orientation of forces acting on the angulated region.

Whilst it is impossible to be certain, the evidence afforded by the present case tends to lend support to Murray's theory. That bending probably occurs in the cartilagenous phase of development is actually suggested by Gaffey, who believed the condition resulted from extra-skeletal forces of compression operating at the
sites of bowing. Potter (1952) adds the qualification "although this (extra-skeletal forces) may be a contributing cause, it seems logical to assume that some predisposing factor must also be present, since the normal foetus does not remain in a constant position in utero."

It seems not impossible that the opposing theories are in fact reconcilable. The demonstration of accompanying abnormalities, developmentally, of the cartilage phase or earlier, provides logical evidence of some predisposing condition, whilst not precluding the superimposed action of extra-skeletal forces.

Hydramnios previously referred to in cases of multiple bowing by Williams (1943) and Bound et al (1952) was present in this case. Hydramnios is recognised as a frequent association of foetal abnormalities. There was no family history of this or other deformities. In two cases observed in siblings by Potter (with X-ray pictures similar to those reported by Caffey) she found the mother to have osteogenesis imperfecta. No evidence of this, however, could be found in relation to the present case.
CONGENITAL BOWING OF THE LONG BONES

Effect of right-angular forces on elastic body. A. Cylinder. B. Longitudinal section of long bone. C. Longitudinal section of long bone when forces have been narrowly applied.

FIG. 20.
Diagrams Reproduced from the Publication of Angle (1954).

Fig. 20 is self explanatory. It illustrates the basis of the purely mechanical theory.
SUMMARY

Detailed anatomical, pathological and radiological examination has been described in an infant showing multiple congenital bowing of the long bones. The accompanying abnormalities have been enumerated in detail with relation to their anatomical and embryological development. From this investigation it has been demonstrated that the two diametrically opposed views as regards pathogenesis may in all probability be reconcilable.
REFERENCES


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CONGENITAL LARYNGEAL ATRESIA

Congenital atresia of the larynx, unless recognised immediately at birth, is incompatible with life. Fortunately it appears to be a rare condition, only two previous cases having been reported, both in the American literature. The British textbooks on diseases of the Ear, Nose and Throat either ignore the condition or dismiss it as being incompatible with life and thus of academic interest only.

Congenital laryngeal atresia has been encountered on two occasions in the present series of autopsies; in one instance in a stillborn baby and in the other in an infant aged 15 minutes. The possibility, however remote, that immediate establishment of an airway might be remedial warrants mention of this atresia, uncommon as it may seem.

Case 1:

The mother, para 0, first pregnancy was noted to have hydramnios. Premature rupture of the membranes occurred at the 28th week, and a small male infant was born weighing 1045 gms. The baby was limp at birth and given Nicamide together
with continuous oxygen. The baby continued to make respiratory efforts and although the heart beat was still detected after fifteen minutes it was noted that respiration was never established. Death took place within twenty minutes of delivery.

Autopsy Report:

The body was that of a small male infant. There was an acute flexion deformity of the right wrist.

Head: The brain and meninges showed no abnormality.

Thorax: The pharynx appeared normal. There was a complete atresia of the larynx and it was impossible to pass a probe downwards into the trachea, even using considerable force. Dissection of the atresia showed a complete fibro-cartilagenous occlusion, about 4 mm. below the true cord. Both true and false cords were easily distinguished. The trachea was moderately dilated and contained a large quantity of white fluid secretion. The major bronchi were similarly distended with secretion. On opening the thorax, the most striking feature was the size of the lungs which were much bigger than might have been expected in a baby of this size. On their
medial aspects the lungs extended well over in front of the heart. The lungs were fairly firm and on section considerable quantities of white secretion exuded from the surface. After section the lungs appeared to decrease considerably in size, presumably on account of the escape of the fluid. There was a complete atresia of the oesophagus, with a long narrow upper pouch which was not distended. There was a gap of about 1\(\frac{1}{2}\) cm. before the commencement of the lower pouch. There was a tracheo-oesophageal fistula extending from the lower pouch of the oesophagus and opening into the trachea in the region of the carina. There was no communication whatsoever between the upper oesophageal pouch and the trachea. The heart was of the expected size and developmentally normal.

**Abdomen:** The stomach was smaller than usual. The large intestine contained bile-stained material. The other abdominal organs showed no abnormality.

**Microscopical Report:**

**Lungs:** Sections of both lungs showed considerable distension by secreted precipitate, of all the air passages and the air spaces, this
being particularly pronounced in relation to the alveoli. No epidermal squames were present.

**Intestine:** Sections of intestine failed to reveal any epidermal squames.

**Kidneys:** These organs showed a well defined neogenic zone in keeping with a prematurity.

**Case 2:**

The mother, para 0, first pregnancy, was noted to have slight hydramnios. Premature labour took place at the thirtieth week, and a small female foetus weighing 1500 gms. was born after an assisted breech delivery.

**Autopsy Report:**

The body was that of a small female foetus. The head was enlarged with the neck very short and webbed. There was a deformity of the cervical spine. A slight varus deformity was evident in the left foot.

**Head:** The lateral and third ventricles were all greatly dilated, and although dilatation was not evident in the fourth ventricle the aqueduct appeared to be patent. The posterior fossa of the skull was small and shallow, but no Arnold-Chiari deformity was present in the hind brain. Only
one vertebra was detected above the seventh cervical spine, but detailed examination without the addition of radiological examination was impracticable.

**Thorax:** The larynx was completely atretic and it was impossible to pass a probe through it either from above or from below. The atresia was fibro-cartilaginous and situated about 4 mm. below the true cord. Both true and false cords were plainly visible. When the trachea was incised a large quantity of grey, slightly blood-stained mucoid fluid poured out. Each pleural sac had a pouch or diverticulum extending upwards behind the clavicle for about 2 cm. and this pouch was occupied by lung substance. The lungs were both very much above the expected size, each weighing 35 gms. Their anterior borders overlay the pericardium. On section of each lung, an enormous quantity of thin mucoid fluid exuded from the surface.

**Abdomen:** The peritoneal sac contained a large quantity of blood, the source of this being a ruptured subcapsular haematoma of the liver. The alimentary tract showed nothing to note. The liver showed one ruptured and two unruptured fairly large subcapsular haematomas.
The other abdominal organs showed nothing of interest.

**Microscopical report:**

**Lungs:** The bronchi and alveoli were grossly dilated and they contained an abundant deposit, partly albuminous and partly mucoid. In spite of the distension the alveolar walls were still comparatively thick, and the lining cells conspicuous, this on account of the immaturity of the lungs.

Microscopy of the other organs, including the ovaries and Fallopian tubes, showed nothing to note.
Section of Lung

The alveoli show pronounced dilatation. The alveolar walls are nevertheless still comparatively thick on account of immaturity. Abundant precipitate is evident within a small bronchus, and also within the alveoli. x 60. Haematoxylin & eosin.
DISCUSSION

The case reported by Jackson and Jackson (1937) was a full-time infant noted by the obstetrician at birth to be making strong respiratory efforts with no evidence of air exchange. A tracheotomy was performed and the infant survived. At the age of ten months, on lifting the epiglottis no aperture could be visualised, the true cords being joined by a sheet of white fibrous tissue, through which their outlines could be established. Efforts to establish a lumen by puncture from above and by retrograde procedure had not at that time been successful. The infant was reported as having other anomalies, such as the Ehlen-Danlos syndrome. Hollinger, Johnson and Shiller (1954) reported the case of a cyanotic baby who had ceased to make respiratory movements immediately after birth. Direct laryngoscopy revealed a complete membranous occlusion of the glottis and a 3 mm. bronchoscope was immediately pushed through the web. At six years of age, examination showed thickened cords.

In the present cases, it is of interest that the atresia was fibro-cartilagenous and actually below the cords. Specialist opinion was sought
from an ear, nose and throat consultant, who was quite emphatic that no bronchoscope could possibly have been pushed through the atresia in the present instances.

Should any such case ever be encountered at birth, ultimate treatment would inevitably present many difficulties. That such an atresia does exist is of considerable importance. A thin, membranous atresia would be liable to be overlooked in routine autopsy work, as it is not common procedure to pass a probe through the larynx in every autopsy, unless other features warrant this act.

At autopsy, the most striking feature in the present cases has been the increased size of the lungs. The histological picture in each case is identical.

The only other condition in which a similar histological appearance of the lung has been encountered was that in heterotopic lung tissue.
REFERENCES


Generalised arterial calcification in childhood is relatively uncommon. The pathogenesis is varied, arterial calcification being seen as a metastatic phenomenon associated with renal or parathyroid disease or as a frequent concomitant of progeria. In the neonatal period the calcification, frequently capricious in its arterial distribution, is always medial and it appears to constitute a distinct entity. Stryker (1946) reviewed 15 recorded cases of infantile arterial calcification, and added another 5 of his own. Cochrane (1954) records 6 cases in infants aged between one and seven months that were recognised over the last 30 years in the Hospital for Sick Children, Toronto. Hughes & Perry (1929) described senile arterial changes in a child dying suddenly aged seven weeks, and this is the only reported case of infantile arterial calcification in the British literature.

The most common clinical features have been a sudden onset of dyspnoea, with death within a few days from congestive cardiac failure.

The present case, the only one of its kind
encountered not only in the present series of autopsies, but in the records in Edinburgh, is unique as regards the clinical presentation. In view of this and in view of the apparent rarity in this country, a full description of the case is included.
CASE REPORT

The baby, a male, birth weight 8 lbs. 4 ozs., was born spontaneously and appeared to thrive until the age of 10 days. At this time he started to vomit and continued to do so for the next 7 days, when he was admitted to hospital with a distended abdomen. On examination the baby was found to be pale and wizened. No bowel sounds could be heard. He was seen by a paediatric surgeon who considered the diagnosis to be Hirschsprung's disease. The child was treated conservatively but progress did not prove satisfactory. At the age of 28 days sudden collapse occurred shortly after a feed. The abdomen was distended and intestinal obstruction was diagnosed. The blood pressure fell and in spite of intravenous plasma it could not be recorded.

Autopsy report:

The body was that of a poorly nourished male infant weighing 3,200 gms. There was pronounced abdominal distension.

Head: The brain and meninges showed no abnormality. The cerebral vessels were healthy.

Thorax: The trachea and oesophagus were
normal. Several of the large vessels of the neck were thickened, calcified and abnormally tortuous. The serous sacs were healthy. The lungs were firmer than usual, especially in both lower lobes and an excess of frothy fluid exuded from the cut surface. The consistence suggested pneumonia. No abnormality was noted in the pulmonary vessels. The heart was of expected size and no abnormality was noted in the size or capacity of the chambers, nor in the thickness of their walls. No evidence of myocardial infarction was present. The coronary arteries were abnormally tortuous, thickened and obviously calcified. The aorta appeared healthy and there was no evidence of atheroma.

**Abdomen:** On opening the abdomen several loops of small intestine were found adherent to the anterior abdominal wall. There were numerous peritoneal adhesions between the anterior abdominal wall and the loops of small intestine. It was possible to unravel the small intestine for about a foot distal to the duodeno-jejunal junction. From this point to about 18 inches above the ileo-caecal junction the coils of small intestine were matted together and the intestinal wall was friable and obviously gangrenous in places.
The small intestine mesentery was considerably thickened. In the root of the mesentery the vessels were thickened, and contained blood clot which might have been of ante-mortem origin. The large intestine contained a quantity of faeces and its appearance did not suggest Hirschsprung's disease. The liver and spleen were of natural size and showed no abnormality on section. The vessels were not calcified. The pancreas appeared normal. The kidneys showed no pathological condition. There was no evidence of calcification either in the parenchyma or in the vessels. The suprarenals showed nothing of note.

Microscopical report:

**Heart:** The descending branch of the left coronary artery presented a striking picture. There was a well defined broad zone of medial calcification which extended uniformly around the entire circumference of the artery. In the midst of the zone of calcification the internal elastic lamina was still perceptible. The intima of the artery showed intense fibroblastic thickening with resultant severe narrowing of the lumen. The myocardium showed no evidence of infarction, recent or old.
Naked Eye Photograph of Heart and Great Vessels: This shows the pronounced tortuosity of the coronary vessels. Above the aorta there is an obviously thickened and abnormally tortuous artery.
Intestine and Mesentery: The intestinal wall was in parts necrotic, but in other areas was replaced by granulation tissue. In the adjacent mesentery there were several vessels all showing medial calcification and severe narrowing of their lumina. No ante-mortem thrombus was evident in any of these vessels, nor was there any recanalisation. The medial calcification in the vessels was essentially patchy and not fully concentric. The calcification in its earlier stages was in the internal elastic lamina with extension later both internally and externally. Sections stained with Sudan showed occasional small aggregations of fat which were related to the areas of calcification. The internal elastic lamina was intact and there was no evidence of its disintegration.

Lungs: Sections showed areas of collapse with inflammatory cell infiltration, mainly histiocytes and polymorph leucocytes. The pulmonary vessels showed early calcification similar to that found in parts of the mesentery, but at an even earlier phase of development. Where calcification was commencing around the internal elastic lamina, giant cell formation was occasionally present in the directly adjacent
intima. There was no fraying of the internal elastic lamina, the earliest manifest change in this being a thickening due to calcium deposition.

**Aorta:** In comparison with the aorta of a child of roughly similar age, the aorta showed irregular thickening of the internal elastic lamina. No other change was present, in particular there was no evidence of medial calcification, giant cell formation or intimal thickening.

**Salivary gland:** A large artery included in the section showed well established calcification, with intimal thickening.

**Suprarenal:** The parenchyma of the gland was normal. The vessels in the periadrenal fat were calcified.

**Pancreas:** The parenchyma was normal, but the section included a large artery in which there was pronounced calcification.

**Kidneys:** The glomeruli and tubules were normal. A medium sized artery showed changes similar to those found in the mesentery.

**Spleen:** The vessels showed early calcification.

**Brain:** Numerous sections were taken to include the cerebral vessels, which, however, were perfectly normal.
MEDIAL CALCIFICATION OF THE ARTERIES IN INFANCY

Descending Branch of Left Coronary Artery: The section shows pronounced medial calcification. The lumen of the artery is considerably reduced by fibroblastic intimal proliferation. x 65. Haematoxylin & eosin.

Peri-adrenal Artery: The lumen of the artery is severely narrowed. The internal elastic lamina can still be distinguished in the midst of the zone of calcification. x 140. Haematoxylin & eosin.
Peri-Adrenal Artery: High power view to show calcification on both sides of the internal elastic lamina.
$x$ 300. Verhoeff's elastic tissue stain.

Pulmonary Artery: Thickening and early calcification of the internal elastic lamina with giant cell formation.
$x$ 675. Haematoxylin & eosin.
DISCUSSION

In relation to the aetiology of arterial calcification in infancy, Stryker (1946) discusses factors such as renal conditions, primary and destructive bone diseases, parathyroid hyperplasia, hypervitaminosis D, and allergy. Some of these factors are well recognised in association with arterial calcification, but others such as allergy and Vitamin D are probably largely speculative.

Approximately fifty cases of arterial calcification in the young have been reported. A considerable number of these can be ascribed to some predisposing pathological condition. There still remains, however, a definite group of cases characterised by a fatal outcome in early infancy in which no aetiological factor related to the arterial calcification has ever been proved.

Traisman et al (1956) in a review of arterial calcification in infancy refer to this condition as a dystrophic calcification in contrast to metastatic calcification. These authors suggest that dystrophic calcification may occur as the result of incomplete development of
the ground substance of the arteries. Cochrane and Bowden reported that the earliest changes were evident in relation to the internal elastic lamina. This was amply demonstrated by Stryker who described calcification both on the internal and external aspect of the internal elastic lamina.

The histological features of the present case show that calcification indeed commences primarily on and around the internal elastic lamina. The extensive medial calcification found in the coronary and other arteries is obviously a later stage of the disease process. The term "medial calcification" is therefore misleading. Moreover, this type of arterial calcification bears no resemblance to that (Monckeberg's sclerosis) found in adult life.

In the present case, the coronary, the visceral and pulmonary arteries, the carotids and peripheral vessels of the neck, were affected, whereas the aorta showed only early changes in the internal elastic lamina. The cerebral arteries were entirely free of both calcification and of any degenerative change. The heart showed no infarction, and vessels in the liver parenchyma were healthy. Although some of the vessels in the kidney were calcified, there was no evidence of glomerular change.
The mesenteric arteries were severely affected and the mesenteric occlusion had ultimately resulted in intestinal infarction. This occurrence, although not unlikely, has not previously been reported. Myocardial ischaemia resulting in death is the most common sequel of this disease. Gross cardiac hypertrophy was constant in the infantile cases reported by Cochrane and Bowden, and in only one instance was the myocardium normal. In spite of the severe coronary occlusion in the present case, no infarction, recent or old, was found in the myocardium. Most interesting, but not novel, is the fact that the cerebral arteries in the present case were unaffected. Absence of calcification in the cerebral arteries has been previously noted by Cochrane and Bowden.

The onset of this disease so early in infancy suggests a congenital origin. One of the cases reported by Stryker was that in a stillborn child in whom polycystic disease of the kidneys was also present. In none of the cases of renal non-function encountered in the present series of autopsies was calcification of the vessels found. Moreover, the foetus in utero is not dependant on renal function, so
that some other underlying mechanism must be present.

As has been previously suggested by Potter (1952) it appears most probable that the primary defect lies in an embryonal defect in the elastic tissue which makes the vessel unusually susceptible to any noxious agent.

In the present case the causative factors of metastatic calcification have as far as possible been excluded.

The clinical diagnosis of "medial calcification" in infancy will always be exceedingly difficult even with electrocardiography. Differentiation from other conditions such as endocardial fibroelastosis will present considerable difficulty. Radiological examination as suggested by Cochrane & Bowden appears of doubtful value. Retrospective examination of radiographs from the present case failed to yield any evidence whatsoever of arterial calcification. As almost the entire number of cases of arterial calcification reported have been in the American literature, it is interesting to speculate as to whether there is indeed any country specific distribution. In this respect further reports of cases in this country will be awaited with interest.
SUMMARY

A case of medial calcification of the arteries in infancy has been described.

Exclusion of cases of metastatic calcification leads to the conclusion that this disease process exists as a distinct entity of its own.

The British literature contains only one reference to this condition. As the other references are almost entirely American, speculation is raised as to whether there is any country specific distribution.

The term "medial calcification" is misleading, the earliest changes being centred in and around the internal elastic lamina.

The probable role of an embryonal defect in elastic tissue as an aetiological agent is discussed.
REFERENCES


STRYKER, W.A. Am.J.Path. 22, 1007. 1946.

RENAL NON-FUNCTION

Severe dysplasia or aplasia of the kidneys and urinary tract was noted in 25 out of a series of 1,947 consecutive autopsies on stillbirths and neonatal deaths. This figure included such malformations as complete absence of the kidneys, bilateral renal cystic dysplasia and congenital urethral obstruction. In these defects, involving severe impairment or absence of renal function, the foetus or infant showed certain accompanying characteristic features, particularly in relation to the face and the hands. The facial appearance only has found previous mention. With the fall in perinatal mortality from other causes and the relative increase in congenital abnormalities, it became apparent that severe renal malformations were likely to be encountered with increasing frequency.

In relation to renal agenesis, Potter (1946) reported twenty cases out of a series of five thousand perinatal autopsies, Bell (1946) reported an incidence of seven cases out of two thousand, four hundred stillbirths and Morison (1952) two out of a corresponding series
of one thousand, three hundred and thirty two autopsies. The incidence in Edinburgh of seven-teen cases of actual renal agenesis (excluding cystic dysplasia) out of 1,947 autopsies, too small a figure to be of substantial value, suggests that this condition is indeed being encountered more frequently than before. In her original description of the facies associated with renal non-function, the cases described by Potter were all instances of bilateral renal agenesis. In her text book, however, on "The pathology of the Foetus and the Newborn" Potter uses the phrase "absence of renal function" in relation to the characteristic facies but quotes no examples other than renal agenesis.

The present series of twenty five cases showing all or some of the features associated with renal non-function, includes seven examples of renal cystic dysplasia, in two of which there was an accompanying urethral obstruction. Complete urethral obstruction with no other congenital malformation was present in one case.

The sex incidence of renal agenesis showed a predominance of male over female, ten males to six females (one case being undetermined),
whereas out of the seven cases of severe renal cystic dysplasia four were female and three were male. The number of cases of cystic dysplasia is much too small and the sex ratio too narrow to be of any significance. It is of interest that the three instances of urethral obstruction were all in males.

The weight range. It is impossible to draw statistical conclusions from the present series, but the figures suggest that even where mature according to mother's dates, the babies with renal agenesis tend to be of low birth weight. Babies with renal cystic dysplasia were relatively heavier than those with renal agenesis.

Potter in her description of the facies associated with renal agenesis noted a number of characteristic features and one of the reasons for this present review was to ascertain whether these features were sufficiently consistent for certain diagnosis. The other reasons were to seek any additional features that would be of help in diagnosis, and to reveal the fallacies likely to be encountered. Any such information would prove extremely helpful to
obstetricians, puzzled as they frequently have been by their failure to resuscitate babies subsequently found to have severe renal malformations, incompatible with a life of only several hours.

The main features in Potter's description of the renal facies consisted of enlargement and abnormal position of the ears; the increased space between the eyes; a prominent epicanthic fold that forms a wide semi-circle on each side of the nose and covers the medial palpabral commissure; slight flattening of the tip of the nose; and a prominent crease below the lower lip with recession of the chin. Of the cases in the series involving renal non-function, in 22 out of 25, the facial appearance was sufficiently pronounced to be diagnostic before commencement of the autopsy. In the remaining three (case numbers 8, 14 and 16), a diagnosis of renal non-function could not be made on the facial appearance alone, and this even on retrospective consideration. Case 16 was a very small foetus, but in cases 8 and 14, both of which were mature babies, the ears, and in case 8 the nose, did not accord with the "characteristic appearance". The characteristic facial appearance
is therefore present very frequently in severe non-function but not in 100 per cent of cases.

Notwithstanding the absence of some of the usual facial features, a diagnosis of renal non-function was still made prior to autopsy in cases 8, 14 and 16 on account of the accompanying appearance of the hands, well illustrated in the photographs. In Table 1 subdivision "appearance of hands" there occurs in seven instances the words "not observed". The reason for this was simply that all these cases occurred before attention happened to light on the hands. Thereafter, examination of the hands revealed a certain particular appearance in every case of renal non-function.

The presence of this appearance has proved of considerable value where the facial features have not been convincing (cases 8, 14 and 16). Likewise has the absence of this appearance been of value where suspicions of renal non-function were aroused from the face, but no definite diagnosis possible on this alone (cases 28 and 31).

The hands in renal non-function appear relatively large and clumsy. They are broad
with the fingers short and squat in comparison with the width across the metacarpals. This appearance has merited the description of "spade-like". On the dorsum of the hands there is often loose redundant skin. X-ray examination has failed to reveal any bony defect.

**Other deformities.** The obstetrician is not likely to be greatly concerned where the foetus might be termed a monster, as in three of the present series (syrenomelia, 13 and 23, and monomelia, 21). Nor, is he likely to be concerned in regard to babies showing either the spina bifida-hydrocephalus complex (22 and 26) or a gross encephalocele (19). Excluding these cases of gross deformity (6 out of 25), it can be seen from Table 1, that in 10 instances out of 19 there was an abnormality in the lower limbs, the most common one being a talipes equino-varus, either unilateral or bilateral.

**Period of Survival.** With the exception of two cases the affected babies were either stillborn or survived no more than ten hours, the average survival period being approximately two hours. (There were 9 stillbirths and 16 livebirths). Of the two exceptions, one
infant was given an exchange transfusion on account of Rh. sensitisation, whilst the other infant was the only instance of urethral atresia per se.

The cause of death in almost all of the 25 cases was most certainly directly related to pulmonary hypoplasia, which was a constant finding in every case. In the majority of cases death was preceded by evidence of respiratory embarrassment. In relation to the respective babies, the lungs at autopsy were constantly small. The lungs microscopically appear more immature than might have been expected. Frequently the bronchi were disproportionately numerous in relation to the alveolar parenchyma and capillary ingrowth of the alveolar walls was less advanced. Blood urea estimation was carried out post-mortem in a number of cases, and without allowing for the death-autopsy interval no significant rise in the estimation was found.

Fallacies in diagnosis from the external features. The facial appearance in cases 28, 30 and 31 might in itself have suggested renal agenesis on account of some, but not necessarily all, of the usual features associated with renal non-function, yet in none of these cases
Section of Lung (still birth)
This is a very good example of the pulmonary hyperplasia associated with renal non function. The bronchi are disproportionately numerous and the alveolar parenchyma has a considerably immature appearance. x 90. Haematoxylin & eosin.

Section of Lung (infant aged 35 hours) Pulmonary Hypoplasia: The lung, which is partly expanded, still possesses an immature appearance. The bronchioles are disproportionately numerous. x 50. Haematoxylin & eosin.
was there any abnormality found in the urinary tract. Consideration has also to be given to the fact that in proved renal non-function variations in single features are encountered.

The experience gained from this series suggests that if the appearance of the face and hands is characteristic and if there is an accompanying abnormality, particularly talipes equino-varus in one or both lower limbs, then a confident diagnosis of renal non-function can be made. Experience, though limited, suggests that where some doubt exists in regard to the facies, the appearance of the hands provides strong supporting evidence of the presence of renal non-function.

To imagine that the facial and hand appearance is secondary to renal non-function borders on the fictitious. It seems much more probable that there is a common basis for all these lesions, probably genetic in origin. To prove or disprove an actual genetic basis on such a series as this is impossible.

In the present series there was no evidence of this abnormality having occurred in siblings. So far no cases in twins have been
reported. Careful documentation and observation in the future can alone provide more information.

Also borne out in the present series is the fact that the characteristic appearance of the hands and face was encountered only in cases involving severe impairment of renal function. In case No. 20, renal cystic dysplasia was present but not of a severe degree. In case No. 27, an infant aged six months showed renal dysplasia but a considerable amount of renal function must have been present to permit survival for such a long period.

It might well be that all the various abnormalities associated with absence of renal function could provide vital clues of extreme value to the geneticist.

Photography. Illustration of the twenty-five cases has proved no simple task. It has been frequently found that photography of the baby in one position has failed to reveal the salient features. For this reason, without the use of stereoscopic photography, three or four exposures were required in each case.
Sex | Wt. in gms. | Age | Renal Abnormality | Appearance of Face | Appearance of Hands | Congenital Abnormalities
--- | --- | --- | --- | --- | --- | ---
F | 1680 | 1½ hrs | Renal Agenesis | F | Not Observed | Recto-vaginal Fistula. Imperforate anus.
M | 2240 | 1 hr. | Cystic Dysplasia. Urethral obstruction. | F | Not Observed | Curving of tibia,
M | 1230 | 10 hrs | Renal Agenesis | F | Not Observed | Bilateral talipes equino-varus.
M | 2000 | 1 hr. | Renal Agenesis | F | Not Observed | Flexion of lower limbs.
M | 1660 SB. | Renal Agenesis | F | Not Observed | Nil.
F | 2260 | 1 hr. | Cystic Dysplasia. | F | Not Observed | Cardiac enlargement of undetermined origin.
F | 2556 | 7 hrs | Cystic dysplasia. | F | H | Genu recurvatum R. lower limb.
M | 1840 SB | Cystic dysplasia. | F? | H | Nil.
M | 1350 | 2 hrs | Renal Agenesis | F | H | Nil.
F | 2300 SB | Renal Agenesis | F | H | Syrenomelia.

Continued on following page.
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Wt. in gms.</th>
<th>Age</th>
<th>Renal Abnormality</th>
<th>Appearance of Face</th>
<th>Appearance of Hands</th>
<th>181 Congenital Other Abnormalities</th>
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<tbody>
<tr>
<td>14</td>
<td>F</td>
<td>2020</td>
<td>1 hr.</td>
<td>Renal Agenesis</td>
<td>-??</td>
<td>H</td>
<td>Short neck. Webbing of</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>1600</td>
<td>5 hrs.</td>
<td>Cystic dysplasia</td>
<td>F</td>
<td>H</td>
<td>Bilateral talipes equino-varus.</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>910 SB</td>
<td>36 hrs.</td>
<td>Renal Agenesis</td>
<td>F?</td>
<td>H</td>
<td>Nil</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>2207</td>
<td></td>
<td>Urethral Obstruction</td>
<td>F Not Observed</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>1480 mins</td>
<td>20</td>
<td>Renal Agenesis</td>
<td>F</td>
<td>H</td>
<td>Bilateral talipes equino-varus.</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>3540</td>
<td>½ hr.</td>
<td>Cystic Dysplasia</td>
<td>F</td>
<td>H</td>
<td>Occipito-encephalocele.</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>2952</td>
<td>1½ hrs.</td>
<td>Cystic Dysplasia (not severe)</td>
<td>-</td>
<td>-</td>
<td>Supernumerary digits. Exompholos.</td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>2140 SB</td>
<td></td>
<td>Renal Agenesis</td>
<td>F</td>
<td>H</td>
<td>Monomelia</td>
</tr>
<tr>
<td>23</td>
<td>??</td>
<td>980 SB</td>
<td></td>
<td>Renal Agenesis</td>
<td>F</td>
<td>H</td>
<td>Syrenomelia.</td>
</tr>
<tr>
<td>24</td>
<td>M</td>
<td>1420</td>
<td>2 hrs.</td>
<td>Renal Agenesis</td>
<td>F</td>
<td>H</td>
<td>Bilateral talipes equino-varus.</td>
</tr>
</tbody>
</table>
DESCRIPTION OF CASES

Photographic numbers correspond with case numbers.

Case 1: A female infant weighing 1680 gms and aged 1½ hours. The facial features were typical of those associated with renal non-function. Autopsy confirmed renal agenesis with an associated pulmonary hypoplasia. The lungs were poorly aerated with diffuse interstitial haemorrhage. Other abnormalities included absence of vagina, rectovaginal fistula and imperforate anus.
Fig 1(a)  

Anterior view.  Epicanthic folds.

Crease below lower lip.
Fig 1(b) Oblique view. Most helpful.
Fig 1(c) Lateral view. Characteristic shape of nose. Ears soft, flattened and low.
Case 2: A male infant weighing 2240 gms and aged 1 hour. The facial features were typical of those associated with renal non-function. Autopsy revealed cystic dysplasia of both kidneys, urethral obstruction with distension of the bladder, and bilateral hydroureter. The infant showed pulmonary hypoplasia with widespread intraseptal haemorrhage.
RENAL CYSTIC DYSPLASIA AND URETHRAL OBSTRUCTION.

Fig 2(a)  *Anterior view.*
RENAL CYSTIC DYSPLASIA AND URETHRAL OBSTRUCTION.

Fig 2(b) Slightly oblique view.
RENAL CYSTIC DYSPLASIA AND URETHRAL OBSTRUCTION.

Fig. 2(c)  **Lateral view.**  Ears prominent.
Fig 2(d) Descending colon on surface of grossly enlarged cystic kidney.
Case 3: A male infant weighing 1239 gms and aged 10 hours.

The facial features were typical of those associated with renal non-function. There was bilateral talipes equino–varus and flexion contracture of both elbows. Autopsy revealed renal agenesis with an associated pulmonary hypoplasia.
Fig 3(a) Lateral view. To show ears and nose.
Fig 3(b) Prominent subepicanthic folds and crease below lower lip.
Case 4: A male infant weighing 2000 gms and aged 1 hour.

The facial features were characteristic of those associated with renal non-function. The lower limbs were flexed in a rather curious way, but there was no talipes deformity. Both testes were present.
Fig 4(a) *Anterior view.* Whole body.
RENAL AGENESIS.

Fig 4(b) Oblique view.
Fig 4(c) Anterior view. Skin folds prominent.
Increased space between eyes.
Fig 4(d) Lateral view. Showing shape of nose and low flat ears.
Case 5: A male foetus weighing 1660 gms and showing the very characteristic facies associated with renal non-function. Both kidneys were entirely absent. The testes were normal.
Fig 5(a) Anterior view. Typical facies.
Fig 5(b) Oblique view. A very good example of renal facies. Recession of chin and shape of nose well shown.
Case 6: A female infant weighing 4 lbs. 15 ozs. and aged 55 minutes.

The facies were characteristic of renal non-function. Both kidneys were enlarged and almost entirely cystic. Other abnormalities included cardiac enlargement of undetermined origin and a hydrocephalus associated with meningeal adhesions secondary to an intra-uterine cerebral haemorrhage.
Fig 6(a)  Lateral view. Ears appear abnormally low but hydrocephalus was also present.
Fig 6(b)  Anterior view. Renal facies.
Case 7: A female infant weighing 2556 gms and aged 7 hours.

The right leg showed a genu recurvatum. The facial features, particularly the shape of the nose, were characteristic of renal non-function. Whereas the ears were large and flattened, they were not particularly low-set. The hands appeared large and spade-like, whilst over the dorsum the skin was loose with soft underlying subcutaneous tissue. The kidneys were small, 1 cm. across, fused and entirely replaced by small cysts. Both ureters were present. Both ovaries were present, but the uterus was hypoplastic. Blood urea nitrogen 24 hours after death was 74 mg.%.
Fig 7(a) Oblique view of face. Skin folds, shape of nose and ears well shown. Note appearance of hands.
Fig 7(b) Lateral view of face. Hands broad, spade-like, relatively short fingers. Face characteristic.
Fig 7(c) Anterior view. Taken to show the hands.
Fig 7(a) Slightly oblique view of face.
Case 8: A male foetus weighing 1840 gms.
The facial appearance was definitely abnormal but did not present the characteristic appearance of renal non-function. The left ear was large, very soft, and set at an oblique angle. The right ear appeared normal. The nose did not present the usual beaked appearance. Epicanthic folds were present, but not the skin crease below the lower lip. The hands were large and clumsy and their appearance sufficiently pronounced as to suggest renal non-function. Both kidneys were exceedingly small and almost entirely cystic. One ureter ended blindly and the bladder was small.
Fig 8(a) Anterior view. Appearance of hands well shown. Face somewhat distorted in this plane. Not typical renal facies.
Fig 8(b) Lateral view. One ear soft, flattened and set at oblique angle. (Other ear appeared normal). Nose certainly not beak-shaped. Hands spade-like.
Fig 8(c) Slightly oblique view. Hands spade-like. No skin fold below lower lip. Face not characteristic.
Case 9: A male infant weighing 2 lbs. 15 ozs. and aged 2 hours.

The facies was characteristic of renal non-function, and the hands showed the usual associated features. The kidneys were entirely absent.
Fig 9(a) **Anterior view.** Facial features of renal non-function. Hands particularly well shown.
Fig 9(b) Lateral view. To show ears. Nose not so striking in photograph as it was at autopsy.
Fig 9(c) **Oblique view.** Nose better shown. Hands, facial features and ears characteristic.
Case 10: A small male infant weighing 1800 gms. and aged 1\(\frac{1}{2}\) hours.

The facial features were characteristic of renal non-function. There was a deformity of the left forearm and hand, with absence of the left thumb. The right arm was normal, but the right hand was broad and clumsy with redundant skin on the back. Both feet were clubbed and the anus was imperforate. Both kidneys were entirely absent.
Fig 10(a) Anterior view. Right hand spade-like.
Deformity of left hand and wrist.
Bilateral talipes equino-varus.
RENAL AGENESIS

Fig 10(b) Oblique view. To show shape of nose and right ear. Facial skin folds also present.
Fig 10(c) Oblique view. To show nose and left ear. Right hand broad and spade-like.
Fig 11(a) Anterior view. Hands broad and clumsy. Chin receding. Facial features somewhat distorted.
Fig 11(b) Lateral view. To show position and shape of ear. Tip of nose slightly turned down. Hands broad and clumsy.
Fig 11(c) Oblique view. This shows the shape of the nose to better advantage.
Case 12: A male infant weighing 2056 gms. and aged $2\frac{1}{2}$ hours.

The infant showed the typical facial features of renal non-function with the associated characteristic appearance of the hands. There was clubbing of the left foot and a suggestion of a similar deformity in the right foot. The right kidney consisted of a small cystic structure and the right ureter was absent. The left kidney was hydronephrotic and the left ureter enlarged, the bladder was distended and a congenital urethral obstruction was found at the site of the posterior urethral valves.
Fig 12(a) *Anterior view.* Face somewhat distorted but increased space between eyes. Prominent epicanthic folds. Hands clumsy and spade-like.
Fig 12(b) Oblique view. This shows the characteristic shape of the nose.
Fig 12(c)  **Lateral view.** Shows recession of chin together with position and shape of ear. Hands characteristic.
Case 13: A syrenomeliasc female monster weighing 2300 gms. and showing the typical facies of renal non-function and the associated characteristic appearance of the hands. Other abnormalities included an umbilical hernia and an imperforate anus. The kidneys were entirely absent. The uterus was hypoplastic, but both gonads were present.
Fig 13(a) Note the clumsy spade-like hands with relatively short fingers. Facial skin folds not evident in this photograph. Single fused lower limb.
Fig 13(b) This shows the receding chin.
Note the position and shape of the ears.
Case 14: A female infant weighing 2020 gms and aged 1 hour.

The facial appearance was abnormal, but certainly not typical of renal non-function. The neck was short with distinct webbing on the left side. Epicanthic folds were present and there was a skin fold below the lower lip. The ears appeared normal. The hands, however, were quite striking, being large, spade-like and with redundant skin on the dorsum. The kidneys were entirely absent. Both ovaries were present but the uterus was extremely small.
Fig 14(a) Anterior view showing subepicanthic folds and fold below lower lip.
Nose not of typical shape.
Hands clumsy and spade-like.
Fig 14(b) Lateral view. Ears not abnormal.
Note short neck. Nose not characteristic of renal facies.
Case 15: A female infant weighing 1600 gms aged 5 hours, and showing the characteristic facies of renal non-function. The ears were soft, but not flattened. The hands were typical of renal non-function and there was clubbing of both feet. Both kidneys were extremely small and entirely cystic. Also present was a subdural haemorrhage associated with tentorial tears.
Fig 15(a) Anterior view. Prominent epicanthic folds at inner angle of eyes.
Hands characteristic.
Fig 15(b) Oblique to lateral view shows slightly receding chin. Ears relatively large and soft but not flattened. Shape of nose poorly demonstrated.
Case 16: A small male foetus weighing 910gms.

The head was definitely abnormal, being more elongated than usual, but this was probably the result of moulding. The ears were larger than usual, and rather low-set. The nose was not unlike that seen in renal non-function, but the bridge not so flattened.
Fig 16(a) **Anterior view.** Facial appearance distorted in this small foetus.

Hands broad and spade-like.

Bilateral talipes equino valgus.
Fig 16(b) Lateral view shows relatively large flattened ears. No diagnostic features recognizable in face but hands clumsy and spade-like.
Case 17: A male infant weighing 5 lbs. 13 ozs. and aged 36 hours.

The facial features were definitely abnormal and highly suggestive of a renal non-function, but not quite sufficiently pronounced to be diagnostic. The ears were not low-set, but flattened, soft and set at an angle. The chin was receding with epicanthic and chin folds present. The bridge of the nose was depressed and the general shape suggestive of that of renal non-function.

Autopsy revealed a complete urethral atresia with small kidneys, microscopy of which showed scarcely any normal remaining renal parenchyma. The kidneys possessed an abundance of primitive mesenchyme with dilatation of the tubules and with what appeared to be capsular spaces. The lungs were not noticed to be small.
Fig 17  Lateral view. Only this one photograph available. Chin receding. Facial skin folds present. Ears relatively large but not so flattened. Nose not well demonstrated.
Case 18: A male infant weighing 1480 gms and aged 23 minutes.

The infant showed all the features associated with renal non-function, the nose, ears, chin and facial skin folds all being in keeping with that picture. The hands were also typical and there was clubbing of both feet. The kidneys were entirely absent.
Fig 18(a) 

Lateral view. Note soft flattened ear; facial features and appearance of hands.
Fig 18(b) **Oblique view.** This shows the shape of the nose to better advantage.
Fig 18(c)  Anterior view. The hands are well shown. Note bilateral club foot deformity.
Case 19: A female infant weighing 3340 gms.

The head was smaller than usual and there was a large occipito-encephalocele. The nose was beak-shaped, the ears soft and flattened, but the epicanthic and chin folds were not apparent. The hands were relatively large and clumsy. Both kidneys were grossly enlarged, and microscopy confirmed a cystic dysplasia.
Fig 19(a) **Anterior view of body.** Head slightly oblique. Note grossly enlarged kidneys and encephalocele. Epicanthic folds not present but shape of nose characteristic. Chin receding.
Fig 19(b) Oblique view. This shows the shape of the nose and the flattened ears. Increased space between the eyes. No epicanthic folds.
Fig 19(c) Lateral view. The hands are clumsy and spade-like.
Case 20: A male infant weighing 2932 gms. and aged 1/2 hour.

Multiple deformities were present including a hare lip, cleft palate, supernumerary digits and an exomphalos. No external features suggestive of a renal non-function were present. Microscopy revealed a cystic dysplasia, but with a considerable amount of remaining normal renal parenchyma.
Fig 20. Facial features not diagnostic.
There are supernumerary digits but the hands are not characteristic of renal non-function.
Considerable amount of apparently normal renal parenchyma present in this case.
Case 21: A stillborn female foetus weighing 4 lbs. 12 ozs.

The abnormality, monomelia, consisted of one central lower limb stump, X-ray of which revealed a single femur and the upper part of a single tibia. The sex, determined only by autopsy, was female. The facial features and the hands were typical of a renal non-function.
Fig 21(a) **Anterior view.** Facies, particularly the nose, characteristic.

Hands show the usual broad clumsy appearance.
Fig 21(b) Lateral view. Ears not as flat as usual but profile characteristic of renal non-function.
Case 22: A small female foetus weighing 780 gms. The facies and hands were typical of a renal non-function, but in addition the foetus presented a spina bifida-hydrocephalus complex and clubbing of both feet. Both kidneys and ureters were entirely absent and the bladder vestigeal. Both ovaries were present, but the Fallopian tubes and uterus were absent, whilst the vagina ended blindly.
Fig 22(a) **Anterior view.** A small foetus with spina bifida and an Arnold-Chiari deformity. Renal facies with the characteristic hands.
Fig 22(b)  *Lateral view.* To show the ears and the nose. In none of the photographs does the shape of the nose appear as typical as it actually was at autopsy.
Fig 22(c) Oblique view. Absence of skin folds below lower lip. True shape of nose not well demonstrated. Hands clumsy and spade-like.
Case 23: A foetus weighing 980 gms.

It was a true syrenomelia, with a fusion of both lower limbs, this being confirmed radiologically. The foetus showed, although somewhat distorted, the facial features and large hands associated with renal non-function. Both kidneys were completely absent and only a vestigial bladder could be found.
Fig 23(a) Anterior view. Note the shape of the hands. Face rather distorted. Nose probably beak-shaped.
Fig 23(b) Posterior view. The ears are flattened, relatively large and soft. Note the hands.
Case 24: A male infant weighing 1420 gms. and aged 2 hours.

This infant showed all the features associated with renal non-function, the facial characteristics and the usual appearance of the hands being noted. There was clubbing of both feet. The kidneys and uterus were absent, but a small vestigial bladder was present. The testes were normal.
Fig 24(a) **Anterior view.** A good example of the renal facies. Note the pronounced appearance of the hands.
Fig 24(b) Lateral view. Showing position and shape of ear. Note bilateral deformity of feet.
Fig 24(c) Oblique view. Shape of nose well shown in this view. Typical renal facies and hands.
Case 25: A male infant weighing 4 lbs. and aged 33 hours.

The infant presented all the features relating to the face and hands usually associated with renal non-function. Both kidneys were entirely absent. An exchange transfusion for Rh. incompatibility was performed on the infant and this may have been associated with the relatively long period of survival for a case of renal agenesis.
Fig 25(a)  **Anterior view.** Epicanthic folds not prominent. Skin folds below lower lip. Hands large and spade-like. (Erb's palsy affecting left hand).
Fig 25(b) Oblique view. Ears large, flattened and low set. Nose beak-shaped. Epicanthic folds not prominent. Skin fold below lower lip. Hands large and spade-like.
Fig 25(c) Lateral view. This shows the ears and nose but not to such good advantage as the oblique view.
Case 26: A small female foetus weighing 4 lbs. 6 ozs.

It showed the typical renal facies with all the usual features present. In addition the hands were characteristic. There was a bilateral talipes equino-varus but this may have been associated with the spina bifida-hydrocephalus complex which was also present. The kidneys were entirely absent.
Fig 26. **Oblique view.** The shape of the nose is characteristic. Ears are large and soft but not flattened. Epicanthic folds present together with skin crease below lower lip. Hands large, clumsy and spade-like.
Case 27: A female infant, aged 6 months, in whom at autopsy the following conditions were found. (1) a terminal pneumonia, (2) cardiac enlargement associated with a patent ductus arteriosus, and (3) enlarged polycystic kidneys. No distinctive facies was present, nor was there any abnormality apparent in the hands or feet. This case illustrates the fact that the renal facies appears to be associated only with severe degrees of renal dysfunction.
Fig 27(a)  **Anterior view.** Female infant aged 6 months. Noted by clinicians to have peculiar facial appearance and also large clumsy hands. Autopsy photograph shows nothing to suggest renal facies and the hands are not significantly abnormal.
Fig 27(b) Lateral view. This shows the hands to better advantage but still nothing diagnostic of renal dysplasia.
Case 28: A small male infant weighing 993gms. and aged 1 hour.

The facial features were suggestive of renal non-function, but there was nothing in the hands to confirm this. The ears, nose and skin folds could all have been those of renal non-function. Both kidneys were present. This case illustrates the difficulty encountered in regard to the facies in a very small baby. In such cases the hands might be of considerable importance.
NO RENAL ABNORMALITY

Fig 28(a) **Lateral view.** Premature baby.
Facial features, particularly ears and nose, suggestive of renal agenesis.
Epicanthic folds and skin crease below lower lip. Hands perfectly normal.
Fig 28(b)  **Anterior view.** Facial features suggestive of renal agenesis. Hands normal and in view of this no diagnosis of renal agenesis was made.
Fig 28(c) Slightly oblique view. In this view facial features still suggestive of renal agenesis but hands are normal.
Case 29: A male foetus weighing 1800 gms.

The epicanthic and chin folds were present, but no other concomitants of the facies of renal non-function were present. The hands were normal. No abnormality was present in the kidneys.
Fig 29(a) **Anterior view.** Prominent epicanthic folds but normal nose and well formed ears. Hands are normal.
Fig 29(b) Prominent epicanthic folds but shape of nose normal. The ears are perfectly normal.
Case 30: A small male infant weighing 1140gms.

Death was attributable to pulmonary hyaline membrane. The ears were relatively low-set, large, soft and flattened, as in the facies associated with renal non-function. The nose and hands were not suggestive of a renal condition.
Fig 30. Oblique view. The ears are large, soft and flattened, but the nose is not of the characteristic shape. The hands are normal.
Case 31: A female infant weighing 7 lbs. and aged 30 minutes.

The ears were low, but not abnormally flat. The nose was to a slight extent beak-shaped but this was probably a false impression as a result of pressure. Epicanthic and chin folds were present. The hands were larger than might have been expected, but the fingers were long and the hands certainly not broad and clumsy.
Fig 31(a) Lateral view. Ears relatively large and flattened. Nose only slightly beak-shaped. Hands are relatively large but not squat and the fingers are long.
Fig 31(c) **Anterior view.** The anterior view of the face could be in keeping with a renal non-function, but the hands are against this diagnosis.
SUMMARY

A survey has been carried out on twenty-five cases involving absence of, or severe impairment of renal function.

The significance of the renal facies in relation to these cases has been discussed. As an aid towards diagnosis, a hitherto unreported accompanying abnormal appearance of the hands has been described, and illustrated.
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ANOXIA

The replacement of the older term asphyxia by the term anoxia signifies a more scientific approach to a problem, the assessment of which is today within the realms of physiological and biochemical research.

There is an abundant literature on the subject of anoxia but comparatively little of definite value to the pathologist confronted sometimes with completely negative post-mortem findings and beset by obstetricians eager for an answer. For this reason no purely histopathological study of cases can be of absolute value. Rather than review the details of hundreds of cases such as were encountered in the present series, and rather than become encumbered with data which only a mechanical device could possibly solve, it has been deemed wiser to reflect the personal impressions of a pathologist now somewhat more knowledgeable as regards the theoretical side of obstetrics.

Much of the stimulus for my interest in this subject is due to Dr. Agnes Macgregor whose Honeyman Gilchrist lecture on the Pathology of Perinatal and Neonatal Asphyxia elucidates the pathological aspects of this subject.

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The term "anoxia" means primarily a lack of
oxygen. The tolerance of the foetus to this lack is well known but on the question of preexisting anoxic susceptibility of the foetus little is as yet known.

The essential pathological findings in haemolytic disease is excessive extra-medullary erythropoiesis. Stimulation of extramedullary red cell formation is an accepted pathological sequela of many haemolytic or obliterative bone marrow diseases. The foetus, with its tissues perhaps not so fully differentiated will react to any such anoxic stimulus more readily and more severely than will the adult.

For this reason in achondroplasia, osteogenesis imperfecta, congenital bowing of the long bones, and other conditions involving bone marrow obliteration, excessive erythropoiesis is found in the liver and spleen - a simulation of haemolytic disease. No haemolytic agents have ever been demonstrated in these conditions although the excessive extramedullary haemopoiesis in achondroplasia produces a histological picture that has frequently been mistaken for haemolytic disease.

In a mature infant at birth erythropoiesis is usually scanty in the liver, and not recognizable
in the spleen, although readily demonstrable in
bones such as the ribs. There may, however, be
considerable variation in the amount of erythro-
poiesis in the liver of a mature infant. When
grossly excessive as it has been in a number of
large infants, the question of post-maturity has
arisen. No pathologist dare broach this subject
of postmaturity without trepidation; it requires
combined obstetrical, physiological and patho-
logical study. Work on the measurement of oxygen
saturation levels has added a further stimulus.
Not all "so-called" post-mature infants have
shown excessive extramedullary erythropoiesis but
it has been observed in a certain number of them
and no doubt can be entertained as to this excess
both in the liver and spleen. Excessive erythro-
poiesis has been found frequently in infants of
diabetic mothers but the reason for this remains
obscure.

The fundamental process, of anoxia resulting
in extramedullary erythropoiesis can be observed
later in the neonatal period. Some forms of
congenital heart disease or conditions affecting
pulmonary oxygen exchange, e.g. pneumonia, may
result in extramedullary erythropoiesis.
Maternal anoxaemia is a subject somewhat outwith the realms of paediatric pathology. Considerable attention is at present focussed on maternal anaemia and one stillbirth in this series may well have been associated with a severe anaemia of this nature. Other maternal factors relating to anoxaemia provide a subject sufficient in itself for lengthy discussion.

Maternal Accidental Haemorrhage

This has been by far the most common individual cause of stillbirth. It is a condition which after diagnosis from the autopsy findings in the foetus, the paediatric pathologist can refer without misgivings to the obstetrician for his further deliberation. The problem from the maternal aspect is essentially obstetrical.

The distinctive autopsy findings in the foetus are multiple subserous petechiae on the lungs, thymus and heart. A few small haemorrhages on the surfaces of the lungs do not warrant the diagnosis of anoxia secondary to accidental haemorrhage, concealed or revealed. The diagnosis of accidental haemorrhage can be given with entire confidence where the florid pathological picture is present. Deflation of the pathologist's ego has more often than not ensued when this diagnosis has already been made from the clinical history, examination of the placenta or the finding of
Heart and Lungs from a case in which there was accidental antepartum haemorrhage.
Note the numerous subpleural haemorrhages on the surfaces of both lungs.
massive retroplacental clot. Pathological confirmation of this diagnosis is, however, always valuable and occasional cases will always be encountered where post-mortem examination has confirmed what may have been only a clinical suspicion.

In most of the cases of accidental haemorrhage the baby is not mature and the diagnosis is easy. In mature babies where there has been accidental haemorrhage, the haemorrhages are less numerous although they tend to be larger, and the diagnosis cannot always be certain.

The subserous petechiae may be ascribed to the amount of blood entering the foetal circulation from the placenta as the foetal heart begins to fail. This contrasts sharply with cord obstruction where the foetal blood volume is limited to that already in the foetal circulation.

It cannot be too strongly emphasised that a diagnosis of accidental haemorrhage should be given by the pathologist only when the pathological picture is typical.

Placenta Praevia.

It has been suggested that the florid picture of multiple subserous petechiae in the foetus might better be regarded as being associated with
premature placental separation. This is in some ways correct but it implies that this picture could also be obtained in placenta praevia. I do not believe this to be so. In placenta praevia a few subserous petechiae can be found in the foetus but the picture is certainly not that associated with accidental haemorrhage. It may well be that the paucity of subserous petechiae in the foetus in placenta praevia is due to the fact that a certain amount of foetal exsanguination occurs in and thus reduces the foetal blood volume.

A considerable number of perinatal deaths, all of distinctive type, present to the pathologist and to the obstetrician a very real challenge. Most of them have been stillbirths. The maternal clinical history and the pathological findings in all these instances have been similar. Such perinatal deaths are particularly distressing to the parents and also to the obstetrician. They are completely unexpected, occurring almost at the last minute, when labour has been proceeding under perfectly normal circumstances. More distressing indeed is it to find that the baby presents no congenital abnormality. Charles Lamb epitomises in words no medical terms could ever express.
"Shall we say that nature blind
Checked her hand and changed her mind,
Just when she had exactly wrought
A finished pattern without fault".

Over the past years one has been prompted as these cases were encountered to enquire with greater detail into the maternal history. This has revealed that the foetal heart not infrequently disappeared only in the terminal stages of labour, probably within 5 to 10 minutes of delivery, without any recognised signs of foetal distress.

Post-mortem examination invariably indicated a foetal anoxia of relatively sudden onset. All the viscera were congested, subserous petechiae were usually absent or minute and sparse. There was no evidence of passage of meconium: the colon was well filled and the umbilical cord not stained.

The important aspect of the maternal history has been the exact time of disappearance of the foetal heart. Whether or not the foetal heart can be heard in the final stage of labour is an obstetrical question. Senior obstetricians have informed me that this can be done with the foetal stethoscope placed low on the abdomen. Admittedly in a number of instances enquiries have
revealed that delivery occurred at a very busy period in the labour ward, and sometimes also considerable doubt has been raised as to the exact time at which the foetal heart was last recorded.

The rechecking of maternity case records in these known cases has proved of little value and there is not the slightest doubt that clinico-pathological assessment has to be made at, or immediately after, post-mortem examination of the foetus. At that time facts may be clearly remembered, which cannot subsequently be found in the obstetrical notes. Nevertheless, this type of anoxic death is still encountered in the best obstetrical practice, where the clinical findings are beyond dispute. On the strength of the clinical history and autopsy findings in the baby, one has come to the conclusion that the most likely cause of the anoxia is an interference with the circulation through the cord. When this opinion has been presented to the obstetrician, it has on the whole been accepted. In the majority of these perinatal deaths the presentation of the foetus has been vertex and the babies have all been in the upper weight range.

The need is apparent for a critical survey of this entire problem, with coordination of the detailed clinical and pathological findings.
ELECTRONIC RECORDING OF THE FOETAL HEART

The results of this experience in perinatal pathology have shown without the slightest doubt that anoxia is the greatest and most important factor in relation to perinatal mortality. Progress has undoubtedly been made as a result of advances in obstetrics, improved concepts of the physiology of the newborn and better methods of resuscitation. It has become apparent that further reduction of perinatal mortality due to anoxia is unlikely to prove successful without advances in the present day knowledge of the mechanisms and the early manifestations of foetal distress. Some cases of anoxia are obviously due to the hazards of difficult labour. Others are secondary to prolapse of the umbilical cord, but in fact the number of proved instances of this has been shown to be remarkably small. Frequently a diagnosis of prolapsed cord has been made only as the result of integration of the pathological findings in the foetus and the maternal obstetrical history. It is well known that there may at times be a comparatively brief interval between compression of the umbilical cord and death of the foetus. This is an accepted hazard of breech, shoulder and other abnormal presentations, but as has been
shown it is not improbable that this complication occurs in normal vertex presentations, when any such compression of the cord is surmised to be occult.

In other instances some capricious movement of the foetus may render the umbilical cord so obstructed that foetal death ensues. It is true that excessive movement of the foetus, funic souffle and meconium-staining of the liquor may indicate foetal distress, but unfortunately these signs are either absent or observed too late for the saving of foetal life. Foetal distress can sometimes, however, be diagnosed by noting alteration in the rate of the heart - excessive rapidity or slowness being significant - or it may be noted that the volume of sound has diminished and the rhythm has become irregular. Such criteria of foetal distress entail constant supervision of labour and do not allow for the inherent fallibility of the human ear. It has in fact been noted during the present series of autopsies that the foetal heart has been heard by extremely competent attendants when in fact autopsy has shown beyond any manner of doubt that no such foetal heart sounds could obviously have
been present. If perinatal mortality in regard to anoxia is to be reduced then further evidence on foetal distress is one of the factors that will prove a necessity.

Human foetal electrocardiograph was first recorded in 1906, but only eight papers on this subject have been reported between 1903 and 1938 (Davis and Mears, 1954). Tiny wave forms were obtained by Steffan and Strassman (1933). Bell (1938) was able to record the foetal electrocardiograph in only 33% of cases, but greater success was obtained in 1939 by Matthews who introduced a balanced-input amplifier.

Lindsay (1942) used an electroencephalograph to record the foetal E.C.G., whilst a number of others, Ward and Kennedy, Bernstein and Mann, Geiger and Munro, all claimed to have recorded at that time the foetal heart with an electrocardiograph.

The value of stethography as a supplement to electrocardiography has been stressed by Sprague (1942 and 1954), and Palmrich (1951) suggests that it may be of greater clinical value. In November 1952, A.L. Gunn and M.C. Wood, using
a machine incorporating about twenty-seven thermionic valves demonstrated a recording of the foetal heart before the Royal Society of Medicine in London. From the practical point of view this machine is of relatively little value.

The original concept was the construction of an electrocardiographic type of amplifier in order to indicate, by using a cathode ray tube directly, the foetal heart action. An amplifier and oscilloscope were accordingly constructed and initial experiments undertaken. Results proved to be very disappointing, however, and expert examination of the amplifier showed it to be hopelessly inadequate for the required purpose.

The now apparent disadvantages of this are:-

(1) Great expense of suitable amplifier and apparatus;
(2) The susceptibility of the very sensitive equipment to external electrical interference - this necessitates careful choice of recording location, and precludes "on-the-spot" examination in
ward or theatre;

(3) Complication of control and critical positioning of electrodes render the equipment unsuitable for use by relatively unskilled staff, and hence defeats the whole object of the required machine which is the prolonged observation, in the ward and during labour, of the foetal heart action, with immediate indication of the onset of any distress.

This project was then abandoned in favour of a phonocardiographic type of instrument. Initial work in the construction of a phonocardiographic instrument was then begun. A commercial audio-frequency amplifier was purchased, and, with a new oscilloscope, of simple type but with a suitably modified time-base, experiments were recommenced.

It was found that the primary problem was now the design of a suitable microphone, or microphone housing. All sorts of extraneous noises intruded, from maternal intestinal noises to slamming doors.

A pre-amplifier is now under construction incorporating filter circuits, which, with the
finalised microphone design, it is hoped might reduce interference to a satisfactory level. Future developments will include the provision of electronic warning devices, to function if the received signal varies, either in amplitude or repetition rate, outside predetermined limits. Consideration is being given to the use of an "air-sonic" electronic stethoscope with special bandpass filter for low frequencies. It seems amazing that the foetal heart, which can best be heard by the simple foetal stethoscope has so far defied practical recording, even with the technical advances of modern electronics. Part of the answer may lie in the exceedingly low frequency of the foetal heart sounds. (Certainly below 40 cs/sec.) It may also be that some perhaps incredibly simple fundamental knowledge is lacking.

Many people have been and are being consulted, and it is only to be hoped that a combination of those to whom the problem appears most acute, obstetrician and pathologist, along with the "brains" of the electronic world, might succeed where all else has failed.

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subject of the recording of the foetal heart is shown in the list of references.
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process. These authors also discuss a case
FOETAL EXSANGUINATION

The purpose of this review is to focus attention on a subject which shows a tendency to become of increasing importance to obstetrician and paediatrician alike. Foetal exsanguination presents many problems; recognition both from the clinical and pathological aspects, particularly the former; explanation of the mode of occurrence and finally proof of this mode in the more obscure cases.

It may well be that in regard to perinatal mortality, the significance of exsanguination has not been fully appreciated. Potter (1952) and Morrison (1952) make no mention of this condition. The cases under review show that whereas some cases of foetal blood loss can be explained, in others no demonstrable cause can be found. Under the title of "Post-haemorrhagic shock in the newborn" Wickster and Christian (1954) have reviewed the causes of foetal blood loss, the bulk of these finding an explanation in placenta praevia, abruptio placentae, Caesarian section, incision into the placenta, or rupture of the umbilical vessels. These authors also demonstrate a case
of occult foetal blood loss, an entity first described by Wiener in 1948. Further work on this subject has been carried out by Chown (1955) who has provided convincing proof of the occurrence of occult foetal blood loss.

The present review deals with twenty cases of exsanguination out of a series of 1,947 consecutive perinatal autopsies. In eight out of twenty cases a possible source of bleeding was revealed, but in the remainder this source proved occult.

CASE 1: The mother had slight bleeding at the 21st week with further severe bleeding at the 32nd week requiring blood transfusion. Blood loss continued and she went into labour. Caesarian section was performed on account of placenta praevia. The infant, birth weight 3\(\frac{1}{2}\) lbs., survived for 11 hours. The most striking feature at autopsy was the extreme pallor of the skin and of the viscera, with relative bloodlessness of the tissues, this last finding being confirmed microscopically. The lungs were moderately aerated, but sections showed the presence of slight hyaline membrane formation.
CASE 2: The mother, at the 37th week, had an ante partum haemorrhage diagnosed placenta praevia. Caesarian section was performed and during extraction of the baby, the cord was nicked, some blood loss being sustained before the cord could be clamped.

The baby was very limp at birth and was stated to show asphyxia pallida. Oxygen and coramine were administered, but no blood transfusion was given. Twenty-four hours later the baby was noted to be cold, with oedema of face, neck and trunk. The infant died aged forty-five hours.

At autopsy, the infant weighing 3280 gms. showed some pallor of the skin and of the viscera. There was an intrapulmonary haemorrhage, but this was of patchy distribution and of relatively minor extent.

CASE 3: The mother was admitted in labour late in the first stage. The total duration of labour was 2½ hours, the foetal heart disappearing during the short second stage. The baby at birth was extremely pale and limp, with no pulsation in the cord. The baby's heart beat, however, was detected and coramine and lobeline were given into the cord.
The baby gave occasional gasps but survived only a few minutes.

Autopsy revealed striking pallor of the skin, with relative bloodlessness of the thoracic and abdominal organs. The lungs were moderately well aerated. Apart from signs of foetal exsanguination, no other pathological condition was found. The placenta was examined macroscopically and microscopically, but no abnormality could be found.

CASE 4: The mother was admitted as an emergency with antepartum haemorrhage. The foetal heart disappeared shortly after admission, and after artificial rupture of the membranes she was delivered of a stillborn foetus. A second degree placenta praevia was present, with a considerable amount of clot retained behind the separated portion of the placenta.

Autopsy was carried out on a female foetus weighing 5 lbs. 13 ozs. The epidermis showed commencing desquamation. Pallor and bloodlessness of the viscera were most striking, but no other pathological condition was found.
CASE 5: Predelivery a tense bag of membranes was noted. This ruptured, producing heavily blood-stained liquor. A thinned out lip of cervix was pushed back over the head of the baby, delivery following fairly rapidly. The total duration of labour was three hours, twenty minutes. The baby was extremely pale at birth, cried feebly and 40 cc. of Rh. neg. blood was given into the anterior fontanelle. The infant’s colour showed little improvement, and death followed nine hours after delivery.

Post-mortem examination revealed severe pallor of the skin, with pallor and bloodlessness of the brain and of the thoracic and abdominal organs. The lungs, though not fully aerated, showed a considerable degree of expansion, more so in the upper lobes. In the placenta there was a villamentous insertion of the cord, with a tear in one of the vessels as it ran through the chorionic membrane.

CASE 6: The mother, aged 26, para 1, had a previous delivery by Caesarian section for failed trial labour associated with a contracted pelvis. The present delivery was spontaneous, and a vertex presentation without forceps. The total duration
of labour was ten hours. The foetal heart was last heard twenty minutes before delivery, but not listened to thereafter. The baby showed asphyxia pallida at birth and gasped twice but the heart beat disappeared five minutes after birth. No ante-, intra-, or post-partum haemorrhage was noted. The placenta was examined by the obstetricians, but no abnormality was found.

Autopsy was carried out on a female infant weighing 7 lbs. 12 ozs. and showing pronounced skin pallor. The brain and the thoracic and abdominal organs were all bloodless. There was pronounced pallor of the liver and kidneys.

CASE 7: A primipara aged 24, had slight pre-eclamptic toxaemia and a degree of contracted pelvis. Artificial rupture of the membranes was performed and blood-stained liquor amnii obtained. The foetal heart later became slow and irregular, after which Caesarian section was carried out. The baby weighed 3300 gms., was limp and pallid at birth, and failed to respond to stimulants. Blood-stained liquor was aspirated from the baby's nose. The obstetricians reported a lateral placenta praevia, with a succenturiate lobe.
At autopsy the presence of generalised pallor of the skin was confirmed. The other findings were those of a foetal blood loss. No respiratory obstruction was found, nor was there any meconium in the lungs.

CASE 8: This baby, weighing 7 lbs. 2 ozs. was delivered in district with both doctor and midwife present. It was a normal spontaneous vertex delivery, in which there was no antepartum haemorrhage and no abnormal post-partum loss. The placenta was examined by the doctor, but no abnormality was found.

The baby was pale at birth and this colour did not improve. Following admission to hospital, oxygen was given, but the baby died aged nine hours.

Post-mortem examination revealed without any dubiety a severe exsanguination. The lungs in this case were poorly expanded.

CASE 9: The mother, para 0, had a normal pregnancy and was perfectly well until just before admission to hospital when the foetal heart sounds disappeared three days before delivery. There was no antepartum haemorrhage and no excess blood loss during
or after delivery. The placenta was examined by the obstetrician and found to be normal.

The foetus, weighing 3240 gms., was found at autopsy to be slightly macerated, but even on external examination it showed pronounced pallor. On dissection all the tissues were pale and there was very much less blood than usual throughout the body. Microscopy confirmed the relative bloodlessness of the tissues.

CASE 10: The mother was aged 32, para 1. Hydramnios was noted. After artificial rupture of the membranes was performed (10 ozs. of liquor obtained), she went into labour within twenty-four hours, being delivered of twin male infants, each weighing 6 lbs. 5 ozs. The total duration of labour was five hours, and there was no post-partum haemorrhage. Examination of the placenta by the obstetrician showed no abnormality.

The first twin, weighing 6 lbs. 5 ozs. was noticed at birth to be very pale and despite recussitation, including stimulants and oxygen, lived for only six hours.

Post-mortem examination showed an exceedingly pale baby, in which the features were those of a
foetal exsanguination. The lungs were comparatively well aerated. The second twin died two weeks later as a result of pneumonia.

CASE 11: The mother, aged 24, para 2, was admitted at thirty-four weeks, with a breech presentation and antepartum haemorrhage. She delivered herself spontaneously of a premature female infant weighing 4 lbs. 4 ozs. The obstetric notes contain a reference to the placenta, stating that the cord snapped off from the placental insertion. No mention is made at what stage this happened. The baby at birth was exceedingly pale and limp. It was given stimulants and oxygen, cried fairly well, but remained pale and died aged thirteen hours.

At autopsy the baby was exsanguinated, with generalised pallor of the viscera. The lungs were comparatively well aerated.

CASE 12: This was a normal fullterm spontaneous delivery. The baby, limp at birth, responded to recussitation after ten minutes. Thirty minutes later the baby was found to be pale and to have lost about 100 ccs. of blood from the cord. The ligature was found to be loose. The baby survived for four hours.
At autopsy the features were consistent with foetal blood loss. The lungs were comparatively well aerated.

CASE 13: Mother aged 20, para 1. Twin pregnancy. Following an assisted breech delivery, the first twin, a male weighing 5 lbs. 7 ozs., survived. The second twin, a male weighing 6 lbs. 6 ozs., an assisted breech delivery, was stillborn. On examination, the obstetrician noted that the second placenta was lying posteriorly in the lower uterine segment with a battledore insertion of the cord at the lower edge.

Autopsy was performed on the baby, which showed pronounced skin pallor. Internal examination revealed evidence of foetal exsanguination with pallor of the viscera and relative bloodlessness. Very slight subdural haemorrhage was present, but the tentorium and falx were intact.

CASE 14: Mother aged 30, para 2. At thirty-eight weeks gestation she had a fairly severe antepartum haemorrhage, following which the foetal heart was not heard. Immediate Caesarian section was performed, but a stillborn foetus obtained. There was a posterior grade 2 placenta praevia with
a villamentous insertion of the cord.

At autopsy the foetus, a female weighing 8 lbs. 2½ ozs., showed all the features of exsanguination, including cutaneous and visceral pallor. The lungs were unaerated.

CASE 15: Mother aged 24. Cardiac grade 2. Twin pregnancy. The first twin, an assisted breech delivery, survived. The second twin, delivered by breech extraction, was stillborn. The foetus, weighing 2335 gms., showed pallor of the skin and absence of lividity.

Post-mortem examination showed evidence of exsanguination. There were numerous minute petechiae on the pleural surfaces, but the underlying lung parenchyma was pale and bloodless. The obstetricians found no pathological condition in the placenta to account for this blood loss.

CASE 16: The mother aged 32, para 0, had pre-eclamptic toxaemia, the highest blood pressure recorded being 170/180. Slight oedema of the ankles was present and the urine contained a trace of albumen. Mid cavity forceps (R.O.A.) were applied. Intra-uterine death was reported as occurring suddenly before the commencement of the
second stage.

At autopsy the foetus, a male weighing 3160 gms., showed early maceration. The most striking feature was the pronounced pallor of the skin and viscera, there being no doubt about the diagnosis of foetal exsanguination. The placenta, weighing 380 gms., was examined by both obstetrician and pathologist, but no source of bleeding was found.

CASE 17: The mother aged 26, para 0, showed a raised blood pressure throughout pregnancy, the last ante-natal reading being 154/110. External accidental haemorrhage occurred with the subsequent birth of a stillborn female foetus, weighing 2800 gms.

Autopsy revealed generalised pallor of the skin and of the viscera, lack of congestion being confirmed microscopically. There was evidence of foetal anoxia, the stump of the umbilical cord was stained green with meconium, and the lungs microscopically contained a considerable quantity of amniotic debris and meconium. The placenta was examined by the obstetrician who noted no abnormality in the umbilical vessels.
CASE 18: The mother aged 30, para 2, had severe ante-partum haemorrhage associated with a placenta praevia.

The baby, after delivery by Caesarian section, remained pale and limp, respiration commencing when coramine was given into the cord. Six hours after delivery the haemoglobin was 75% Sahli. The direct Coomb's test was negative. The child remained pale and limp, death taking place at the age of thirty-five hours.

At autopsy the infant weighed 2840 gms.

The skin and viscera were extremely pale. Both lungs were pale and moderately aerated. Microscopically they showed neither amniotic debris nor meconium.

CASE 19: The mother aged 21, para 2, was delivered of a stillborn male child weighing 3140 gms. It was a normal spontaneous delivery.

At autopsy the foetus, weighing 3140 gms., showed faint meconium staining of the umbilical cord. The skin was unusually pale and there was a complete absence of lividity. The upper respiratory passages all contained a considerable
quantity of blood. Microscopically the bronchi contained fresh blood and masses of cornified squames. The lungs showed groups of alveoli filled with blood and yet there was a generalised absence of congestion. The viscera were all pale and bloodless. The inference was that there had been foetal exsanguination with inhalation of blood, presumably derived from rupture of an umbilical vessel into the amniotic fluid. The placenta was not available for pathological examination. No abnormality was noted by the obstetrician as regards the umbilical vessels.

CASE 20: A twin pregnancy, the mother aged 22, para 1. She weighed 19 stones and had a mild pre-eclamptic toxaemia. The first twin survived but the second twin, in spite of oxygen and Synkavit, lived only three hours.

At autopsy, the infant, a female weighing 2670 gms., showed striking pallor of the skin and mucous membranes, with relative bloodlessness and pallor of the brain and viscera.

The placentae, weighing 860 gms., were joined over a distance of 5-6 cms. Each had a separate amniotic and chorionic sac, the two chorions
meeting in the centre at the ridge joining the two placentae. The cords both had a villamentous insertion. Viewed from the maternal side, the placenta belonging to the dead twin showed pronounced pallor in comparison with the other. In the placenta of the dead twin the cord was inserted into the membranes about 4-5 cms. from the margin of the placenta, and on the inner aspect a bleeding umbilical vessel was found.

The presence of this bleeding vessel, the striking pallor in one half of the placenta, and the obvious blood loss in the infant, all showed that traumatic rupture of the umbilical vessel had resulted in exsanguination of the infant.

**DISCUSSION**

The macroscopical picture in severe foetal exsanguination should not present any difficulty to one conversant with perinatal pathology. The skin is pale and there is generally an absence of lividity. Bloodlessness can be noted in the brain and particularly on removal of the thoracic and abdominal organs. The lungs and heart are pale and there is complete absence of congestion in the liver. The whole picture contrasts sharply
with the usual appearance in an asphyxiated baby. Microscopy is an additional guide in that absence of congestion can be noted in the liver, adrenals, and to a lesser extent in the lungs. Nevertheless, constant awareness of this condition is required and the pathologist must be prepared to adhere to such a diagnosis even in the absence of negative obstetrical findings. Foetal exsanguination can be seen frequently in babies presenting the spina bifida-hydrocephalus complex where perforation of the skull has been performed for obstetrical reasons. An appropriate standard of control can thus be obtained.

It is evident from the accompanying table that in many of the cases under review "asphyxia pallida" was noted at birth.

It is not proposed to enquire into the subject of asphyxia pallida, but attention must be drawn to the confusion in diagnosis presented by exsanguination.

Six of the twenty cases were directly associated with placenta praevia; five were directly attributable to bleeding from the cord or foetal vessels; one was of doubtful origin, but associated with an antepartum haemorrhage;
one occurred in conjunction with a "revealed" accidental haemorrhage; and in the remaining seven cases no direct source of foetal bleeding was found. In two cases Caesarian section was performed. Three of the cases were in twin pregnancies. In three instances the foetus was macerated.

Excluding case no. 12, because the haemorrhage from the cord was postnatal, two of the infants survived over 24 hours, seven survived for periods of three - eleven hours, and two lived only a matter of minutes. The remainder (eight) were stillborn, three of them macerated. In none of the cases was there any question of haemolytic disease.

Caesarian section was performed in four of the cases, and in all, antepartum haemorrhage had been noted. In one of these four cases, nicking of the cord occurred during the operation but in the other three, clinical evidence afforded no reason to suppose that foetal blood loss was associated with the Caesarian section. The supposition remains therefore that foetal blood loss took place along with and was masked by the maternal loss. When the bleeding source lies in the umbilical vessels, heavily bloodstained liquor might be encountered, as in case no. 5. This
bloodstained liquor could then be inhaled by the foetus, now anoxic, and consequently at autopsy found in the upper respiratory passages and the lungs of the foetus, as in case no.19.

The group comprising those cases without any recognisable source of foetal blood loss present the greatest problem. Although the number of cases is too small to be of significance it is of interest that all the babies with one exception in the mature group, where associated with twin pregnancies the causation in some instances remains a matter of conjecture. Blood loss could conceivably take place across the junction of the placentae. Unfortunately few placentae were available for pathological examination in the present series. That considerable blood loss may occur from the foetal into the maternal circulation has been already proved by Choron. Proof of this lies in (1) the estimation of the percentage of foetal haemoglobin in the maternal circulation, and (2) by detecting sensitised foetal blood corpuscles in the maternal circulation. This latter method will not always be available, as it depends primarily on the absence of AB incompatibility and the presence of Rh incompatibility, when the sensitized foetal cells in the maternal circulation are
still detectable. Chown indeed suggests that where the mother is already sensitized and bleeding occurs from foetal to maternal circulation, a transfusion reaction might ensue in the mother.

A limited amount of information has been gained from this small inadequate series of cases.

(1) Foetal exsanguination, as regards the existence of which there can be no doubt, occurs more frequently than is imagined.

(2) The blood loss in the majority of the present cases was associated with the following conditions - placenta praevia, rupture of the umbilical vessels, and accidental haemorrhage.

(3) Six cases of so called "occult" placental haemorrhage have been described. No proof of the mode of occurrence has been afforded. With awareness of the obstetricians of this condition detailed investigation can be carried out with hopes of elucidation in what is at present a difficult obstetric, paediatric and pathological problem.
<table>
<thead>
<tr>
<th>CASE NO.</th>
<th>AGE (gms.)</th>
<th>WEIGHT</th>
<th>POSSIBLE SOURCE OF BLEEDING</th>
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<tr>
<td>1</td>
<td>11 hours</td>
<td>1587</td>
<td>Placenta praevia.</td>
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<td>2</td>
<td>45 hours</td>
<td>3280</td>
<td>Nicking of cord at Caesarian section.</td>
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<td>3</td>
<td>Few mins.</td>
<td>3060</td>
<td>Not ascertained.</td>
</tr>
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<td>4</td>
<td>SB Macerated</td>
<td>2630</td>
<td>Placenta praevia.</td>
</tr>
<tr>
<td>5</td>
<td>9 hours</td>
<td>3175</td>
<td>Rupture of umbilical vessel.</td>
</tr>
<tr>
<td>6</td>
<td>5 mins.</td>
<td>3140</td>
<td>Not ascertained.</td>
</tr>
<tr>
<td>7</td>
<td>SB</td>
<td>3300</td>
<td>Placenta praevia. Succenturiate lobe of placenta. Caesarian section.</td>
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<tr>
<td>8</td>
<td>9 hours</td>
<td>3220</td>
<td>Not ascertained.</td>
</tr>
<tr>
<td>9</td>
<td>SB Macerated</td>
<td>3240</td>
<td>Not ascertained.</td>
</tr>
<tr>
<td>10</td>
<td>6 hours</td>
<td>2875</td>
<td>Not ascertained (twin).</td>
</tr>
<tr>
<td>11</td>
<td>13 hours</td>
<td>2860</td>
<td>? Antepartum haemorrhage.</td>
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<tr>
<td>12</td>
<td>4 hours</td>
<td>3447</td>
<td>Haemorrhage from cord after birth.</td>
</tr>
<tr>
<td>13</td>
<td>SB</td>
<td>2857</td>
<td>Placenta posterior, low lying. (twin)</td>
</tr>
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</table>

METHOD OF DELIVERY:

- Caesarian section.
- Spontaneous vertex.
- Artificial rupture of membranes.
- Spontaneous vertex.
- "
- Artificial rupture of membranes. Vertex.
- Spontaneous vertex.
- "
- "
- Assisted breech.
<table>
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<th>CASE NO.</th>
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<th>WEIGHT (gms.)</th>
<th>POSSIBLE SOURCE OF BLEEDING</th>
<th>METHOD OF DELIVERY</th>
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<tr>
<td>14</td>
<td>SB</td>
<td>3700</td>
<td>Placenta praevia.</td>
<td>Caesarian section.</td>
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<td>15</td>
<td>SB</td>
<td>2335</td>
<td>Not ascertained (twin).</td>
<td>Breech extraction.</td>
</tr>
<tr>
<td>16</td>
<td>SB</td>
<td>3160</td>
<td>Not ascertained.</td>
<td>Mid cavity forceps.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Right occipito-anterior.</td>
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<tr>
<td>17</td>
<td>SB</td>
<td>2800</td>
<td>&quot;Revealed&quot; accidental haemorrhage.</td>
<td>Spontaneous vertex.</td>
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<tr>
<td>18</td>
<td>35 hours</td>
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<td>Placenta praevia.</td>
<td>Caesarian section.</td>
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<tr>
<td>19</td>
<td>SB</td>
<td>3140</td>
<td>Rupture of umbilical vessel.</td>
<td>Spontaneous vertex.</td>
</tr>
<tr>
<td>20</td>
<td>3 hours</td>
<td>2670</td>
<td>Rupture of umbilical vessel (twin).</td>
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REFERENCES

CHOWN, B. Lancet 1, 1213. 1954.
CHOWN, B. Am. J. Obst. & Gyn. 70. 1298. 1955.
<table>
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<tr>
<th>Summary of underlying causes</th>
<th>No. of Cases</th>
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<td>Administration of endotracheal oxygen</td>
<td>5</td>
</tr>
<tr>
<td>Inhalation of meconium</td>
<td>12</td>
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</tbody>
</table>

PNEUMOTHORAX AND INTERSTITIAL EMPHYSEMA
INTERSTITIAL EMPHYSEMA: PNEUMOTHORAX

Summary of underlying causes

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of Cases</th>
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<tr>
<td>Administration of endotracheal oxygen</td>
<td>6</td>
</tr>
<tr>
<td>Mouth to mouth insufflation</td>
<td>1</td>
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<tr>
<td>Renal cystic dysplasia</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary hyaline membrane</td>
<td>4</td>
</tr>
<tr>
<td>Inhalation of meconium</td>
<td>12</td>
</tr>
</tbody>
</table>

The literature on this subject, especially from a pathological point of view, it was only recently that the work of MacKin and Weiss (1948) has done much in bringing to light the inter-relationship of interstitial emphysema and pneumothorax. Various authors, Davis & Stevens (1930) and Solis, Cohen & Buck (1933) demonstrated radiologically an incidence of pneumothorax of 1% in the newborn; Anderson (1930) accepts an
PULMONARY INTERSTITIAL EMPHYSEMA AND PNEUMOTHORAX

Interstitial emphysema and pneumothorax in the newborn are to the pathologist not merely problems in recognition. They invoke the field of pathology as a study of disease process. It might be that in the alteration of the haemodynamics of the pulmonary and cardiac circulation which ensues there lies the answer to a number of pathologically unexplained deaths in the neonatal period. It might also be that the presence of interstitial emphysematous bullae in the developing lung parenchyma produces changes, not merely of moment, but changes persisting till later childhood or even till adult life. Such are the thoughts which must arouse pathological interest in a condition perhaps much under-rated and too often neglected.

The literature on this subject, especially from a pathological point of view is none too plentiful, but the work of Macklin and Macklin (1944) has done much in bringing to light the inter-relationship of interstitial emphysema and pneumothorax. Various authors, Davis & Stevens (1930) and Solis, Cohen & Bruck (1934) demonstrated radiologically an incidence of pneumothorax of 1-2% in the newborn; Anderson (1950) accepts an
incidence of 1-2% pneumothorax in newborn infants. Morrison (1952) stresses the fact that pneumothorax and resultant pulmonary collapse are not always recognised. Potter (1952) states that "in all but rare cases of interstitial emphysema and pneumothorax in the newborn, a history of artificial resuscitation can be obtained."

It was hoped, therefore, that elucidation on some of these aspects of this condition might be obtained by consideration of the cases encountered in the course of the present series of autopsies. Cases of pneumothorax have been described over the years, but the literature is singularly devoid of a review of the pathology of a comparable number of cases.

Many factors may influence the development of pneumothorax in the newborn.

Congenital anomalies of the lung are undoubtedly responsible in a number of cases. The association between the pulmonary hypoplasia of renal nonfunction and the development of interstitial emphysema with resultant pneumothorax, is all too evident in the present series of cases. In two of the five cases of pneumothorax described
by Frane, Gordon & Humphries (1952) severe renal dysplasia was found. With the outcome in renal non-function inevitable interstitial emphysema and pneumothorax in this condition are but of academic interest. Of the resuscitative measures mouth to mouth breathing, as has been stressed by Emmett (1930), is especially dangerous. One case in this series was directly attributable to this form of resuscitation. Great care must obviously be exercised in attributing death to pneumothorax when resuscitative measures, perhaps of excessive exuberance, have been applied to a child already moribund. Whether the child be moribund or not it is obvious that mouth to mouth breathing is exceedingly dangerous and can at the least provide a coup de grâce: the dangers of endotracheal insufflation especially in unskilled hands are well recognised. Although not strictly comparable, several skilled operators at some of the hospitals in this region, have been surprised at the degree of emphysema that can be produced in dead infants by the endotracheal administration of oxygen. In six of the present cases endotracheal oxygen was used.

That emphysema and pneumothorax can occur without artificial mechanical resuscitation is beyond question, and there is no reason to doubt
the corroborated statements previously obtained in relation to the present cases. The use of coramine or lobeline as stimulants appears to be almost universal. Whereas direct mechanical resuscitation can be excluded, it is impossible to ascertain the consequences, if any, of respiratory stimulation in the presence of intrinsic obstruction in the bronchial tree. It is of considerable interest that bronchial obstruction might be caused not only by mucus, vernix caseosa, meconium or inflammatory exudate, but also by "hyaline membrane". The recordings of foetal respiratory movements by Donald (1955) revealed the strength of these respiratory efforts, especially in association with hyaline membrane; thus the development of bullous interstitial emphysema is not unexpected. It is indeed surprising that this condition is not encountered much more frequently.

In the assessment of the significance of pneumothorax one cannot exclude pathological findings elsewhere in the body. Three of the present series of cases also had subdural haemorrhage, in two of them slight and in one of considerable amount. It is impossible, in the light of present knowledge of the significance of
slight subdural haemorrhage, to ascribe death to one or other of the causes in two of these cases. In one of the infants, a premature baby, an intraventricular cerebral haemorrhage was found and death was most probably attributable to this.

The recognition of pneumothorax and the associated interstitial emphysema are indeed a problem to the pathologist, especially when it is so often unsuspected during life. Pneumothorax under tension might well be suspected on opening the abdomen, the liver is often pushed downwards and there is pronounced flattening of the diaphragm. Opening of the thorax presents yet another problem. It is plainly impossible to open the thorax routinely under water. It is all too easy to miss pneumothorax, especially if not under considerable tension, by opening the thorax in the usual way with an incision lateral to each side of the sternum. An incision along one side only of the sternum with reflection of this bone upwards and laterally is the only way of successfully demonstrating pneumothorax. The disadvantage is, however, that pneumothorax is inevitably not proven on the side of the incision. Despite much thought no other method has yet been devised for the detection of pneumothorax in routine autopsy work.
Evidence of pneumothorax is, however, often provided by the appearance of the affected lung which is found to be lying far back in the pleural cavity. The lung may be crepitant and yet appear collapsed. Further supporting evidence may be found in the presence of interstitial bullous emphysema. The question arises, however, as to what may happen to the bullae should they not be pronounced. It is conceivable, especially where there is air under pressure in the pleural space, that the lungs are compressed, and widening of the interlobular septa remain the only evidence. This has been observed in this series of cases, and subsequently confirmed microscopically.

Relationship of Interstitial Emphysema to Lung Cysts:

Congenital cysts in the lung are undoubtedly encountered, but such cysts are exceedingly rare. None was encountered in the present series of autopsies.

Conway (1951) in a review of lung cysts in childhood concluded that most of these cysts were the result of bronchial inflammation and obstruction. Considerable attention has lately been focussed on the so-called Pneumatocele, a
cavity found in the lungs of children. The conception that pneumatoceles arise in relation to these cavities or cysts is based on certain particular features; association with pneumonia, variability as regards size and number, rapid development, fluctuation in size and tendency to early and complete resolution. In this respect emphysema is a well recognised concomitant of pneumonia in childhood and this was demonstrated in 1929 by McNeil, Macgregor and Alexander.

That many pneumatoceles are not related to emphysematous alveoli but are in fact interstitial pockets of air has been previously suggested by Conway (1951). This is a view which in light of present experience tends to be supported by the finding of microscopical evidence of interstitial emphysema accompanying pneumonia in the neonatal period.

The following case is not included in the present series of deaths in the neonatal period. It is, however, of outstanding interest and importance in relation to this question of "pneumatocele" and interstitial emphysema, and discussion of this question would certainly not be complete without its inclusion.
CASE REPORT

The child, 5 weeks premature, was delivered by Caesarian section. Resuscitation was difficult. On the fifth day he had a severe cyanotic attack and was placed in an oxygen tent where he remained for 3 weeks, having several cyanotic attacks during this period. He was discharged home, but readmitted to hospital underweight and having cyanotic episodes and severe spasms of coughing. He died suddenly at the age of 9 weeks, with a massive haemoptysis before X-rays could be taken.

Autopsy report:

The body was that of a rather poorly nourished male infant.

Head: The brain and meninges showed no abnormality.

Thorax: The trachea contained a quantity of blood. The visceral and parietal layers of pleura were adherent over the upper lobe of the left lung. In this lobe there was a large cavity, fully 3 cms. in diameter, which had a smooth shiny lining and was filled with recent blood clot. It was impossible to pass a probe
from the left major bronchus through an extremely narrow opening into this cavity. The site of the haemorrhage appeared to be a small ruptured blood vessel which coursed over the lining of this cyst or cavity. The lung parenchyma surrounding the cavity was firm with distinct abscess formation in its midst. Cultures from the pus yielded a growth of staphylococcus aureus. In the extreme apex of the right upper lobe there was a cyst, 1.5 cms. in diameter. This cyst also possessed a clear shiny lining. A smaller cyst similar to that in the right upper lobe was present in the right lower lobe, and over the diaphragmatic surface of this lobe there was interstitial emphysema, with small distended air vesicles under the pleura.

The heart was of appropriate size and developmentally normal.

**Abdomen:** The abdominal organs showed nothing of pathological interest.

**Microscopical report:**

**Lung:** Sections from the large cyst in the left upper lobe showed that it had no epithelial lining. In the lung tissue surrounding the cyst there was an acute inflammatory reaction, with pronounced polymorph leucocyte
infiltration. Sections through the cysts elsewhere in the lungs showed these to be undoubtedly of emphysematous origin, and in the right lower lobe there was distinct interstitial emphysema.

Liver: Sections from the liver showed numerous islands of erythropoiesis, an abnormal finding in a baby of this age, and probably associated with a continued anoxia.

Comment: This case presented many interesting points, the most significant being the finding of several pulmonary cysts, undoubtedly of interstitial emphysematous origin. The large cyst in the left upper lobe possessed no epithelial lining, and it appeared reasonable to assume that it was of similar origin. The clinical history suggested that the pulmonary lesion had been present since soon after birth.
Lung of a newborn infant showing numerous subpleural interstitial emphysematous bullae tracking along the interlobular septa.

Lung of a newborn infant. Large and small emphysematous bullae in the interlobular septa. Haematoxylin and eosin. x 12.
Lung of premature infant. Large emphysematous bullae in interlobular septa. Haematoxylin and eosin. x 40.

PNEUMATOCELE

Lungs of 9 week old baby (see case report). The large cyst which contained blood clot can be seen in the left upper lobe. In the right upper lobe and left lower lobe are cysts of emphysematous origin.
PNEUMATOCELE

X-ray of autopsy specimen showing large lung cysts.

Section including smaller cyst (same case). The emphysematous nature of this cyst can be clearly seen. Pneumonia is present in the surrounding lung parenchyma. Haematoxylin and eosin. x 75.
SUMMARY

Pneumothorax and interstitial emphysema in the newborn have been briefly reviewed and the dangers attendant on certain mechanical methods of resuscitation stressed. Pneumothorax has been shown to occur in cases where no mechanical resuscitation has been employed. It was found in association with a massive inhalation of meconium and with hyaline membrane. The difficulties encountered in the pathological diagnosis of pneumothorax have been discussed. The question has also been raised as to the relationship of interstitial emphysema to the so-called pneumatocele. One case has been demonstrated showing a large pneumatocele existing in association with interstitial emphysematous bullae.
<table>
<thead>
<tr>
<th>Weight</th>
<th>Age</th>
<th>Emphysema</th>
<th>Pneumothorax</th>
<th>Other Pathological Conditions</th>
<th>Mechanical Resuscitative Measures</th>
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<td>4200</td>
<td>9 hrs.</td>
<td>Bullae on both lungs.</td>
<td>Pneumothorax, probably bilateral.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2210</td>
<td>56 mins.</td>
<td>Bullae on both lungs.</td>
<td>Bilateral tension pneumothorax.</td>
<td>Subdural haemorrhage.</td>
<td>Mouth to mouth breathing.</td>
</tr>
<tr>
<td>2700</td>
<td>24 hrs.</td>
<td>Bullae on both lungs.</td>
<td>Probably bilateral pneumothorax.</td>
<td>Patchy areas of intrapulmonary haemorrhage.</td>
<td></td>
</tr>
<tr>
<td>3855</td>
<td>Minutes</td>
<td>Bullae on both lungs.</td>
<td>Probably Pneumothorax.</td>
<td>No inhalation of meconium.</td>
<td>Impossible to be certain whether or not.</td>
</tr>
<tr>
<td>Weight</td>
<td>Age</td>
<td>Emphysema</td>
<td>Pneumothorax</td>
<td>Other Pathological Conditions</td>
<td>Mechanical Resuscitative Measures</td>
</tr>
<tr>
<td>--------</td>
<td>-----</td>
<td>-----------</td>
<td>--------------</td>
<td>------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>3260</td>
<td>16\frac{1}{2} hrs.</td>
<td>Bullae on both lungs</td>
<td>Left pneumothorax</td>
<td>Mediastinal emphysema. Inhalation of meconium.</td>
<td>Endotracheal oxygen.</td>
</tr>
<tr>
<td>3700</td>
<td>7 sb.</td>
<td>Bullae on both lungs</td>
<td>Bilateral tension pneumothorax.</td>
<td>Inhalation of meconium.</td>
<td></td>
</tr>
<tr>
<td>3100</td>
<td>7\frac{1}{2} hrs.</td>
<td>Bullae on both lungs</td>
<td>Right tension pneumothorax. Left pneumothorax probably not under tension.</td>
<td>Inhalation of meconium.</td>
<td></td>
</tr>
<tr>
<td>1600</td>
<td>5 hrs.</td>
<td>Bullae on left lung</td>
<td>Left pneumothorax.</td>
<td>Mediastinal emphysema.</td>
<td></td>
</tr>
<tr>
<td>3600</td>
<td>1\frac{1}{2} hrs.</td>
<td>Bullae on both lungs</td>
<td>Probably pneumothorax.</td>
<td>Mediastinal emphysema. Perinatal pneumonia. Inhalation of meconium.</td>
<td>Endotracheal oxygen.</td>
</tr>
<tr>
<td>3410</td>
<td>1\frac{1}{2} hrs.</td>
<td>Small bullae on both lungs</td>
<td>No evidence of pneumothorax</td>
<td>Inhalation of meconium.</td>
<td>Clearing of airway. Oxygen.</td>
</tr>
<tr>
<td>3800</td>
<td>7\frac{1}{2} hrs.</td>
<td>Bullae on left lower lobe.</td>
<td>Uncertain of pneumothorax.</td>
<td>Inhalation of meconium. Perinatal pneumonia. Slight subdural haemorrhage.</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>Age</td>
<td>Emphysema</td>
<td>Pneumothorax</td>
<td>Other Pathological Conditions</td>
<td>Mechanical Resuscitative Measures</td>
</tr>
<tr>
<td>--------</td>
<td>---------</td>
<td>----------------------------</td>
<td>-------------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>3340</td>
<td>1/2 hr.</td>
<td>Bullae on both lungs.</td>
<td>Bilateral pneumothorax.</td>
<td>Renal Cystic dysplasia</td>
<td></td>
</tr>
<tr>
<td>1416</td>
<td>1 1/2 hrs.</td>
<td>Bullae on right lung.</td>
<td>Most probably pneumothorax on right side.</td>
<td>Intraventricular cerebral haemorrhage.</td>
<td></td>
</tr>
<tr>
<td>2267</td>
<td>1 1/2 hrs.</td>
<td>Bullae on both lungs.</td>
<td>Tension pneumothorax on right.</td>
<td>Renal cystic dysplasia.</td>
<td></td>
</tr>
<tr>
<td>2600</td>
<td>4 1/2 hrs.</td>
<td>Bullae on both lungs.</td>
<td>Tension pneumothorax on right.</td>
<td>Inhalation of meconium.</td>
<td></td>
</tr>
<tr>
<td>2695</td>
<td>26 days.</td>
<td>Bullae on right lung.</td>
<td>? pneumothorax</td>
<td>Subdural haemorrhage.</td>
<td></td>
</tr>
<tr>
<td>2220</td>
<td>66 hrs.</td>
<td>Microdiagnosis of emphysema only.</td>
<td>Left pneumothorax under tension demonstrated by both pathology and radiology.</td>
<td>Hyaline membrane.</td>
<td></td>
</tr>
<tr>
<td>3739</td>
<td>A few minutes</td>
<td>Bullae on both lungs.</td>
<td>Bilateral pneumothorax.</td>
<td>Subcutaneous emphysema.</td>
<td>Endotracheal oxygen</td>
</tr>
<tr>
<td>2876</td>
<td>A few minutes, Classified as S.B.</td>
<td>Bullae on right lung.</td>
<td>Right tension pneumothorax.</td>
<td>Mediastinal emphysema. Severe subdural haemorrhage.</td>
<td>Endotracheal oxygen</td>
</tr>
<tr>
<td>1160</td>
<td>3 days.</td>
<td>No bullae evident. (left interstitial emphysema. microdiagnosis only.)</td>
<td>Left tension pneumothorax.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>Age</td>
<td>Emphysema</td>
<td>Pneumothorax</td>
<td>Other Pathological Conditions</td>
<td>Mechanical Resuscitative Measures</td>
</tr>
<tr>
<td>--------</td>
<td>---------</td>
<td>----------------------------</td>
<td>------------------</td>
<td>-------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>3073</td>
<td>10 mins</td>
<td>No bullae. Lungs abnormally crepitant.</td>
<td>Uncertain</td>
<td>Inhalation of meconium.</td>
<td></td>
</tr>
<tr>
<td>3900</td>
<td>25 mins</td>
<td>Bullae on both lungs.</td>
<td>Bilateral tension pneumothorax.</td>
<td>Inhalation of meconium.</td>
<td></td>
</tr>
<tr>
<td>3830</td>
<td>1 day</td>
<td>Bullae on right lung.</td>
<td>Uncertain.</td>
<td>Inhalation of meconium. Perinatal pneumonia.</td>
<td></td>
</tr>
<tr>
<td>3529</td>
<td>7 hrs.</td>
<td>No bullae, but lung compressed.</td>
<td>Left tension pneumothorax. Probably right pneumothorax.</td>
<td>Inhalation of meconium.</td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES


SUBDURAL HAEMORRHAGE

TABLE A
Total Number of Cases: 90

<table>
<thead>
<tr>
<th>Birth Weight (gm.)</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 1500</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td>1501 - 2500</td>
<td>20 (22.2%)</td>
</tr>
<tr>
<td>2501 - 3500</td>
<td>(44.4%)</td>
</tr>
</tbody>
</table>

TABLE B
Extent of subdural haemorrhage

<table>
<thead>
<tr>
<th></th>
<th>++</th>
<th>+++</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tearing of slight</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Tentorium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(moderate)</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>(severe)</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Absence of tears</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Tearing of eyes</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Total: 11 32 22
**SUBDURAL HAEMORRHAGE**

**TABLE A**

Total Number of Cases 90

<table>
<thead>
<tr>
<th>Birth Weight (gm.)</th>
<th>No. of Cases</th>
<th>(% of Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 1500</td>
<td>4</td>
<td>4.4%</td>
</tr>
<tr>
<td>1501 - 2500</td>
<td>20</td>
<td>22.2%</td>
</tr>
<tr>
<td>2501 - 3500</td>
<td>40</td>
<td>44.4%</td>
</tr>
<tr>
<td>Above 3501</td>
<td>26</td>
<td>28.9%</td>
</tr>
</tbody>
</table>

**TABLE B**

Extent of subdural haemorrhage

<table>
<thead>
<tr>
<th></th>
<th>+</th>
<th>++</th>
<th>+++</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tearing of (slight tentorium)</td>
<td>15</td>
<td>13</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>(moderate)</td>
<td>5</td>
<td>9</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>(severe)</td>
<td>2</td>
<td>6</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Absence of tearing</td>
<td>9</td>
<td>8</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Tearing of falx</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>37</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>
**TABLE C**

Total stillbirths 44.
Number surviving over 3 days 7.

<table>
<thead>
<tr>
<th>Subdural haemorrhage</th>
<th>+</th>
<th>++</th>
<th>+++</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirths</td>
<td>19</td>
<td>17</td>
<td>8</td>
<td>44 (48.9%)</td>
</tr>
<tr>
<td>Live births</td>
<td>12</td>
<td>20</td>
<td>14</td>
<td>46 (51.1%)</td>
</tr>
</tbody>
</table>

**TABLE D**

Method of Delivery

<table>
<thead>
<tr>
<th>Method of Delivery</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breech deliveries</td>
<td>32</td>
<td>(35.5%)</td>
</tr>
<tr>
<td>Spontaneous vertex</td>
<td>27</td>
<td>(30%)</td>
</tr>
<tr>
<td>Vertex with forceps</td>
<td>24</td>
<td>(26.7%)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>3</td>
<td>(3.3%)</td>
</tr>
<tr>
<td>Forceps (brow)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Forceps (presentation not certain)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
SUBDURAL HAEMORRHAGE

TABLE E

<table>
<thead>
<tr>
<th>No. of Parity</th>
<th>Extent of subdural haemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>3 &amp; over</td>
<td>5</td>
</tr>
<tr>
<td>not known</td>
<td>3</td>
</tr>
</tbody>
</table>

Subdural haemorrhage has long been known particularly in relation to subdural haemorrhage of the large series occurring previously. Nevertheless, the 90 cases of subdural haemorrhage in the present series constitute a formidable figure. These cases have been briefly analysed in an attempt to obtain a clearer picture of the underlying factors, which, however, is often clearly opposed to differentiation. Parental anxiety, for example, may well be the prime factor necessitating obstetrical interference and this in turn may be responsible for death from subdural haemorrhage. In this class, therefore, no cases of satisfactory and unexpected to provide a conclusive answer.

The question now arises whether in statistical meetings as is the matter of subdural haemorrhage as is the matter of subdural haemorrhage. But the death of the case of subdural haemorrhage has been continually brought to attention. As ever the answer, further research has been
Subdural haemorrhage has long been known as a source of perinatal mortality. Over the years, however, conditions have greatly changed, particularly in relation to subdural haemorrhage. The large space occupying, encysted subdural haemorrhage of former days is rarely if ever encountered in hospital autopsies today. Nevertheless, the 90 cases of subdural haemorrhage in the present series constitute a formidable figure. These cases have been briefly analysed in an attempt to obtain a clearer picture of the underlying factors, between which, however, it is often clearly impossible to differentiate. Foetal anoxia, for example, might well be the prime factor necessitating obstetrical interference and this in turn be responsible for death from subdural haemorrhage. In this sense therefore, no review of autopsies can be expected to provide a conclusive answer.

The question has often arisen at obstetrical meetings as to whether a particular subdural haemorrhage has in fact been responsible for the death of the baby. As a pathologist I have been continually pressed to answer yes or no. Whatever the answer, further cross-examination has ensued and ultimately "I came out by the same Door as in I went."
Experience has shown that reviews of subdural haemorrhage, none of them recent, fail to assist materially in regard to the assessment of subdural haemorrhage such as is generally found in perinatal autopsies at maternity hospitals today.

The classification of subdural haemorrhage into the groups slight, moderate or severe is merely arbitrary and it must be realised that this classification is only a personal assessment.

At the bottom of Table B. are the percentages of the various groups of subdural haemorrhage. Moderate and slight amounts of subdural haemorrhage account for the greater proportion of cases.

Tearing of the tentorium has been estimated as slight, moderate or severe and this again is only a personal assessment.

In Table B it will be seen that the extent of subdural haemorrhage corresponds approximately with the degree of tearing of the tentorium. Allowing for the varying numbers of cases in each group absence of tearing of the tentorium is approximately the same in all groups.

In many of the instances where tentorial tears were absent bleeding presumably originated
in rupture of the great cerebral vein, or its tributaries. Quite frequently a mass of blood and blood clot was found around the midbrain, and in these instances it has proved impossible to demonstrate any ruptured vessel. This particularly applies to the group of cases in which severe haemorrhage was found.

**Weight range** (Table A.), shows that surprisingly many cases of subdural haemorrhage fall into the premature group, a fact generally not realised. In considering the number of cases above 3500 gms, the number of babies born altogether in this weight range must be taken into account. It would appear that larger babies are exposed to a greater risk of subdural haemorrhage.

Table C shows age of baby in relation to extent of subdural haemorrhage. It is significant that there were 44 stillbirths and that, of the live births only 7 survived more than 3 days. Perusal of the summary of the cases in the appendix will show that of these 7 cases a number also displayed other pathological conditions such as kernicterus of prematurity, or haemolytic disease.

**Method of delivery**, Table D. In 35.5 per cent of cases there was breech delivery. Full information on the actual method of breech delivery
was not available. Fourteen cases were assisted breech deliveries, 11 cases were extracted breech deliveries and in 6 cases forceps were stated to have been used. In one case of breech delivery no details were known. Of the vertex deliveries 24 were deliveries with forceps and 27 spontaneous deliveries without forceps. In 3 cases Caesarian section was undertaken as an emergency procedure. The interest lies in the number of spontaneous deliveries resulting in subdural haemorrhage.

Table E shows the mothers parity in relation to the extent of the subdural haemorrhage. The numbers are too small to be of any significant value. It would appear, however, after taking into account the relatively greater number of first babies born in hospital that parity has little direct influence on the production of subdural haemorrhage.

Subtentorial haemorrhage.

The diagnosis of subtentorial haemorrhage I find extremely difficult. With the greatest care in the world it has been found frequently impossible to assess the presence or extent of subtentorial haemorrhage.

Subtentorial haemorrhage can undoubtedly be diagnosed if the baby has lived for several days,
the blood is clotted and compression of the cerebellum evident. But in many instances the blood is fluid and any attempt to remove the brain merely results in further haemorrhage, obscuring any pathological findings. In this series there was a high proportion of stillbirths and deaths shortly after birth; this may account for the extreme difficulty in diagnosing sub-tentorial haemorrhage.

In conclusion, to express a personal opinion, I have found that where there is severe subdural haemorrhage, with or without tentorial tears, an adequate cause of death has been found.

When subdural haemorrhage is slight, or moderate, care must be taken in attributing death to this condition. In some instances death has been obviously of anoxic origin. Whereas in numerous cases of subdural haemorrhage other factors such as anoxia, haemolytic disease, etc. have been present, those conditions without other superimposed factors cannot be regarded as responsible for subdural haemorrhage.
<table>
<thead>
<tr>
<th>Weight</th>
<th>Sex</th>
<th>Age</th>
<th>Subdural</th>
<th>Tentorial Tears</th>
<th>Other Conditions in Foetus</th>
<th>Mother's Age</th>
<th>Parity</th>
<th>Presentation</th>
<th>Delivery</th>
<th>Other Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1600</td>
<td>M</td>
<td>1 day</td>
<td>++</td>
<td>Falx</td>
<td>Pulmonary haemorrhage</td>
<td>23</td>
<td>1</td>
<td>R.O.A. S.D.</td>
<td></td>
<td>Spontaneous extrapartum haemorrhage</td>
</tr>
<tr>
<td>1600</td>
<td>M</td>
<td>S.B.</td>
<td>+++</td>
<td>Severe</td>
<td>Anoxia</td>
<td>30</td>
<td>1</td>
<td>R.O.A. S.D.</td>
<td></td>
<td>Spontaneous Rapid vertex haemorrhage</td>
</tr>
<tr>
<td>2600</td>
<td>F</td>
<td>S.B.</td>
<td>+</td>
<td>Severe</td>
<td>Anoxia</td>
<td>37</td>
<td>1</td>
<td>M.C. forceps</td>
<td></td>
<td>Mid cavity I.U.</td>
</tr>
<tr>
<td>1800</td>
<td>M</td>
<td>6 days</td>
<td>+++</td>
<td>Severe</td>
<td>-</td>
<td>21</td>
<td>1</td>
<td>F.A.H.</td>
<td>Assisted breech</td>
<td></td>
</tr>
<tr>
<td>3510</td>
<td>F</td>
<td>12 hrs</td>
<td>+++</td>
<td>Falx</td>
<td>Fracture spine, ribs &amp; clavicle</td>
<td>33</td>
<td>3</td>
<td>Breech</td>
<td>Breech extraction</td>
<td></td>
</tr>
<tr>
<td>3060</td>
<td>M</td>
<td>10 days</td>
<td>++</td>
<td>Slight</td>
<td>Fracture skull Extravascular haemorrhage</td>
<td>31</td>
<td>6</td>
<td>Caesarian</td>
<td>Obstructed labour Section</td>
<td>Failed forceps</td>
</tr>
<tr>
<td>4360</td>
<td>M</td>
<td>19½hrs</td>
<td>++</td>
<td>-</td>
<td>?exsanguination</td>
<td>28</td>
<td>1</td>
<td>Vertex</td>
<td></td>
<td>Spontaneous Cord vertex round neck Foetal distress</td>
</tr>
<tr>
<td>2600</td>
<td>M</td>
<td>S.B.</td>
<td>+</td>
<td>Slight</td>
<td>Anoxia (slightly macerated)</td>
<td>24</td>
<td>2</td>
<td>Vertex</td>
<td></td>
<td>Spontaneous Accidental haemorrhage</td>
</tr>
<tr>
<td>3320</td>
<td>M</td>
<td>S.B.</td>
<td>+++</td>
<td>Severe</td>
<td>Pneumonia.</td>
<td>25</td>
<td>3</td>
<td>Shoulder</td>
<td></td>
<td>Breech Ante-natal extraction, variable presentation</td>
</tr>
<tr>
<td>1900</td>
<td>M</td>
<td>3 days</td>
<td>+</td>
<td>-</td>
<td>Patchy I.P. haemorrhage</td>
<td>20</td>
<td>1</td>
<td>L.O.A.</td>
<td></td>
<td>Spontaneous vertex</td>
</tr>
</tbody>
</table>

362
<table>
<thead>
<tr>
<th>Weight</th>
<th>Sex</th>
<th>Age</th>
<th>Subdural tears</th>
<th>Tentorial tears</th>
<th>Other conditions in foetus</th>
<th>Mother's age</th>
<th>Parity</th>
<th>Presentation</th>
<th>Delivery</th>
<th>Other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>3200</td>
<td>F</td>
<td>SB</td>
<td>+</td>
<td>-</td>
<td>fractured parietal bone</td>
<td>27</td>
<td>0</td>
<td>breech</td>
<td>assisted breech forceps to head</td>
<td>difficulty with head</td>
</tr>
<tr>
<td>2985</td>
<td>M</td>
<td>5hrs</td>
<td>+++</td>
<td>severe</td>
<td>haemolytic disease</td>
<td>36</td>
<td>3</td>
<td>vertex</td>
<td>vertex LOA</td>
<td>spontaneous</td>
</tr>
<tr>
<td>3700</td>
<td>M</td>
<td>40mins</td>
<td>++</td>
<td>moderate</td>
<td>-</td>
<td>26</td>
<td>1</td>
<td>VLOL</td>
<td>spontaneous</td>
<td>baby died during exchange transfusion</td>
</tr>
<tr>
<td>3840</td>
<td>M</td>
<td>SB</td>
<td>+++</td>
<td>-</td>
<td>evidence of foetal anoxia</td>
<td>27</td>
<td>0</td>
<td>vertex</td>
<td>vertex ROA</td>
<td>spontaneous</td>
</tr>
<tr>
<td>2540</td>
<td>F</td>
<td>30mins</td>
<td>+</td>
<td>moderate</td>
<td>pneumonia</td>
<td>21</td>
<td>1</td>
<td>vertex</td>
<td>vertex forceps</td>
<td>revealed accidental haemorrhage</td>
</tr>
<tr>
<td>3100</td>
<td>F</td>
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<td>++</td>
<td>-</td>
<td>emphysema</td>
<td>25</td>
<td>3</td>
<td>breech</td>
<td>breech</td>
<td>arms extended manual rotation of head</td>
</tr>
<tr>
<td>3073</td>
<td>F</td>
<td>10 mins</td>
<td>+</td>
<td>moderate</td>
<td>inhalation of meconium</td>
<td>33</td>
<td>0</td>
<td>vertex</td>
<td>Caesarian section</td>
<td>prolonged labour</td>
</tr>
<tr>
<td>Weight</td>
<td>Sex</td>
<td>Age</td>
<td>Subdural</td>
<td>Tentorial Tears</td>
<td>Other Conditions in Foetus</td>
<td>Mother's Age</td>
<td>Parity</td>
<td>Presentation</td>
<td>Method of Delivery</td>
<td>Other Factors</td>
</tr>
<tr>
<td>--------</td>
<td>-----</td>
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<td>----------</td>
<td>----------------</td>
<td>---------------------------</td>
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<td>-------</td>
<td>--------------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>2340</td>
<td>F</td>
<td>8days</td>
<td>-</td>
<td>-</td>
<td>Haemolytic disease.</td>
<td>27</td>
<td>3</td>
<td>V.L.O.A.</td>
<td>Spontaneous baby had subdural tap. 40cc removed.</td>
<td></td>
</tr>
<tr>
<td>2210</td>
<td>M</td>
<td>50mins.</td>
<td>++</td>
<td>Subtentorial</td>
<td>Pneumothorax</td>
<td>31</td>
<td>2</td>
<td>Vertex</td>
<td>Vertex delivery</td>
<td>Premature rupture of membranes.</td>
</tr>
<tr>
<td>4040</td>
<td>M</td>
<td>S.B.</td>
<td>+</td>
<td>Slight</td>
<td>Path-anoxia.</td>
<td>40</td>
<td>4</td>
<td>Vertex</td>
<td>Caes. section.</td>
<td>Ruptured uterus.</td>
</tr>
<tr>
<td>3980</td>
<td>F</td>
<td>80mins.</td>
<td>++</td>
<td>Severe</td>
<td>Pneumonia. Meconium.</td>
<td>27</td>
<td>3</td>
<td>Breech</td>
<td>Breech with forceps</td>
<td>Flat pelvis</td>
</tr>
<tr>
<td>2721</td>
<td>M</td>
<td>S.B.</td>
<td>? subtentorial</td>
<td>-</td>
<td>Anoxia. Pneumonia.</td>
<td>24</td>
<td>2</td>
<td>Vertex</td>
<td>Forceps</td>
<td>Foetal distress</td>
</tr>
<tr>
<td>3260</td>
<td>F</td>
<td>1\frac{1}{2}hrs</td>
<td>+</td>
<td>-</td>
<td>Urogenital &amp; pulmonary hyperplasia.</td>
<td>31</td>
<td>2</td>
<td>Vertex</td>
<td>Spontaneous vertex</td>
<td>-</td>
</tr>
<tr>
<td>Weight</td>
<td>Sex</td>
<td>Age</td>
<td>Subdural</td>
<td>Tentorial tears.</td>
<td>Other conditions in foetus</td>
<td>Mother's Age</td>
<td>Parity</td>
<td>Presentation</td>
<td>Method of delivery</td>
<td>Other Factors</td>
</tr>
<tr>
<td>--------</td>
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<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>4620</td>
<td>M</td>
<td>S.B.</td>
<td>++</td>
<td>Severe</td>
<td>Pneumonia. Inhalation of liquor.</td>
<td>27</td>
<td>0</td>
<td>Breech</td>
<td>Pre-eclamptic toxaemia. Difficulty with breech extraction.</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>F</td>
<td>S.B.</td>
<td>++</td>
<td>Moderate</td>
<td></td>
<td>?0</td>
<td>0</td>
<td>Breech</td>
<td>Forces to head.</td>
<td>Dilatation of cervix.</td>
</tr>
<tr>
<td>2690</td>
<td>F</td>
<td>S.B.</td>
<td>++</td>
<td>Moderate</td>
<td>Foetal anoxia. Inhalation.</td>
<td>Not known - Private</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3065</td>
<td>F</td>
<td>S.B.</td>
<td>++</td>
<td>Severe</td>
<td>-</td>
<td>24</td>
<td>0</td>
<td>Vertex</td>
<td>Forceps.</td>
<td>Foetal distress. Prolonged 2nd stage; cord round neck.</td>
</tr>
<tr>
<td>Weight</td>
<td>Sex</td>
<td>Age</td>
<td>Subdural</td>
<td>Tentorial tears</td>
<td>Other conditions in foetus</td>
<td>Mother’s age</td>
<td>Parity</td>
<td>Presentation</td>
<td>Delivery</td>
<td>Other factors</td>
</tr>
<tr>
<td>--------</td>
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<td>-----------------</td>
<td>--------------------------</td>
<td>--------------</td>
<td>--------</td>
<td>--------------</td>
<td>----------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>3300</td>
<td>F</td>
<td>SB</td>
<td>+</td>
<td>small</td>
<td>foetal blood loss</td>
<td>24</td>
<td>0</td>
<td>vertex</td>
<td>Caesarean section</td>
<td>accidental ante partum haemorrhage</td>
</tr>
<tr>
<td>4750</td>
<td>M</td>
<td>SB</td>
<td>++</td>
<td>small</td>
<td>-</td>
<td>31</td>
<td>1</td>
<td>vertex</td>
<td>forceps</td>
<td>forceps at home</td>
</tr>
<tr>
<td>3825</td>
<td>M</td>
<td>SB</td>
<td>++</td>
<td>moderate severe</td>
<td>anoxia</td>
<td>26</td>
<td>0</td>
<td>vertex</td>
<td>low forceps</td>
<td>accidental haemorrhage</td>
</tr>
<tr>
<td>3356</td>
<td>F</td>
<td>SB</td>
<td>+</td>
<td>slight</td>
<td>-</td>
<td>24</td>
<td>0</td>
<td>breech</td>
<td>forceps to after coming head</td>
<td>concealed accidental haemorrhage</td>
</tr>
<tr>
<td>3160</td>
<td>F</td>
<td>?mins</td>
<td>+++</td>
<td>-</td>
<td>anoxia slight</td>
<td>25</td>
<td>0</td>
<td>VLOA</td>
<td>forceps</td>
<td></td>
</tr>
</tbody>
</table>
MISCELLANEOUS CONDITIONS
THE MACERATED FOETUS.

Examination of the macerated foetus is frequently disappointing. Gross deformities can often be distinguished. Haemolytic disease and congenital syphilis can still be ascertained in spite of advanced maceration.

In the early stages of maceration the subserous petechiae associated with accidental haemorrhage can still be observed, but with advancing maceration these rapidly fade. Apart from those severely macerated histological examination of the lungs reveals in many evidence of foetal anoxia. Histological examination of the kidney may yield an approximate appraisal of maturity as the neogenic zone tends to be better preserved. Detailed histological examination of other organs tends to be rendered valueless by maceration.

Nevertheless, post-mortem examination of the macerated foetus is undoubtedly valuable as success in diagnosing an unexpected condition such as haemolytic disease or toxoplasmosis contributes not only to academic knowledge but may prove life-saving for future infants.
PREMATURITY

Prematurity presents one of the greatest clinical, pathological and physiological problems of today. Without more fundamental knowledge on the physiology of this period, pathological contributions are necessarily limited.

Autopsy failed to reveal any specific cause of death in 69 liveborn premature infants (9.5% of total neonatal deaths) in the present series. This figure includes infants below 1200 gms birth weight. Even in infants below 1000 gms birth weight, infection after the third day is now, with antibiotic coverage, a relatively insignificant cause of mortality. Below 1000 gms hyaline membrane is uncommon but not unknown and a pathological diagnosis of physiological immaturity is always unsatisfactory.

Specific Causes of Death in Premature Infants.

Pulmonary hyaline membrane is a subject about the nature of which there is at present much controversy. The original concept of a "vernix membrane" is no longer tenable and opinion is nowadays in favour of an endogenous origin. The nature of this is, however, still obscure, histochemical studies having been advanced in
support of both a secretory and an exudative basis. The solution of this problem is no less difficult on account of the failure to demonstrate "hyaline membrane" in animals. This does not of necessity imply that it does not occur in animals as veterinary pathology is still in its infancy. I have examined the lungs of a few newborn lambs, but no hyaline membrane has been found.

There can be little question as to the striking incidence of "hyaline membrane" in relation to perinatal mortality. In the present series there were 228 cases. This amounts to 23.9% of the total neonatal deaths. Of the infants with this condition only five, on a weight basis, were mature, maturity being confirmed on histological examination.

Intraventricular cerebral haemorrhage was found in 21 of the premature infants who had hyaline membrane.

**Intraventricular Cerebral Haemorrhage.**

Intraventricular cerebral haemorrhage is not uncommon in premature infants but is rarely found in mature. Seventy-six cases of intraventricular haemorrhage were encountered in the present series, three in stillbirths, and twenty-one
Brain. The lateral ventricle is distended with a mass of blood clot.
in association with hyaline membrane. Only two cases were found in mature babies, both of which also had subdural haemorrhage. In one of these mature babies a subdural tap had been performed. The other mature baby had been severely anoxic. There can be no doubt as to the frequent association of intraventricular cerebral haemorrhage with prematurity. Often the source of the haemorrhage could be traced to a ruptured subependymal haemorrhage. The walls of the unsupported veins coursing in the subependymal regions over the surface of the thalamus in the floor of the lateral ventricles seem, in the premature infant, abnormally sensitive to damage. The role of anoxia as a factor in relation to this vascular damage requires investigation.

The remarkable frequency with which intraventricular cerebral haemorrhage is found in abortions is extremely interesting.

In intraventricular cerebral haemorrhage the blood clot often forms a complete cast of the lateral ventricles and such a cast can be found even when maceration is fairly well advanced.

The occurrence of intraventricular cerebral haemorrhage before birth is of considerable interest. One newborn infant in the present series
died aged a few hours as a result of hydrocephalus secondary to meningeal adhesions which were associated with abundant haemosiderin deposition. A large subependymal haemorrhage, not of recent origin, was found in the floor of one lateral ventricle and haemosiderin staining of the entire ependyma supported the contention that rupture of this haemorrhage had taken place in utero.
Kernicterus associated with prematurity was not recognised until 1950, when Aidin et al in this country and Zuelzer and Mudgett in America first described this condition. Since then, there has been a number of reports on the problem of kernicterus of prematurity with particular reference to the use of exchange transfusion as a preventative. Claireaux, Cole & Lathe (1953) have produced convincing evidence that the pigment in the brains of the affected premature infants is bilirubin, and identical with that in infants with haemolytic disease.

The exact mechanism by which selected areas of the brain become pigmented is, however, not as yet clear. Whether high bilirubin levels in the blood have a direct toxic action or whether, as it now seems improbable, selective cell damage in the nervous system precedes actual pigmentaion is not yet clear. That such pigmentation is related to a hyperbilirubinaemia is now beyond doubt. Until recently little information was available on the normal values of the serum bilirubin in premature and mature babies. Billing, Cole & Lathe (1954) and Maclean, Lucey & Harris (1955) have furnished information on bilirubin estimations in infancy. More recently
Meyer, in a study of serum bilirubin levels, found that in babies under 2,000 gms. the levels were still rising on the sixth day, whereas in those over 2,500 gms. the level at this period was falling. In premature babies developing kernicterus the levels of bilirubin were generally found to be higher, the majority having levels of over 18 mgm.% at the onset of symptoms. He further states that kernicterus is likely to occur where serum bilirubin levels rise above 18 mgm.%.

The problem facing paediatricians to-day is to determine the indications for transfusion and to weigh the possible life saving or morbidity saving results against the risk of exchange transfusion in such small babies.

Experience in one hospital group in this region has suggested that the initial level of serum bilirubin as stated by Meyer may be on the low side, but it is interesting that he states that exchange transfusion may be effective in babies whose rate of rise of serum bilirubin is rapid.

It is becoming apparent that two factors must be taken into account (1) the actual level
of serum bilirubin and (2) the rate of rise of this level estimated frequently at stipulated intervals.

The purpose underlying exchange transfusion is to remove the bilirubin in the blood until such time as this can be converted by the infant into the direct reacting pigment which experience has shown to be apparently innocuous to the central nervous system.

It is extremely unfortunate that serum bilirubin estimations have been performed in only one of the fourteen cases found at post-mortem examination. Without such estimations, pathological confirmation of kernicterus is relatively valueless.

The distribution of the pigmentation in the brain in all cases has shown much the same pattern, with involvement of the basal ganglia and the area surrounding the 4th ventricle. Staining of the dentate nucleus of the cerebellum has not been evident. Histological examination of the brain has proved disappointing, no definite evidence of nerve cell change having been found.

Two premature infants died suddenly during exchange transfusion. Neither of these infants
showed kernicterus. Pathologically the cause of death was not ascertained. There was no pathological evidence of overloading of the circulation and whether it could be associated with the use of citrated blood is at the moment merely speculative.

The technique of the estimation of serum bilirubin may be open to question, but this is certainly not a serious consideration.

When small quantities of serum are used, the reading may be low if the method applied for such estimations is similar to that used in the adult. Using small quantities of serum measurements must be absolutely accurate as the dilution error in such instances is liable to be greater. The fact that a number of babies quite deeply jaundiced never develop signs or symptoms of kernicterus necessitates consideration of an obstructive element. The presence of a direct van der Berg reaction on the serum of some premature babies suggests such an obstruction, and as already mentioned, the direct reacting pigment is apparently innocuous to the brain. More information on serological results relating to this is eagerly awaited.

Much work obviously remains to be carried
out on this question of kernicterus of prematurity and its relation to mental defect in later childhood. A single serum bilirubin level performed on those infants shortly before death is not likely to prove of great clinical value.
<table>
<thead>
<tr>
<th>Body Weight (gms.)</th>
<th>Autopsy Weight (gms.)</th>
<th>Sex</th>
<th>Age</th>
<th>Lesions. Cerebral Pigmentation.</th>
<th>Other pathological conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1247</td>
<td>1020</td>
<td>F</td>
<td>6 days</td>
<td>Definite pigmentation, basal ganglia, midbrain, floor of 4th ventricle, flocculus of cerebellum.</td>
<td></td>
</tr>
<tr>
<td>1814</td>
<td>1640</td>
<td>M</td>
<td>6 days</td>
<td>Basal ganglia, midbrain. Around 4th ventricle.</td>
<td></td>
</tr>
<tr>
<td>1029</td>
<td>746</td>
<td>F</td>
<td>5 days</td>
<td>Faint pigmentation in basal ganglia and around 4th ventricle.</td>
<td></td>
</tr>
<tr>
<td>1270</td>
<td>845</td>
<td>M</td>
<td>7 days</td>
<td>Deep staining of basal ganglia, patchy pulmonary around 4th ventricle and involving peduncles.</td>
<td></td>
</tr>
<tr>
<td>1587</td>
<td>1340</td>
<td>M</td>
<td>6 days</td>
<td>Pigmentation in basal ganglia and around 4th ventricle.</td>
<td>Pneumonia.</td>
</tr>
<tr>
<td>1607</td>
<td>1435</td>
<td>M</td>
<td>4½ days</td>
<td>Pigmentation around 4th ventricle, but not in basal ganglia.</td>
<td>Early pneumonia.</td>
</tr>
<tr>
<td>2177</td>
<td>1680</td>
<td>M</td>
<td>7½ days</td>
<td>Early pigmentation in basal ganglia.</td>
<td>Intra-ventricular haemorrhage.</td>
</tr>
<tr>
<td>2151</td>
<td>1860</td>
<td>M</td>
<td>12½ days</td>
<td>Pigmentation limited to basal ganglia.</td>
<td></td>
</tr>
<tr>
<td>Body Weight (gms.)</td>
<td>Autopsy Weight (gms.)</td>
<td>Sex</td>
<td>Age</td>
<td>Lesions. Cerebral Pigmentation.</td>
<td>Other pathological conditions</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------</td>
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<td>------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>2222</td>
<td>1900</td>
<td>M</td>
<td>5 days</td>
<td>Pronounced pigmentation in basal ganglia. Less evident pigmentation around 4th ventricle.</td>
<td></td>
</tr>
<tr>
<td>1587</td>
<td>1160</td>
<td>M</td>
<td>7 days</td>
<td>Pigmentation in basal ganglia and around 4th ventricle.</td>
<td>Subdural haemorrhage.</td>
</tr>
<tr>
<td>1927</td>
<td>1420</td>
<td>F</td>
<td>7 days</td>
<td>Pigmentation in basal ganglia and around 4th ventricle. Not in cerebellum.</td>
<td></td>
</tr>
<tr>
<td>940</td>
<td>680</td>
<td>F</td>
<td>7 days</td>
<td>Deep pigmentation basal ganglia and around 4th ventricle.</td>
<td>Intrapulmonary haemorrhage.</td>
</tr>
<tr>
<td>1814</td>
<td>1445</td>
<td>M</td>
<td>7 days</td>
<td></td>
<td></td>
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</tbody>
</table>

**Case No. 13:** Serum bilirubin mgm.%.

<table>
<thead>
<tr>
<th></th>
<th>4th day</th>
<th>5th day</th>
<th>6th day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin</td>
<td>23</td>
<td>26</td>
<td>29</td>
</tr>
</tbody>
</table>
REFERENCES


There being considerable variation in the extent of cells affected, whilst the inner cortical zone was most frequently affected, cytomegalic change was occasionally found extending outwards for some distance, but never involving the subcortical regions.

The affected cells were irregularly enlarged both as regards cytoplasm and nucleus.

The nucleus was hypochromatic and often found to contain a clear spherical body, probably nuclear which defined staining by such specific methods as Phloxin-tartrazine. These bodies in no way resembled viral inclusions.
ADRENAL CYTOMEGALY

Adrenal cytomegaly is a change occasionally found affecting the constituent cells of the adrenal glands in the newborn. Potter (1952) found that adrenal cytomegaly had not previously been described. She observed the condition in ten foetuses and newborn infants, but could provide no information as to its significance. This change affects principally the cells of the inner cortical zone. In the present cases, twenty-two in number, the change was sometimes localised and sometimes diffuse, there being considerable variation in the extent of cells affected. Whilst the inner cortical zone was most frequently affected, cytomegalic change was occasionally found extending outwards for some distance, but never involving the subcapsular regions.

The affected cells were irregularly enlarged both as regards cytoplasm and nucleus. The nucleus was hyperchromatic and often found to contain a clear spherical body, probably nucleolar which defined staining by such specific methods as Phloxin-tartrazine. These bodies in no way resembled virus inclusions. Acidophilic
ADRENAL CYTOMEGALY

Section of Adrenal Gland

The foetal cortex shows pronounced cytomegaly. In the cells both cytoplasm and nucleus are enlarged. x 80. Haematoxylin & eosin.
granules were sometimes found in the cytoplasm, which contained not infrequently small peripheral vacuoles. No intracytoplasmic inclusions were ever demonstrated.

Of the twenty-two instances in which this condition was found, eleven were in males and eleven in females.

The weight range was wide, ten of the infants being above 2,000 gms. and three below 1,000 gms.

On only four occasions was adrenal cytomegaly found in cases of severe foetal malformation.

On eleven occasions the cytomegaly was bilateral and on seven occasions it was unilateral. In the remaining three cases only one adrenal was sectioned.

The most interesting case was that involving a two-day old premature male infant weighing 1,587 gms. This baby, the first of twins, died as the result of intrapulmonary haemorrhage. Microscopical examination revealed bilateral adrenal cytomegaly. In one section of the lung, however, there was found a nodule of tissue, 1 to
2 mm. in diameter, composed of cells bearing a strong resemblance to those of the adrenal cortex, even to the point of showing a cytomegalic change. No mitotic figures were found in this nodule. It was situated directly adjacent to a vein. The significance of this nodule remains obscure. There would appear to be little doubt that it was in fact adrenal cortical tissue, but a heterotopia of this nature in the lung must be exceedingly rare and difficult to explain from the embryological point of view. To regard this nodule as a neoplastic deposit is exceedingly difficult. For the present, at least, its significance remains undetermined. The second twin as far as is known has remained healthy.

The review of twenty-two cases of adrenal cytomegaly has shown that this condition bears no relationship to birth weight, sex or congenital defects. It was present in both premature and mature infants and was even found at the age of four weeks. There is no reason to believe that adrenal cytomegaly is a virus infection. Moreover in no way does it resemble the usual involutionary changes that normally occur in the foetal cortex. Little is known of the physiology
and biochemistry of the foetal adrenal cortex and it may well be that between these and adrenal cytomegaly there exists some functional relationship. For the present, at least, adrenal cytomegaly can be regarded as of little significance, although an interesting academic problem.
Section of lung from infant aged 2 days
The section shows the rounded nodule composed apparently of adrenal cortical tissue. x 40. Haematoxylin & eosin.

Section of nodule in lung
At this magnification the cytomegalic change is plainly visible. x 165. Haematoxylin & eosin.
<table>
<thead>
<tr>
<th>Weight (gms.)</th>
<th>Sex</th>
<th>Age</th>
<th>Unilateral or Bilateral</th>
<th>Cause of Death/Condition</th>
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<tbody>
<tr>
<td>930</td>
<td>F</td>
<td>S.B.</td>
<td>bilateral</td>
<td>Twin 2. Holocardiacephalus</td>
</tr>
<tr>
<td>2932</td>
<td>M</td>
<td>1/2 hr.</td>
<td>bilateral</td>
<td>Exompholos hare lip.</td>
</tr>
<tr>
<td>2985</td>
<td>M</td>
<td>5 hrs.</td>
<td>Only 1 gland examined</td>
<td>Haemolytic disease.</td>
</tr>
<tr>
<td>1920</td>
<td>F</td>
<td>1 day</td>
<td>unilateral</td>
<td>Hyaline membrane.</td>
</tr>
<tr>
<td>1780</td>
<td>F</td>
<td>9 hrs.</td>
<td>unilateral</td>
<td>Hyaline membrane.</td>
</tr>
<tr>
<td>3170</td>
<td>F</td>
<td>S.B.</td>
<td>unilateral</td>
<td>Anoxic perinatal pneumonia.</td>
</tr>
<tr>
<td>2267</td>
<td>M</td>
<td>21/2 days</td>
<td>unilateral</td>
<td>Not ascertained.</td>
</tr>
<tr>
<td>2545</td>
<td>M</td>
<td>3 days</td>
<td>bilateral</td>
<td>Cerebral infarction. Pneumonia.</td>
</tr>
<tr>
<td>2900</td>
<td>M</td>
<td>21/2 days</td>
<td>bilateral</td>
<td>Hyaline membrane.</td>
</tr>
<tr>
<td>740</td>
<td>F</td>
<td>S.B.</td>
<td>unilateral</td>
<td>Cyclops.</td>
</tr>
<tr>
<td>1750</td>
<td>F</td>
<td>1 day</td>
<td>Only 1 gland examined</td>
<td>Prematurity.</td>
</tr>
<tr>
<td>980</td>
<td>F</td>
<td>3 days</td>
<td>bilateral</td>
<td>Extreme prematurity.</td>
</tr>
<tr>
<td>2285</td>
<td>M</td>
<td>4 wks.</td>
<td>bilateral</td>
<td>Not ascertained.</td>
</tr>
<tr>
<td>4600</td>
<td>M</td>
<td>5 hrs.</td>
<td>bilateral</td>
<td>Subdural haemorrhage.</td>
</tr>
<tr>
<td>1587</td>
<td>M</td>
<td>2 days</td>
<td>bilateral</td>
<td>Intrapulmonary haemorrhage. Metastasis.</td>
</tr>
<tr>
<td>1070</td>
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<td>S.B.</td>
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<td>Anoxia.</td>
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SUMMARY

Twenty-two cases of adrenal cytomegaly have been encountered in the present series of autopsies. The number of cases has been sufficient for investigation as regards sex, birth weight, and presence of foetal malformations. In half of the cases the cytomegalic change was bilateral. One case has been described in which a nodule, apparently of adrenal cortical tissue was found in the lungs of a premature twin infant. This nodule showed cytomegalic changes similar to those found in both adrenal glands.
TUMOURS IN THE NEWBORN

Tumours in the newborn are a complex and difficult subject. The information obtained from a limited series of autopsies is insignificant and only of value when incorporated in a wide comprehensive scheme for systematic documentation. As such the tumours in this series are incorporated in the tumour register instigated by Dr. Agnes Macgregor through the Scottish Surgical Paediatric Club.

The tumours encountered in the course of this series of autopsies consisted of:-

Cystic lymphangioma of the neck ..... 2 cases
Potential neuroblastoma ............... 5 cases
Myeloid leukaemia .................... 1 case

"Cystic hygroma" now generally regarded as not truly neoplastic occurs most frequently in the neck and axilla, proving lethal only as a consequence of obstructive effects in neighbouring structures. The following case is of interest in view of the interference with delivery resulting from the massive size of the hygroma. This is a rare occurrence, but peculiarly a similar instance was recorded from
the same hospital by Professor R.W. Johnstone in 1933. As the case is being published more fully by the obstetricians only brief mention is necessary.

The mother was aged 28, para 8. The maturity was estimated as 40 weeks and she was admitted to hospital after "failed forceps" at home. Deep transverse arrest of the head had occurred and the baby was delivered only after an extremely difficult forceps application. The child was stillborn.

Autopsy was performed on a male foetus weighing 5175 gms., a considerable proportion of the weight being accounted for by cystic swelling in the neck. Figs. 1 & 2 show this multiloculated tumour which extended around the entire circumference of the neck, cysts being present even in deeper muscles. The cysts penetrated the upper part of the face and the lower part of the scalp.

Histologically it showed the typical structure of a lymphangioma with numerous dilated cystic spaces of varying size. Plain muscle was present in the walls of some of the channels and there were occasional foci of
Fig. 1: Massive Cystic Hygroma of Neck. As a result of the tumour, delivery was extremely difficult.

Fig. 2: Cystic Hygroma of Neck. (same case) Complete section through head and neck. The multiloculated structure of the hygroma is plainly visible.
lymphoid tissue.

The second instance of cervical lymphangiomata resulted in death from respiratory obstruction at the age of 5 hours. The infant weighing 2494 gms. was delivered without any undue difficulty. The cyst (Fig. 3.) was huge, unilocular, and possessed a smooth, thin membranous lining. No connection was found between the cyst and any of the deeper structures of the neck. The cyst contained clear fluid. Histological examination of the cyst wall showed it to be composed mainly of dense fibrous tissue. There was no epithelial lining.
Fig. 3: Large Lymphangiomatous Unilocular Cyst of Neck.
The infant died as a result of the obstructive effects produced by the cyst.
CONGENITAL NEUROBLASTOMA

Neuroblastoma (sympathicoblastoma) is the commonest malignant tumour of childhood. In relation to this the recognition of rests of primitive cells in the newborn assumes considerable importance, but the significance of these rests in developing tissues is frequently open to question. It is beyond doubt that the zone of neogenic tissue in the kidney of the immature infant persists for several weeks of life. On the other hand, some of the nodules of sympathicoblasts found in the adrenals in the course of the present series of autopsies show certain features which cannot be overlooked in regard to the consideration of malignancy or potential malignancy.

CASE 1:

A small premature female infant weighing 1220 gms. died aged 7 days as the result of congenital cardiac defects. Macroscopically, no abnormality was noted in either suprarenal. Microscopical sections of one suprarenal showed masses of sympathicoblasts, not only in the medullary region, but extending into a thin cortex.
Fragments of foetal cortex were still evident amidst these primitive cells. Typical rosette formation was present, but no mitotic figures were seen.

CASE 2:
A small premature male infant aged 7 days, autopsy weight 1680 gms., died as a result of kernicterus and intraventricular cerebral haemorrhage. Macroscopically no abnormality was noted in either suprarenal. Microscopical sections of one gland showed in the medullary region a considerable sized nodule of tissue composed of neuroblasts, which varied in size and showed typical rosette formation.

CASE 3:
A male infant, birth weight 7 lbs. 3 ozs. died aged 14 days as the result of pneumonia and staphylococcal abscess formation in the lungs. Macroscopically no abnormality was noted in either suprarenal. Microscopical sections of one gland showed a nodule in the medullary region composed of groups of neuroblasts arranged in clumps and acinar-like formations. A number of mitoses were evident. Amidst the groups of
neuroblasts were numbers of apparently normal chromaffin cells.

CASE 4:
A small male infant, the second of twins, weighing 3 lbs. 3 ozs. died 21 hours with pulmonary hyaline membrane formation. Macroscopically no abnormality was noted in either suprarenal. Microscopical sections of one suprarenal showed a small cellular nodule composed of neuroblasts forming a number of very typical rosettes and having a delicate vascular stroma. This nodule was situated close to the central vein. It was not separated from the adjacent suprarenal tissue by any fibrous capsule and at its margins it extended into the suprarenal cortex.

CASE 5:
A fullterm male infant, birth weight 7 lbs. 5 ozs., died aged 9 days as a result of fibrocystic disease of the pancreas. No abnormality was noted macroscopically in either adrenal. Sections were taken routinely from both adrenal glands and in one of these there was an irregular mass of neuroblasts. Fine bands of stroma were evident in this nodule and a few of the cells were in mitotic division.
Fig. 4: Section of Adrenal (case no. 2).
Nodule from adrenal composed of neuroblasts,
with distinct rosette formation.
x 30. Haematoxylin & eosin.

Fig. 5: Section of Adrenal (case no. 5).
This section shows the irregular mass of
neuroblasts. No rosette formation is evident.
x 55. Haematoxylin & eosin.
CONGENITAL NEUROBLASTOMA

Fig. 6: Section of Adrenal (case no. 5.)

The groups of neuroblasts are separated by thin fibrous bands. This picture is very suggestive of a neuroblastoma.

X 250. Haematoxylin & Eosin.
DISCUSSION

Landau (1912) reported the finding in a newborn infant of a suprarenal neuroblastoma accompanied by hepatic metastasis. Wells (1940) in an excellent review of the subject reported four neuroblastomas limited to the suprarenal in the course of 3,000 autopsies on stillborn and newly born children. Morison (1952) recorded in a series of 1,500 consecutive perinatal autopsies the finding of three such tumour nodules. He (Morison) regards many of these small nodules as probably not true neoplasms.

Of the present cases, three of these aggregations of neuroblasts were found in premature infants aged no more than 7 days, whereas two were found in mature infants, both over the age of one week.

The question as to whether these groups of cells might have undergone normal maturation will always remain unsolved. Suffice it to say that such findings are not usual, and when extension, which is not merely the result of plane of section, is present into the foetal cortex, then potential malignancy must be seriously considered.
Myeloid leukaemia is uncommon in infancy. Gauld, Innes and Robson (1953) in a review of 647 cases of leukaemia from the East of Scotland found that the youngest patient with chronic myeloid leukaemia was 7 years of age. In the Royal Hospital for Sick Children, Edinburgh, myeloid leukaemia has been once recently encountered at the age of 14 months. Cook (1953) found that in one hospital over a 25 year period, there had been 6 children under the age of 2½ years with chronic myeloid leukaemia. Single cases of myeloid leukaemia under the age of 2 years have previously been recorded by Poncher et al (1942), Keith (1945), Crissali and Nonato (1949). Potter (1952) describes the pathological findings in a case of myelogenous leukaemia in a 2 day old infant.

It is of considerable interest that myeloid leukaemia should occur so early in childhood. Criteria for the diagnosis of leukaemia at this young age must be precise, and leukaemic infiltration of the liver and spleen must not be mistaken for extramedullary haemopoiesis.

The following case of myeloid leukaemia
merits description on account of the age of the infant at death and the absence at this time of lymph gland enlargement.

The baby, birth weight 6 lbs. was born at home after a forceps delivery. The baby was reported as being comparatively well until the age of 3 weeks. Thereafter there was a history of vomiting with epistaxis. When seen aged 26 days, the baby was obviously ill, but afebrile, with a purpuric rash over the fingertips, toes, dorsum of feet and ankles and around the anus. The liver and spleen were both enlarged, and a blood count showed 20,000 white cells per cu.mm. The blood film was reported as showing "roughly" 45% polymorphs, but no further examination was carried out and no comment was made on abnormal cells. Unfortunately the blood films were not examined by the pathologist. X-rays of the long bones and of the skull were negative. The Wasserman reaction was negative. The blood biochemistry was normal. Examination of the cerebro-spinal fluid was entirely negative. The infant became oedematous and died aged 28 days.

Autopsy report:

The body was that of a poorly nourished male infant weighing 3,300 gms. There was
generalised oedema of the subcutaneous tissues.

**Head:** The brain and meninges showed no external abnormality. In the right half of the cerebellum in the region of the dentate nucleus, there was a small area of recent haemorrhage, barely 1 cm. across. No other pathological lesion was found.

**Thorax:** The lungs were firmer than usual and dark purplish. The consistence was highly suggestive of haemorrhage. Very dark cyanotic blood exuded from the cut surface. The heart was slightly larger than usual, this being on account of a right-sided dilatation, but no congenital defect was found.

**Abdomen:** The peritoneal sac contained a slight excess of free fluid. Alimentary tract showed no abnormality. The liver was enlarged to fully 1½ times the usual size, and uniformly brick-red. Section showed no obvious parenchymatous abnormality. The spleen was enlarged to fully twice the normal size, firm, and showed on section a very homogeneous parenchyma. The kidneys were of normal size. When the capsule was stripped, numerous small pin-point areas of haemorrhage were evident on the cortical surface. The suprarenals were normal.
Bacteriological report:

Cultures from the lung, intestine and blood yielded negative results.

Microscopical report:

Liver: Sections from both right and left lobes showed throughout the sinusoids an abundant infiltration by primitive blood cells, amongst which a number of myelocytes could be distinguished. The portal tracts were not particularly involved.

Spleen: In the spleen, although the Malpighian bodies were reasonably defined, there was throughout the pulp an easily distinguished and pronounced myelocytic infiltration.

Lungs: There were irregularly distributed patches of intra-alveolar haemorrhage. There were occasional small foci of early bronchopneumonia but the areas of haemorrhage were not always related to these. Examination of the pulmonary vessels showed a considerable proportion of the white cells present to be of the myelocyte series.

Bone marrow: As in the spleen, the most pronounced feature was the myelocytic infiltration, and whilst individual cell determination in the
paraffin section was difficult, the general histological picture was compatible with a myelogenous leukaemia.

**Heart:** The heart showed early infiltration with primitive white cells around the coronary vessels. There was no involvement of the myocardium.

**Lymph glands:** Routine sections from the abdominal lymph glands showed no changes specific for myelogenous leukaemia.

**Brain:** Sections from the cerebellum showed the area of haemorrhage to be of some duration. There were numerous haemosiderin-laden histiocytes and surrounding gliosis.
Fig. 7: Liver. Abundant infiltration of sinusoids by primitive cells. x 220. Haematoxylin & eosin.

Fig. 8: Liver. High power view showing infiltration of sinusoids by primitive cells amidst which are a number of myelocytes. x 600. Haematoxylin & eosin.
DISCUSSION

Leukaemia in the new born is rare, and unique in that it is invariably myelogenous. Morison (1952) quotes 15 of the reported cases of congenital leukaemia as being acceptable. Kelsey and Anderson (1939) provide an excellent review of the subject and describe a case of myelogenous leukaemia in which skin tumours were present at birth, the infant dying on the 4th day of life. No doubt can also be entertained about the case of myelogenous leukaemia described by Potter (1952). This infant died aged 2 days. There were numerous indented, flat or elevated lesions of the skin, the liver was enlarged, and histological examination of the tissues revealed infiltration of almost all tissues of the body by primitive cells of the myelogenous series. The blood count immediately after birth was 369,000 nucleated cells per cu.mm.

In the present case, clinical examination of the blood was inadequate, but from histological examination of the white cells in the blood vessels, a considerable proportion of those in the ante-mortem blood film unquestionably must have been of primitive type.
The distribution of the primitive myeloid infiltration throughout the sinusoids of the liver is entirely different from any reaction produced as a result of infection in infancy. The number of myelocytes in the spleen, a striking picture, provides strong supporting evidence for a diagnosis of leukaemia. The histological appearance of the lymph glands is odd but no definite myeloid infiltration is apparent. Whereas paraffin section of the bone marrow are never satisfactory in blood dyscrasias, the picture in the present case, taken in conjunction with the changes in the liver and spleen, leaves little doubt about the diagnosis. It might be debatable as to whether this case should be described as "congenital" or not. Occurring at so early an age it is permissible to ascribe such a prefix. Applying a strict classification, however, would exclude this and many other cases, leaving only those very few with skin nodules evident at birth.

There was no history of disease in the mother in the present case. Erf (1947) carried out a survey of infants born of mothers with leukaemia during pregnancy, but could find no single instance of leukaemia in the child. This is of interest in relation to the controversial question of the neoplastic or viral origin of leukaemia.
REFERENCES


These figures have been supplied by the various Maternity Units at which the autopsies in this series were performed. The majority of the Maternity Units hold monthly meetings at which stillbirths, neonatal deaths and other obstetrical subjects are discussed. The presence of the pathologist at these meetings is beneficial to all. At Hospital D. the attendance of local general practitioners has proved highly successful, and their interest in perinatal pathology stimulated. Consequently, the scope of the meetings is gradually extending.

Samples of the data issued at the various meetings are included after the hospital figures.
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Percentage of autopsies on perinatal deaths over whole period - 95.5.

L.B. = live birth.
HOSPITAL D.

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Percentage of autopsies on perinatal deaths over the whole period - 57.8.

L.B. = live birth
M.R. = mortality rate

This figure is low on account of the years 1952-53, when paediatric pathology was in the process of being introduced to the hospital.
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Percentage of autopsies on perinatal deaths over whole period - 79.04.

L.B. = live birth
M.R. = mortality rate.
## S.M.M.P.

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Percentage of autopsies on perinatal deaths over the whole period - 83.2%.

Since there are no obstetrical reports for the years 1953-4 these figures are given on a weight basis calling 2½ lbs. or less an abortion.

L.B. = live birth
M.R. = mortality rate.
T.B. = total birth.
**HOSPITAL B.**

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Percentage of autopsies on perinatal deaths over the whole period - 73.07.

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M.R. = mortality rate.
T.B. = total birth.
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<td>50.8</td>
<td>55.0</td>
<td>64.0</td>
<td>50.5</td>
</tr>
</tbody>
</table>

Percentage of autopsies on perinatal deaths over the whole period - 52.5.

This figure is low on account of the years 1952-3 when paediatric pathology was in the process of being introduced to the hospital.

L.B. = live birth  
M.R. = mortality rate  
T.B. = total birth.
HOSPITAL E.G.

<table>
<thead>
<tr>
<th></th>
<th>1952</th>
<th>1953</th>
<th>1954</th>
<th>1955 - 30th June, 1956</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of deliveries</td>
<td>1301</td>
<td>1339</td>
<td>1420</td>
<td>1281</td>
</tr>
<tr>
<td>No. of live births</td>
<td>1275</td>
<td>1314</td>
<td>1391</td>
<td>1252</td>
</tr>
<tr>
<td>No. of stillbirths</td>
<td>26</td>
<td>25</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>S.B. rate per 1,000 total births</td>
<td>20.0</td>
<td>18.7</td>
<td>20.4</td>
<td>22.6</td>
</tr>
<tr>
<td>No. of neonatal deaths</td>
<td>20</td>
<td>15</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td>Neonatal M.R. per 1,000 L.Bs.</td>
<td>15.7</td>
<td>11.4</td>
<td>13.7</td>
<td>21.6</td>
</tr>
<tr>
<td>Perinatal M.R. per 1,000 T.Bs.</td>
<td>35.4</td>
<td>29.9</td>
<td>33.8</td>
<td>43.7</td>
</tr>
</tbody>
</table>

Percentage of autopsies on perinatal deaths over the whole period - 76.7.

L.B. = live birth
M.R. = mortality rate.
T.B. = total births
Patients delivered
Primigravidae
Twins
S.B.
N,R.D.
A,N. Admissions

Mode of Delivery
Spontaneous Vertex
Forceps
Breach
C.S.

Details of B.B.

<table>
<thead>
<tr>
<th>B.B.</th>
<th>N.B.</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hay</td>
<td>para 0</td>
<td>inertia - forceps - 6.10 - lived minutes.</td>
</tr>
<tr>
<td>Reid</td>
<td>para 0</td>
<td>inertia - forceps - 9.8 - lived minutes.</td>
</tr>
<tr>
<td>Fortune</td>
<td>para 0</td>
<td>3.15 - died during transfusion.</td>
</tr>
<tr>
<td>Dommachie</td>
<td>para 4</td>
<td>7.0 - Rh. incompatibility.</td>
</tr>
</tbody>
</table>

Forces

| O'Neill | B. para 0 | stage II delay - low = 7.7 alive |
| Laidlay | N.B. para 0 | inertia - Kielland = 7.2 alive. |
| B. | | |

N.B. | see N.N.D. |

| N.B. | para 0 | stage II delay - low = 6.9 alive |
| neW. | para 0 | stage II delay - mid = 8.5 |
| McCarron | para 0 | stage II delay - low = 7.13 alive |
| Cowan | para 0 | F.E.T. - low = 8.2 alive |
| Mohaner | para 0 | stage II delay - low = 7.14 alive |
| Smith | para 0 | stage II delay - mid = 6.0 alive |
| Ellick | para 0 |

| B. | para 2 | (8.6,8) - unstable lie - elective L.S.C.S. 8.6 alive. |
| B. | para 3 | (1 C.S.) - cont. pelvis - elective L.S.C.S. 8.5 alive. |
| B. | para 0 | inertia - L.S.C.S. 8.5 alive. |
| B. | para 1 | (0.S.) - disp. + inertia - L.S.C.S. 8.5 alive. |
| B. | para 0 | cont. pelvis failed trial - L.S.C.S. 8.0 alive. |
| N.B. | para 0 | trans. lie in labour - L.S.C.S. |
| N.B. | para 0 | conc. acc. haem. - L.S.C.S. 6.6 alive. |

| B. | para 0 | Extraction - 8.6 alive |
| B. | para 1 | trans. lie, 2nd twin - internal version breech extraction - 7.9 alive. |
| N.B. | para 0 | Assisted - 6.11 alive |
| B. | para 2 | Ass. F.A.C.H. - 5.15 alive |
| B. | para 0 | " - 7.11 alive |
| B. | para 0 | " - 7.0 alive |

Manual Removals - 2; P.P.H. - 9; Pyrexia - 5.
CLINICAL CONFERENCE

Wednesday 29th August, 1956.

(July Cases)

DUNE:

Age 41. Second pregnancy, the first one having ended in an abortion at the 14th week. Attended the ante-natal clinic from the 12th to the 25th week. At the 14th week the patient's blood pressure was observed to be 156/94. She was not admitted, but was advised to rest at home and tabs. Veriloid and Nauioid were prescribed. At the 16th week blood pressure was 140/90. Thereafter it dropped to normal at about 120/70 until the 24th week when it rose to 140/90 was again observed. She went into labour spontaneously on 25.7.56 and after a very short labour of about 1½ hours, was spontaneously delivered of a female, premature, macerated foetus weighing 1 lb 10 ons. As the duration of pregnancy was estimated to be about 28-29 weeks, this must be recorded as a still-birth. N.B. The patient's blood pressure on admission was 23/120, but she responded very rapidly (within 4 days) to the administration of Veriloid 4 mgm. 6-hourly, and three days later her blood pressure was 120/80 and it remained at a normal level until discharge from Hospital on the 11th day. No post-mortem was performed.

NEONATAL DEATHS

KELLY:

Age 30. Sixth pregnancy. Five previous normal deliveries. Attended the ante-natal clinic from the 16th to the 37th week. No complications until the 37th week when blood pressure was observed to be 135/100. She was given tabs. Veriloid 2 mgm. q.i.d., on 12.7.56. On 17.7.56 she was admitted in labour which lasted 3 hours 15 minutes and resulted in the birth of a live female, mature infant weighing 6½ lbs 12½ ozs. The infant was limp at birth, due perhaps to the cord having been wound tightly round the neck. It responded to mucous extraction and the administration of oxygen. The infant survived 1½ hours. The result of the post-mortem report showed interstitial emphysema of both lungs and pneumothorax on right side.

WARDEN:

Age 26. Second pregnancy. Attended the ante-natal clinic from the 10th to the 32nd week. She gained 4 lbs in weight between the 30th and 32nd week. Twin pregnancy. She went into labour on 29.6.56 when estimated to be 32 weeks pregnant. Twin delivery - both spontaneous. Weight 6½ lbs 1 oz. and 5 lbs 9½ ozs respectively. Both were slightly limp at birth, but responded to the administration of oxygen and both were placed in an oxygen tent. The second twin, although it became active some time after birth, died 40 hours later. The post-mortem report showed pulmonary hyaline membrane with a very early pneumonia and pulmonary oedema. The second twin's condition was satisfactory and was discharged.

CORSTORPHINE:

Age 45. Ninth pregnancy. Attended the ante-natal clinic from the 14th to the 40th week. At the first visit she was noted to be suffering from anaemia - Hb. 70%. Ferrumyn was prescribed. When seen at the 23rd week the Hb. had dropped to between 60% and 70%. This woman, by the way, is an old case of tuberculosis. The upper zone of her left lung showed a fibrotic area and the condition was diagnosed by Dr. Fraser as now inactive.
ACKNOWLEDGEMENTS

I must thank the obstetricians and the paediatricians at the various hospitals, whose support has everywhere been most gratifying.

Dr. John Thomson has enlightened me on, and encouraged me to undertake a statistical approach to paediatric pathology in the years to come.

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Mr. T.C. Dodds and his staff of the Photomicrography Unit, University of Edinburgh have put their resources at my disposal. Mr. Dodds wishes to disclaim any responsibility for some poor photographs, which are obviously amateurish and were taken by myself.

Miss Brydon of the Photographic Department, Royal Hospital for Sick Children, Edinburgh has also helped considerably with photography.

Lastly, I have to thank the secretarial staff of the Pathology Departments at the University of Edinburgh and the Royal Hospital for Sick Children, who have suffered me so gladly.