A STUDY OF FACTORS CONCERNED IN VARIATIONS
OF THE TUBERCULIN SKIN REACTION OCCURRING
IN HEALTH AND DISEASE DURING ADULT AND
CHILD LIFE.

by

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GENERAL INDEX.

PART 1. Historical.  1.
PART 3. Record of Observations.  28.
PART 4. Discussion.  70.
PART 5. Summary and Conclusions.  135.

PART 7. Appendix: Diagrams and Tables.
PART I.

HISTORICAL.
PART 1.
HISTORICAL.

Contents.

Varieties of tuberculin skin tests. 1
The type of reaction in relation to technique. 2
The type of reaction in relation to the site of test area. 2
The type of reaction in relation to age. 3
The type of reaction in relation to sex. 3
The type of reaction in relation to race. 3
The type of reaction in relation to the season of the year. 4
The type of reaction in relation to infectious diseases. 4
The type of reaction in relation to fever. 5
The type of reaction in relation to anaemia. 5
The type of reaction in relation to normal bodily function. 5
The type of reaction in relation to physiological events in the female life. 6
The type of reaction in relation to anaesthesia. 7
The type of reaction in relation to the severity of the underlying tuberculous infection. 7
The type of reaction in relation to the course of the underlying tuberculous infection. 11
The type of reaction in relation to particular clinical forms of tuberculous infection. 12
The type of reaction in relation to a history of contact. 13
The type of reaction in relation to prognosis. 13
The time at which initial tuberculin skin sensitivity is acquired. 14
PART 1.

HISTORICAL.

The skin response of individuals infected with tuberculosis to products of the growth of the tubercle bacillus, has formed the basis of numerous varieties of tuberculin tests. Of these, the following in chronological order have been given searching trial:

(1.) The subcutaneous test (41. 42).
(2.) "Stichreaktion" (27. 31).
(3.) The cutaneous test (and modifications.) (71. 72. 55. 56).
(4.) The conjunctival test (10).
(5.) The percutaneous test (63).
(6.) The intracutaneous test (58).
(7.) The multiple puncture test (and modifications) (12, 25, 87, 13, 14).

For a given time each of the above tests has been in especial favour, but all have had their critics with the result that a number of them are no longer generally used. The subcutaneous test has proved too cumbersome and not without danger, the "stichreaktion" has never won favour outside Germany and Austria, and the conjunctival test has fallen into disuse on account of its unreliability and painfulness. The percutaneous method is still employed by some workers but its use is limited.

At the present time, there are in every day use the/
the von Pirquet cutaneous test, the intracutaneous method of Mantoux and the multiple puncture test. Within recent years the popularity of the Mantoux method has gained at the expense of the von Pirquet test and its modifications on account of the greater sensitivity claimed for the former and, because of the fact that the Mantoux test can be applied quantitatively (31). In connection with the multiple puncture test Wahl and Gerstenberger (87) confirmed the findings of Craig (12) regarding its reliability, and with the modified form employed by us we have found the method as accurate as the Mantoux and other tests (14).

Since the value of tuberculin skin tests became appreciated it has been recognised that irrespective of the form of test employed the intensity of the skin reaction is subject to modification by various factors. The importance of these factors has been investigated by a large number of workers.

Technique. King (40) quotes Smith as finding that the intensity of the reaction depends upon the actual amount of fluid - "tuberculin plus diluent" - introduced into the skin. Pirquet (73) on the other hand believed the severity of the cutaneous reaction varied according to the strength of tuberculin employed.

Site chosen for test. Baldwin (3) notes that/
that the tuberculin reaction varies in intensity according to the site chosen for applying the test, the inner arm and chest being among the more sensitive areas.

Age. Krause (45) considers that infected children as a class give more vigorous skin reactions than adults. Heimbeck (34) notes lessened sensitivity in old age, and Cummins (15) finds greater skin reactivity in cases of juvenile tuberculosis than in those with the adult form of the disease. Among children, Dickey (20) considers a gradual increase in the size of the reaction takes place up to the age of six years, and Slater and Jordan (80) note a greater skin response in the young.

Sex. Dickey (20) maintains that sex is not a factor in the determination of the degree of skin sensitivity occurring in children, but Cummins and Evans (17) consider that in healthy clinically non-tuberculous subjects, females show more marked tuberculin reactivity than males.

Race. Working in the United States of America, Dickey (20) determined the existence of a racial predisposition towards severe tuberculin skin reactions among Orientals, and McCain (54) found a greater incidence of tuberculin sensitivity among coloured than white children. Cummins and Evans (17) point out/
out that both sexes of European race show less reactivity than native South Africans.

Season of the year. Seasonal differences in the intensity of the tuberculin reaction in children have been reported by Hamburger (28) and Peyrer (68), and in adults by Schnippenkötter (79). The children were found to give stronger reactions in spring than in autumn, and in adults the reactions were less intense in winter and early spring than during the rest of the year.

Infectious diseases. In 1907 von Pirquet (74) demonstrated the temporary loss of sensitivity occurring during the eruptive phase of measles and this has been confirmed by Lesné and Coffin (51), Lereboullet and Baize (50), Krause (46, 47), Krause and Willis (49) and Koch (43). Koch (43) also recorded an unusually severe case of rubella in which a positive tuberculin reaction became negative at the time of the rash.

Bloomfield and Mateer (6) report depression of sensitivity in diphtheria, typhoid and influenza, and Krause (46, 47) and Krause and Willis (48) agree with their findings in influenza while Baldwin (3) mentions the occurrence of such depression in typhoid fever.

Loss of some degree of skin reactivity has been found both in pneumonia and whooping cough by Nobécourt and Forgeron (64). Similar findings were met with by Rolly (76) and are referred to by Baldwin (3) in connection/
connection with scarlet fever, and Burhans (9) suggests that depression of tuberculin skin sensitivity may occur in all acute infections.

Lelong (22) considers that loss of skin sensitivity to tuberculin occurs in cases of secondary syphilis.

Fever. Fever, irrespective of the underlying cause, is believed to give rise to diminished skin reactions by Krause (46) and Smith (81).

Anaemia. A similar desensitising influence is said to be associated with anaemia, and Krause (47) has described the case of a severely anaemic child who reacted strongly to tuberculin following blood transfusion although negative to all earlier skin tests.

Depression of normal bodily activity. A number of workers refer to the depression of skin sensitivity in individuals in a debilitated state or suffering from malnutrition. Rominger (78) and Krause (47) are among those who attach importance to the observation. Krause (47) also considers that fatigue probably tends to diminish skin reactivity and Burhans (9) suggests that dehydration and circulatory failure may be influencing factors. On the other hand, Andrus (1) maintains that well marked reactions are more common in undernourished than well nourished individuals. It is of interest to note that in so far as debility is a not uncommon accompaniment of advancing/
advancing years, Heimbeck (34) finds that sensitivity lessens with old age. Attention has been drawn by Krause (47) to the importance of the depression of physiological function underlying these various conditions, and he predicts that investigations will show that modification of the tuberculin reaction follows such depression. In this connection there is significance in the statement of Balint and Weiss (4) that a change in the acid–base equilibrium exerts a considerable influence on the intensity of the tuberculin skin reaction. They find that sensitivity is increased or decreased according as the reaction of the blood is displaced to the acid or the alkaline side. It is recognised that changes occur in the acid–base equilibrium of the body during the terminal stages of most fatal conditions and particularly those associated with fever, but the exact nature of the changes has not been definitely established. Dautrebranche and Davies (18) however, found a definite increase in the alkali reserve in all of seven cases of extensive pulmonary tuberculosis. No such increase was found by Meakins and Davies (62) in pulmonary tuberculosis where the lesions were localised.

**Physiological events in the female life.**

Loss of skin sensitivity has been found to occur during pregnancy by Nobécourt and Paraf (65), Krause (47, 49) and Krause and Willis (48). Similar results were/
were obtained by Krause and Willis in animal experiments (48). Coulaud (11), and more recently Thrap-Meyer (84) noted temporary loss of skin reactivity during the menstrual period in women.

Anaesthesia. Loss of power of the skin to react to tuberculin is said by Decressac and Jacquelin (19) to follow anaesthesia. They consider this occurs after all forms of anaesthesia but more frequently following the use of ether than chloroform. Tuberculin sensitivity was found to be lost in forty per cent of cases given ether and twenty-six per cent of cases given a regional anaesthetic.

The Severity of the tuberculous infection. Failures of skin reactions in clinically tuberculous individuals have been reported as occurring almost exclusively in what have been described as cases of "massive" or "overwhelming" tuberculosis, and Kolmer (44) mentions the "cachexia" skin reaction of terminal miliary tuberculosis in which a faint discolouration of the tested area is unaccompanied by any papular eruption. In this connection loss of skin reactivity has been emphasised as occurring in miliary tuberculosis by Mantoux (59), Happ and Casparis (30), Hart (31), Dickey (20), Wahl and Gerstenberger (87) and Sutherland (83); in advanced adult tuberculosis by Cummins (18); in tuberculous meningitis by Happ and Casparis (30), Dickey (20), Sutherland (83) and Brown/
Brown (8); in cachetic and moribund cases, and cases tested within a week of death by von Pirquet (75), Krause (46), Sutherland (83), Dickey (20), Brown (8) and Hart (31). Kolmer (44) also finds that tuberculous infection of serous membranes is associated with a certain degree of unreliability of tuberculin skin tests. Burhans (9) considers that weak reactions are common in cases of overwhelming tuberculous infection and, as already mentioned, suggests that they are the result of the dehydration and circulatory failure present in these individuals.

Many attempts have been made to determine a relationship between the intensity of the skin reaction, apart from complete failure to react, and the severity of the underlying infection. Topley and Wilson (85), using the term "secondary reaction" to indicate one which is either slow in developing or occurs only after a second inoculation, and the term "primary reaction" to indicate one developing within forty-eight hours of a first inoculation, attribute a special significance to these two types. They are of the opinion that the secondary reaction points to a healing old lesion and, that the primary reaction is found in cases recently infected but not necessarily active. Secondary reactions have also been met with by Heimbeck (35), Bass (5) and Ström (82). Ellermann and Erlandsen (23) consider that a secondary reaction results/
results from an increase in existing sensitivity following the deposit of tuberculin in the tissues associated with previous negative tests. On the other hand Smith (81) is of the opinion that secondary reactions are to be explained by errors in technique having given rise to falsely negative results at the time of the first skin test.

Cases labelled as "latent" were found by Dickey (20) to give reactions averaging slightly less in size than the general average, but he does not consider that the size of the reaction provides a reliable measure of the activity of the infection. Cummins (16) observes that the incidence of clinically recognisable tuberculosis in adults is greatest in those with low or negative tuberculin sensitivity. Austrian (2), studying variations in skin reactivity, was unable to establish a relationship between the intensity of the reaction and what he calls the "clinical status" of the children tested. Referring to European adults, Cummins (16) states that a strongly positive reaction does not point to activity, and King (40) considers that tuberculin tests in general are worthless as indicators of activity in existing tuberculous lesions. Ustvedt (86), after a series of tests on infected adults, concluded that no information concerning the nature of a tuberculous process/
process was to be obtained from the size of the skin reaction. On the other hand Holmes (38) believes hypersensitivity is related to the activity of the infection as well as to the patient's response, although he also states that an increase in skin test response never precedes an exacerbation but merely confirms it.

Stimulated by Römer's (77) animal, experimental studies which suggested that a parallelism existed between the severity of infection and the degree of reaction, Holmes (38) pursued a similar line of investigation in sanatorium patients but failed to determine any connection between the amount of pulmonary involvement and the degree of sensitivity. On the other hand, Willis (88) not only concludes from the results of experiments with guinea-pigs that cutaneous reactivity varies with the extent and intensity of tuberculous infection, but considers that a similar relationship exists in human beings. According to Andrus (1) severe skin reactions occur in early tuberculous cases, while diminished sensitivity is met with in advanced lesions. Reference to Römer's work is also made by Kolmer (44) who argues that no fixed relationship exists between the severity of the infection and the intensity of the skin reaction in man, although in general, marked skin reactivity is associated with severe infection.

The/
The course of the tuberculous infection. Austrian (2), as the result of his observations on variations in skin reactions over long periods, concludes that these variations virtually mirror the progress - stabilisation or retrogression - of the tuberculous infection and this view has the support of Holmes (38) and Baldwin (3). Hamburger (29) advanced the theory that in the event of tuberculous infection becoming extinct the intensity of the skin reaction diminishes. Wolff and Stone (89) maintain that tuberculous infection may become extinct and that tuberculin sensitivity disappears with it. In support of this, they record cases in which the existence of calcified tracheo-bronchial glands was demonstrated by X-rays but in which tuberculin tests were negative.

At the present time however, there is an increasing belief that complete loss of tuberculin skin sensitivity never occurs and that, as Bass (5) among others states, failures of tests are due to insufficient tuberculin being introduced into the tissues of the test area. It was shewn by Engel (24) that the accuracy of the Mantoux test was increased if negative results were not accepted until increasingly higher concentrations of tuberculin had been employed. Happ and Casparis (30) established the truth of Engel's work and further demonstrated that every tuberculous person, irrespective of the clinical nature of the disease, gives a positive skin reaction if sufficient/
sufficient tuberculin is used. Experimenting with animals Willis (88) concluded that once tuberculin sensitivity has been established, and as long as the basis - "the anatomic tubercle" - remains, skin response persists. Willis considers that such terms as "disappearance" and "inhibition" applied to tuberculin skin reactivity have only a relative significance.

Austrian (2), observing tuberculin sensitivity in children over a period of twelve years, found that no individual entirely lost his power to react to the Mantoux test, although several previously positive were negative with the cutaneous method. Austrian is of the opinion that the discrepancy in results was due to the greater quantity of tuberculin injected using the Mantoux test and that complete loss of tuberculin skin response never occurs. Similar conclusions have been arrived at independently by Krause (46, 49), King (40) and Hart (31). Lloyd and MacPherson (52) found ninety-six per cent of positive reactors still positive after eighteen months interval.

**Particular forms of tuberculous disease.**

The occurrence of heightened skin sensitivity in particular clinical forms of tuberculous infection has been recorded. Hart (31) notes this in quiescent tuberculosis with bone and joint manifestations, and Dickey (20) has made similar observations but also records the occurrence of reactions above the average size/
size in cases of phlyctenular conjunctivitis and lymph node infection. McNeil (57) notes that severe tuberculin reactions are met with in cases of scrofula associated with the condition status lymphaticus. In Dickey's series (20) cases with hilar disease did not present marked skin reactions.

**History of contact with infection.** Dickey (20) finds that children with a history of contact with infection give skin reactions exceeding the average in size. Lloyd and MacPherson (52) also believe that tuberculin sensitivity is more marked in contact than non-contact children.

**The value of tuberculin tests in prognosis.** Other workers have studied the problem of tuberculin skin sensitivity in its relation to prognosis. Lobban (53) considers that increasing tuberculin sensitivity is a good prognostic sign, and that lessening response to skin tests occurs in tuberculous patients on the decline. From the prognostic point of view Gelien and Hamman (26) prefer low grade to high grade sensitivity in early, moderately advanced cases of pulmonary tuberculosis. They also emphasise that a high level of sensitivity rebellious to tuberculin treatment is of particularly unfavourable prognostic import.

Burhans (9) draws attention to the fact that there are so many unknown factors involved in tuberculin/
tuberculin skin reactivity that it is unsafe to base any prognosis upon the intensity of the reaction. Among recent workers Marman (60) attaches no prognostic value to the Pirquet test, and Hart (31) considers that estimations of the degree of response to quantitative Mantoux tests are of little prognostic value. In this connection Gelien and Hamman (26) find that the severity of the skin reaction in persons dying from tuberculosis gives no indication as to the probable duration of life, reactors and non-reactors occurring irrespective of the length of life after testing. Holmes (38) considers that a reaction which decreases in size points to subsidence of the tuberculous infection.

Basing their deductions on the results of tuberculin tests carried out on children, Opie and McPhedran (67) and Opie (66) state that the severer the tuberculin skin response, the greater is the likelihood of the infection becoming manifest and taking a grave form. Cummins and Evans (17) are also of the opinion that pronounced cutaneous sensitivity is associated with liability to severe tuberculosis.

The time at which initial tuberculin skin sensitivity is acquired. Reference has already been made to the large amount of work devoted to the study of variations in the intensity of tuberculin skin reactions, but of paramount importance in this connection/
connection according to Philip (69. 70), is the determination of the time in an individual's life at which sensitivity is first acquired. Philip advocates the routine periodic application of tuberculin skin tests in children until such a time as a positive reaction is recorded. In this way he argues, the presence of tuberculous infection is established in its initial stage even in the absence of clinical signs or symptoms. By detecting the time of first infection he points out that a more exact interpretation is possible of many of the vague yet worrying disturbances in the life history of the child. "The finger prints of tuberculous toxaemia"(21) are thus anticipated. Recognition of these is less easy at a later date, as is shewn by Heckscher's work. Using recruits in the Danish army as material, Heckscher (32. 33) failed to correlate the subsequent sickness records of these men with changes in the skin response to tuberculin noted during the earlier days of military service. On the other hand, support of Philip's contention regarding the importance of routine tuberculin testing in the anticipation and prevention of clinically manifest disease, is to be found in Heimbeck's investigations (36). Probationers who were commencing their training in Oslo Municipal Hospital, and who were exposed to daily contact with tuberculous patients, were tuberculin tested at the commencement and/
and termination of their three years course. Of the four hundred and fifty-four positive reactors 2.6 per cent developed clinical tuberculosis as compared with 29.6 per cent of the two hundred and fifty-three originally negative reactors. In addition a number of non-reactors were vaccinated, and of the eighty-eight who subsequently gave positive reactions only one developed manifest signs of infection, whereas sixteen became clinically tuberculous of the sixty whose reaction remained negative despite vaccination.
PART II.

NATURE OF PRESENT INVESTIGATION.
# PART 2.

## THE NATURE OF THE PRESENT INVESTIGATION.

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The nature of the investigation.</td>
<td>18</td>
</tr>
<tr>
<td>2. The clinical material.</td>
<td>19</td>
</tr>
<tr>
<td>3. The technique.</td>
<td>21</td>
</tr>
<tr>
<td>4. The method of recording observations.</td>
<td>23</td>
</tr>
<tr>
<td>5. Definition of terms employed.</td>
<td>25</td>
</tr>
</tbody>
</table>
PART 2.

THE NATURE OF THE PRESENT INVESTIGATION.

In the investigation forming this thesis the tuberculin skin test was carried out on two thousand four hundred and forty seven individuals. Of these two thousand and nine consisted of unselected cases and the positive and negative reactors were recorded in their various age groups. To the one thousand four hundred and fifty-eight positive reactors two hundred and eleven further selected cases were added. Of these one thousand six hundred and fifty eight individuals with positive tuberculin skin reactions, detailed records were kept of the clinical histories, findings on examination, diagnostic investigations carried out, and of progress as well as of the nature of the tuberculin reaction, in nine hundred and sixty-two. These cases were divided into two main groups:

(1.) Cases clinically non-tuberculous.
(2.) Cases clinically tuberculous.

The type of tuberculin reaction was studied in relation to:

(1.) Age.
(2.) Sex.
(3.) Season of the year.
(4.) Condition of the skin.
(5.) Disease of the vessels.
(6.)/
(6.) Blood pressure and pulse volume.
(7.) Prolonged confinement to bed.
(8.) Anaemia.
(9.) Malnutrition.
(10.) Different clinical conditions.
(11.) Infection in general.
(12.) Specific infectious diseases.
(13.) Fever.
(14.) Physiological events in the female life.
(15.) Anaesthesia.
(16.) A history of household contact.
(17.) Fatal forms of tuberculous infection.
(18.) Different clinical forms of tuberculous infection.

Clinical material.

The investigation involved the study of individuals varying in age from a few weeks to ninety-four years. Included among them were a number of healthy individuals, but the great majority were suffering from one of many varied diseases or complaints. Cases in which the presence of tuberculous infection was proved by bacteriological, histological or radiological methods were considered separately. The sources and nature of the material drawn from were as follows:

(A.)/
(A.) Edinburgh.

1. Royal Hospital for Sick Children.
   a. Children in the medical and surgical wards.
   b. Children attending the medical outpatient department.
   c. Parents and other relatives of a few of the cases in the medical wards.

2. Western General Municipal Hospital.
   a. Inmates of the wards of the children's unit, including healthy Poor Law admissions.
   b. Parents and other relatives of a few of the children in the wards.

3. A few individuals of the hospital class, patients of general practitioners.

(B.) Bradford (Yorks.)

   a. Inmates of the children's wards:
      these included acute and chronic, medical and surgical conditions, with in addition a number of healthy Poor Law admissions.
   b. Patients in the general medical and surgical wards (male and female);
      these included all types of acute and chronic medical cases as well as a large number of Poor Law admissions.
21.

c. Women in the maternity wards.
d. Men in the "Casual Ward", admitted at the end of the week and under observation for forty-eight hours.
e. Inmates of the male and female "Tuberculosis Wards".
f. Other members of the households of certain hospital admissions.

2. Hospital for Sick Children.
a. Children in the medical and surgical wards.

3. City Hospital for Infectious Diseases.
a. Children and adults of both sexes suffering from all types of infectious disease.

4. A few individuals of the hospital class, patients of general practitioners.

The Technique.

The multiple puncture test previously described by us (13) was used as being the method most suited to an extensive investigation involving the routine testing of a large number of individuals. Prolonged experience with the method convinced us of its reliability (14). Further recommendations in its favour were, that it caused the minimum amount of trauma (12), and involving a test area constant in form/
form and dimensions gave rise to a symmetrical reaction (circular) where skin sensitivity was present.

Throughout the investigation one instrument was used, and after each fifty tests the needles were examined to ensure that there had been no displacement of their points. Undiluted Old Tuberculins (P.D. & Co.) was used throughout.

Tests were noted as positive or negative forty-eight to ninety-six hours after their application and cases not reacting were examined at regular intervals for a further six days. In the case of positive reactions, estimations were then made in connection with the intensity of the reaction. These estimations were based upon the following:

(1.) The size of the diameter of the reacting area. Where the customary nodular eruption was bounded by a sharply demarcated peripheral zone of erythema the diameter was taken to include this erythematous portion. The base of the actual nodule was invariably circular, but where an associated erythematous zone was not symmetrical the measurement taken was the diameter of the largest circle contained by the outer margin of the erythema.

(2) The intensity of the hyperaemia of the reaction. It was not found possible to evolve a scheme whereby reactions could be matched with control shades, but by/
by noting only the extremes, a violently angry or markedly pale colour, as plus or minus respectively and by considering all intermediate degrees as "normal", the more gross variations in colour were recorded with reasonable accuracy.

(3.) The degree of the nodularity of the reaction. Here as with hyperaemia, only the extremes of variation were considered as abnormal. The pad of the right middle finger was drawn lightly across the skin test area, first in the long axis of the subject's arm and afterwards at right angles to it. Reactions which in this way could only be appreciated as slight, gentle elevations were considered as showing diminished nodularity. On the other hand, increased nodularity was considered as being a characteristic when the reaction was felt as a marked prominence with abrupt margins.

The method of recording observations.

All observations are given in tabular and graphic form, and where percentages have been determined these are similarly recorded. In the tables percentages are shewn in red.

A constant method has been employed in connection with the diagrams for the various clinical series studied. Each square millimetre represents a positively reacting individual and, its distance from the left hand margin as measured by the millimetre scale along/
along the base gives the size of the diameter of the reaction in the particular individual. Red verticals are drawn in a number of the diagrams and these enclose the normal range of size as determined in Section 1.

Red verticals are employed also in diagrams showing the percentage incidence of reactions in relation to the normal range of size: the percentage indicated between the red verticals refers to reactions within the normal range, those to the left and right, to reactions of diminished and increased size respectively.

All graphs are based upon observations made in individuals in whom the colour, nodularity and size of the reactions showed proportionate parallel variations. Thus, the size of the diameter in relation to normal in these cases indicates any general tendency in the intensity of an individual reaction towards increase or diminution. The observations are therefore expressed in terms of size.

Although actual measurements form the basis of a large part of this thesis, these have only an absolute significance in connection with the present investigation as they are dependent upon the size of instrument employed. The relative values of these measurements however, allow of conclusions being arrived at which have a general application.
Definition of terms employed.

(1.) The terms "test" and "tuberculin test", unless otherwise stated, imply that the method referred to is the multiple puncture tuberculin skin test.

(2.) A "positive tuberculin skin reaction" indicates the local response appearing in the region of the skin test. The term does not include reactions occurring immediately after application of the test, or reactions not persisting more than forty-eight hours. "Positive reaction" and "skin reaction" are terms used synonymously.

(3.) A "reactor" is an individual giving a positive tuberculin skin reaction.

(4.) A "non-reactor" is an individual showing no skin response to tuberculin.

(5.) "Sensitivity", "tuberculin sensitivity" and "skin sensitivity" are terms used to indicate the occurrence of a positive response to tuberculin tests.

(6.) The term "tuberculous infection" applied to an individual indicates the presence of the tubercle bacillus in that individual, irrespective of whether the organism can be demonstrated or whether the site of infection can be localised.

(7.) The term "clinically tuberculous" is applied to individuals in whom the presence of tuberculous/

*(False reactions were previously shewn not to be given rise to by the glycerine and phenol contained in the preparation of Old Tuberculin employed. (13))*
tuberculous infection has been demonstrated by bacteriological, histological or radiological methods.

(8.) The term "clinically non-tuberculous" is applied to individuals in whom the sole evidence of tuberculous infection is the presence of a positive tuberculin skin reaction.

(9.) The term "size of reaction" refers to the area of skin involved by the reaction. The reaction being circular, its diameter is a function of the area and therefore a large diameter indicates a large area of reaction and a small diameter a small area of reaction. "Diameter" and "size of reaction" (with reference to surface area) are used as synonymous terms throughout.

(10.) "The normal range of size of diameter". This has been determined for each age period (Section 1). Terms used synonymously are "normal range" and "limits of normal".

(11.) A "large reaction (diameter)" is one whose diameter falls outside the maximum limit of "normal range". Other terms used in the same sense are "increased sensitivity", "marked reaction", "increased reaction (diameter)", "reaction (diameter) above the average size" and "reaction (diameter) above the normal range".

A "normal reaction (diameter)" is one in which the diameter falls within the limits of "normal range", and/
and is also referred to as a "reaction (diameter) of average size".

A "small reaction (diameter)" is one whose diameter falls below the lower limit of normal. "Diminished sensitivity", "diminished reaction (diameter)", "reaction (diameter) below the average size", and "reaction (diameter) below normal" are used synonymously.

(12) The term "desensitising factor" is applied to bodily conditions which are associated with diminution in the intensity of the tuberculin skin reaction. Where cases have been excluded from certain tables on account of the presence of more than one such "desensitising factor", "correction" of the tables is said to have been carried out.
PART III.

RECORD OF OBSERVATIONS.
PART 3.

RECORD OF OBSERVATIONS.

Contents.

GROUP (A.) Clinically non-tuberculous individuals.

Section 1. The type of the reaction in relation to age.

Section 2. The type of the reaction in relation to sex.

Section 3. The type of the reaction in relation to the season of the year.

Section 4. The type of the reaction in relation to the condition of the skin.

Section 5. The type of the reaction in relation to disease of the vessels.

Series 6. The type of the reaction in relation to blood pressure and pulse volume.

Section 7. The type of the reaction in relation to prolonged confinement to bed.

Section 8. The type of the reaction in relation to anaemia.

Section 9. The type of the reaction in relation to malnutrition.

Section 10. The type of the reaction in relation to certain clinical groups:

a. Anaemia.

b. Malnutrition.

c. Syphilis.

d. Cardiac insufficiency.

e./
e. Malignancy.
f. Influenza.
g. Cerebral damage of vascular origin.
h. Diseases of the central nervous system.
i. Asthma.
j. Endocrine dysfunction.
k. Alimentary infection.
l. Chronic urinary infection.
m. Rheumatism.

Section 11. The type of the reaction in relation to respiratory disease.

Section 12. The type of the reaction in relation to infection.

Section 13. The type of the reaction in relation to certain specific infectious diseases.

Section 14. The type of the reaction in relation to fever.

Section 15. The type of the reaction in relation to physiological events in the female life.

Section 16. The type of the reaction in relation to anaesthesia.

Section 17. The type of the reaction in relation to a history of household contact.

Section 18. Reactions in which colour and/or nodularity and/or size varied disproportionately.

Section 19. Negative reactions occurring in clinically non-tuberculous adults.
GROUP (B.) Clinically tuberculous individuals.

Section 20. Details concerning the clinically tuberculous individuals of the series.

Section 21. The type of the reaction in relation to prominent features in the patient's general condition.

Section 22. The type of the reaction in fatal cases.

Section 23. The type of the reaction in relation to different clinical forms of tuberculous infection.

Section 24. A comparative study of the type of reaction in clinically tuberculous and clinically non-tuberculous individuals.

Section 25. The type of the reaction in relation to the season of the year.

Section 26. The type of the reaction in relation to anaesthesia.

Section 27. Reactions in which colour and/or nodularity and/or size varied disproportionately.

Section 28. Negative reactions occurring in clinically tuberculous individuals.

Section 29./
Section 29. Reactions above the average size in clinically non-tuberculous subjects who later became clinically tuberculous.
PART 3.
RECORD OF OBSERVATIONS.

(A.) Clinically Non-tuberculous Individuals.

Section 1. THE TYPE OF THE REACTION IN RELATION TO AGE.

In determining whether age in any way influenced the tuberculin skin reaction it was necessary to make certain that misleading results were not obtained on account of the presence of other modifying factors. A careful selection of material was indicated, and in the group studied there were only included individuals who although showing skin sensitivity to tuberculin were in apparently excellent health. All these individuals were leading an active life in keeping with their age, complained of no symptoms, had not been recently exposed to any known tuberculous infection and on examination showed no evidence of any disease, tuberculous or otherwise.

Table 1 represents the results of tuberculin skin tests carried out in the series of unselected cases of all ages. Almost one hundred per cent (99.7%) of individuals over the age of twenty-five years were positive reactors. A further point not brought out in the table was the great variation in intensity of the reaction met with during the period of late adolescence and early manhood. In addition, reactions of maximum intensity were most common during/
during these periods. These findings were taken into account in considering the effect of age, and the following age groups were decided upon:

(i) Birth to five years ... the period during which a positive reaction is generally accepted as being of vital significance (31).
(ii) Five to twelve years ... the period of late childhood.
(iii) Twelve to twenty years ... the period of adolescence.
(iv) Twenty to twenty-five years ... the period of young adult life.
(v) Twenty-five to fifty-five years ... the period of active adult life during which tuberculin sensitivity is almost universal.
(vi) Fifty-five years and over ... the period during which at any time the effects of old age may appear, tuberculin sensitivity still being almost universal.

From diagram 1 it is seen that for each of the age groups five to twelve years and fifty-five years and upwards, the sizes of all the diameters fell within a definite range indicated by the red verticals. In the case of each of the age groups from birth to five/
five years and twelve to twenty years, only one result fell outside the range indicated by the red verticals. All the diameters with the exception of two for the age period twenty-five to fifty-five years came within the range between the verticals, and these two represented only five per cent of the total.

Consideration of the age groups from birth to five years, five to twelve years, twelve to twenty years, twenty-five to fifty-five years and over therefore, shows that for each of them there existed an approximate range of size within which the majority of the diameters (never less than 95%) fell (Table 2 and Diagram 2).

Basing the estimate on the fact that eighty-five per cent of the diameters measured between twenty-seven and forty-two millimetres (inclusive) in the age group twenty to twenty-five years, an arbitrary "normal range" of twenty-five to fifty millimetres was decided upon, simultaneous allowance thus being made for the tendency noted above for great variations, and for large reactions to occur. The arithmetical mean of all diameters obtained for this particular age group falls almost in the centre of the range and points to the accuracy of the estimated range.

Diagrams 1 and 2 and the figures in table 2 show that the ranges enclosed within the red verticals represent the true normal for each age group. The "normal/
"normal ranges" for the last two age periods were the same, and the difference between those for the periods from birth to five years and five to twelve years was sufficiently small to be negligible for practical purposes. In table 3 the children under twelve years of age have been considered as a single group, and adults over twenty-five years as another, and the ranges enclosed between the verticals are again seen to be representative of normal for these larger groups of individuals. This is shown graphically in diagrams 3 and 4. Diagram 5 gives the curves of arithmetical mean diameters for all ages of the series.

Section 2. THE TYPE OF THE REACTION IN RELATION TO SEX.

In a study of the variations occurring in the type of skin reaction it was important to determine the presence or absence of any influence attributable to the sex of the individual. With a view to investigating the question individuals were drawn from the following two groups:

(A.) those studied in Section 1 in connection with the factor of age. As already indicated these individuals all had in common excellent health and tuberculin skin sensitivity, and they differed only in the matter of their sex.

(B.) medical and surgical hospital patients other than those with recognisable evidence of tuberculous/
tuberculous infection. Correction of this group was afterwards carried out by eliminating cases of prolonged confinement to bed, anaemia, malnutrition, cardiac insufficiency and syphilis (See Sections 7, 8, 9, 10, 38, 39, 40 and 41). Menstruating women were not included.

The observations in connection with the males and females of group A are shewn in diagrams 6, 7 and 8 and those of group B in diagrams 9, 10 and 11. Table 4 gives the observations in tabular form.

Section 3. THE TYPE OF THE REACTION IN RELATION TO THE SEASON OF THE YEAR.

The fact that seasonal variations in the type of tuberculin reactions have been reported and that cases in the present investigation were tested during all periods of the year demanded the study of the question.

Note was made of the dates when tuberculin tests were carried out. Cases among children under twelve years of age were tested during all seasons of the year but the majority of the tests on older individuals were carried out between the months of October and March (inclusive). The following are the groups into which the material was divided:

A. Children (Birth to twelve years).

Spring ..... March, April and May.
Summer ..... June, July and August.
Autumn ..... September, October and November.
Winter ..... December, January and February.
B. Individuals twenty-five years of age and over.

Winter and early spring ... December, January, February and March.

Late spring, summer and autumn ... May to November (inclusive).

The observations made in connection with children are given in diagrams 12 and 13 and table 5, and in connection with adults after correction for confinement to bed, anaemia, malnutrition, cardiac insufficiency and syphilis (See Sections 7, 8, 9, 10, 38, 39, 40 and 41) in diagrams 14, 15 and 16 and table 6.

Section 4. THE TYPE OF THE REACTION IN RELATION TO THE CONDITION OF THE SKIN.

Consideration of a test involving the deposit of tuberculin in the deeper layers of the skin and underlying tissues raised the question as to whether the condition of the skin did not in some measure determine the degree of local reaction obtained.

In all cases the nature of the skin was noted, particular attention being paid to dryness and lack of elasticity. Although assessment of these properties could only be based upon individual observations, a constant standard of comparison was obtained as all observations were made personally by the writer. Details regarding the nature of the skin as a whole were found to apply equally well to the condition of the skin at the site of test area. By classifying as/
as unhealthy only those skins possessing grossly abnormal properties, the danger was avoided of a single observer's standard being too exacting. Cases with severe anaemia, malnutrition, cardiac insufficiency, a positive Wassermann reaction or which had been long confined to bed were excluded (see Sections 7, 8, 9, 10, 38, 39, 40 and 41).

Skins considered to be wholly inelastic and of exceptional dryness all occurred in those over sixty-five years of age. A noteworthy fact was that all the individuals included in the group of unhealthy skins were suffering from one of the chronic ailments of old age (bronchitis, cerebral anaemia, arteriosclerosis etc.). To determine the effect of the skin factor upon the tuberculin reaction a control group was taken of unselected cases of over sixty-five years of age with healthy skins but suffering from some such chronic ailment.

The observations made are given in table 7 and are shewn graphically in diagrams 17 and 18.

Section 5. THE TYPE OF THE REACTION IN RELATION TO DISEASE OF THE VESSELS.

The fact that the tuberculin skin reaction shows among other characteristics local hyperaemia implies local changes in the state of the vascular supply to the tissues involved. It was necessary to determine therefore whether reactions were subject to modifying/
modifying influences arising from disease of the vessels.

In order to study this, attention was directed to what were considered to be cases of senile arteriosclerosis. Individuals with positive Wassermann reactions, arterial hypertension or chronic renal damage were not included in the group, and in addition patients showing anaemia or under-nourishment or who were bed-ridden were not considered (See Sections 7, 8, 9, 10, 38, 39, 40 and 41). It was noted that even in the absence of any clinical feature other than that of sclerosis of the vessels, many of these cases were characterised by a general debility disproportionate with their age. As this could not be directly related to the condition of the vessels a further correction was made by eliminating cases showing marked general debility.

The observations made in this group of arteriosclerotic cases, and the effect of correction for debility are given in diagrams 19 and 20 and in table 8.

Section 6. THE TYPE OF THE REACTION IN RELATION TO BLOOD PRESSURE AND PULSE VOLUME.

Being dependent upon cardio-vascular and bodily function, blood pressure was considered as possibly exerting some influence upon the hyperaemic manifestations of the tuberculin skin reaction.
Blood pressure readings were carried out as a routine measure on adolescents and adults admitted to hospital. The diameters of tuberculin reactions obtained have been plotted against the corresponding systolic and diastolic blood pressures in diagrams 21 and 22 and against the corresponding pulse volume in diagram 23.

Table 9 gives the observations made among adults in relation to both lowered and raised blood pressure.

Section 7. THE TYPE OF THE REACTION IN RELATION TO PROLONGED CONFINEMENT TO BED.

The hyperaemia associated with a positive tuberculin reaction indicates the occurrence of local vascular changes and where, as in patients confined to bed over long periods, the absence of normal physical and physiological activity involves alteration both in the distribution and circulation of the blood, it was considered that tuberculin skin sensitivity might be subject to modification.

Patients included in the group studied had all been confined to bed for a minimum period of two months and their physical limitations were such as to require constant skilled nursing. The older individuals were mainly cases of cerebral haemorrhage, those below fifty years of age individuals suffering from disseminated sclerosis, encephalitis lethargica or rheumatoid arthritis. Cases were excluded with a positive/
positive Wassermann reaction, bronchitis or any chronic infective malady as well as those showing anaemia, malnutrition or cardiac insufficiency (See Sections 7, 8, 9, 10, 38, 39, 40 and 41). Two months was the minimum period that any one patient had been confined to bed but in the majority of cases it had been considerably longer.

The observations made in different age-groups are given in diagram 24 and table 10, and the percentage incidence of reactions in relation to the normal range for the entire series of bedridden cases in table 10 and diagram 25.

Section 8. THE TYPE OF THE REACTION IN RELATION TO ANAEMIA.

Marked diminution in the intensity of reactions was a noteworthy feature in many cases of anaemia and the question of the relationship between the type of tuberculin reaction and the condition of the blood was studied along the following lines:

(i) Cases falling within the age period twenty-five to fifty years with a blood count below three million red cells were selected. The sizes of the reactions in these cases are given in diagram 26 and their percentage relationship to the normal range in table 11 and diagram 27.

(ii) The size of the skin reaction and the red cell blood count at the time of tuberculin testing were/
were recorded in a number of individuals. These have been plotted against one another in diagram 28 and include cases of primary and secondary anaemia as well as a few cases in which the blood showed no abnormalities. Table 12 gives the observations in connection with this group.

(iii) Four severe cases of pernicious anaemia were selected and red cell blood counts and tuberculin skin tests were carried out simultaneously, at the time of admission and at intervals during the course of successful treatment. In each of the cases the condition was of sufficient severity to call for the administration of intravenous liver therapy.

The observations made in this series are given in table 13. The curves in diagram 29 were obtained by plotting the diameter of the reaction against the corresponding red cell blood count at various stages of the illness in each individual.

(iv) Three cases of carcinoma beyond operative aid which were under observation during the last six weeks of life (three months in one case) were subjected to simultaneous tuberculin testing and blood examination at intervals during their time in hospital. The final diagnoses (See table 14) in these cases were based upon autopsy findings.

Observations are recorded in the same manner as in the group of primary anaemias and are given in table 14 and diagram 30.
With the exception of the case of pancreatic carcinoma included in table 14 all the cases studied were under fifty years of age. Cases showing gross malnutrition (except those in table 14 in their later stages), those with cardiac insufficiency and those with positive Wassermann reactions were not studied in connection with anaemia (See Sections 9, 10, 40 and 41).

Section 9. THE TYPE OF REACTION IN RELATION TO MALNUTRITION.

The occurrence of diminished skin reactions in poorly nourished individuals and the contradictory findings of other workers in this connection pointed to the need for consideration of the question of nutrition.

The cases chosen for study were drawn mainly from Poor Law patients and hospital admissions of the Casual type. In each instance a careful examination was carried out to exclude the presence of any conditions other than weakness and emaciation. Two examples of scurvy were included. Although cases of primary and pronounced secondary anaemia were excluded, owing to the frequent co-existence of some degree of anaemia with malnutrition it was not possible wholly to dissociate the two factors. However, in all those in the series, malnutrition was the pre-dominant/
predominant feature in the individual's clinical condition.

A control group was formed of individuals of the same age period selected solely on account of their general good health and well nourished state.

The observations made in connection with these two groups are given in diagrams 31 and 32 and in table 15. Table 16 shows the alteration in size of the reaction noted in certain of the cases between the times of admission and discharge.

Section 10. THE TYPE OF REACTION IN RELATION TO CERTAIN CLINICAL GROUPS.

As it was thought that certain clinical conditions might exert a modifying influence upon tuberculin skin sensitivity, all the patients between the ages of twenty-five and fifty-five years who gave a positive reaction were arranged in the following clinical groups:

(i.) Anaemia (See Section 8).

Included:—

a. Primary anaemia.

b. Severe secondary anaemia.

(ii.) Malnutrition (See Section 9).

Included:—

a. Undernourishment.

b. Scurvy.

(iii.) Syphilis.

Included all cases with positive Wassermann reactions.

(iv.)/
Respiratory diseases (See Section 11).

Included:
- a. Pneumonia (all except influenzal types.)
- b. Bronchitis (acute and chronic).
- c. Bronchiectasis.
- d. Lung abscess.

Did not include cases of pleural effusion.

Cardiac Insufficiency.

Included cases showing cardiac insufficiency associated with:
- a. Valvular disease.
- b. Myocardial weakness.
- c. Arrhythmia.
- d. Anuria.
- e. Anasarca.

Bronchitis secondary to the cardiac condition was frequently present.

Did not include cases with a positive Wassermann reaction.

Malignancy.

Included malignant conditions of all types.

Influenza.

Included only cases of a severe type with pulmonary and, in most instances gastric symptoms.

Cerebral Damage of Vascular Origin.

Included:
- a. Cerebral haemorrhage.
- b. Cerebral thrombosis.
- c. Subarachnoid haemorrhage.

Did not include cases with a positive /
positive Wassermann reaction.

(ix.) Diseases of the Central Nervous System.

              b. Poliomyelitis.
              c. Encephalitis lethargica.
              d. Subacute combined degeneration.

Did not include: -
               a. Cases with a positive Wassermann reaction.
               b. Epilepsy.

(x.) Asthma.

Included only cases of true asthma.

Did not include: - a. "Renal asthma".
               b. "Cardiac asthma".
               c. Asthmatic bronchitis.

(xi.) Endocrine Dysfunction.

               b. Hypothyroidism.
               c. Hypoglycaemia.
               d. Acromegaly.
               e. Diabetes mellitus.

(xii.) Alimentary Infection.

               b. Diverticulitis.

(xiii.) Chronic Infection of Urinary Tract.

(xiv.) Acute Rheumatism.

The observations made in cases occurring in the clinical/
clinical groups of anaemia, malnutrition, syphilis and cardiac insufficiency are given in table 17 and diagram 33, and those in connection with the remaining clinical groups (except that of Respiratory diseases) in table 18 and diagram 34. The figures and graphs dealing with anaemia and malnutrition are reproduced from tables 11 and 15, and diagrams 26 and 31.

In addition the observations for each clinical group were corrected by eliminating cases with severe anaemia, and cases which were undernourished or had been long confined to bed, or in which cardiac failure was present. The corrected observations are given in tables 17 and 18 and diagrams 35 and 36.

The percentage incidence of reactions in relation to normal range is given in tables 34 and 35 and is shewn graphically in diagrams 37 and 38.

Section 11. THE TYPE OF THE REACTION IN RELATION TO RESPIRATORY DISEASE.

The cases considered included:

(a.) Pneumonia (all types other than influenzal).
(b.) Empyema (meta-pneumonic and syn-pneumonic).
(c.) Bronchitis (acute and chronic).
(d.) Bronchiectasis.
(e.) Lung abscess.

The diameters obtained in the complete series are given in table 19 and diagram 39, and are expressed/
expressed as percentages in relation to the normal range in table 19 and diagram 40, before and after correction for anaemia, malnutrition, syphilis and prolonged confinement to bed (See Sections 7, 8, 9, 10, 38, 39, 40 and 41).

The observations made in the cases of pneumonia were further subdivided as follows into:

Cases skin tested (a.) during the pyrexial period.
(b.) after stabilisation of the temperature.
(c.) following rapid recovery.
(d.) during a prolonged course with or without complications.
(e.) with extreme physical exhaustion in convalescence.
(f.) shewing little exhaustion after the crisis or later.

Table 20 and diagram 41 deal with the above subgroups.

It was not found possible to make separate allowance for the presence of anaemia or impaired nutrition as these two factors were present in all cases in differing degree.

Section 12. THE TYPE OF THE REACTION IN RELATION TO INFECTION IN GENERAL.

The fact that acute infections have been reported as modifying tuberculin skin sensitivity raised/
raised the question as to whether the depression of the skin reaction was the result of the actual infection or of other factors associated with the severity of the illness. The influence of infection upon tuberculin skin reactions was studied by considering all the individuals included in the investigations. After excluding cases in which known modifying factors existed (e.g. anaemia, malnutrition, prolonged confinement to bed, cardiac disease and syphilis: Sections 7, 8, 9, 10, 38, 39, 40 and 41) they were divided into the following groups:

(1.) Infectious conditions ... in which a non-tuberculous infective element existed.

(2.) Non-infectious conditions ... in which there was no clinical evidence of any infective element.

(3.) Doubtful conditions ... included conditions of doubtful aetiology - this group was not considered further.

The group of Infectious conditions included:

(a.) All respiratory infections.

(b.) Coliform and other infections of the urinary tract.

(c.) Meningitis.

(d.) Rheumatism.

(e.) Malignancy with secondary infection.

(f.)/
(f.) Surgical conditions,
  e.g. (1.) infections of the hand.
  (2.) moist gangrene.
  (3.) septic burns.
  (4.) appendicitis.
  (5.) cholecystitis.

Syphilis, the exanthemata, erysipelas, paratyphoid and dysentery are considered separately elsewhere (Sections 10, 13, 18, 41, 44 and 49).

The group of Non-infectious conditions contained:—
  (a.) Asthma without an infective basis.
  (b.) Hyperthyroidism.
  (c.) Hypothyroidism.
  (d.) Hyperpiesis.
  (e.) Senility.
  (f.) Neurasthenia.
  (g.) Chronic alcoholism.
  (h.) Epilepsy.
  (i.) Paget's disease.

Group 1 was further subdivided into:—

A. Acute infections, including:—
  (a.) Pneumonia.
  (b.) Acute bronchitis.
  (c.) Meningitis.
  (d.) Severe surgical infections.

B. Chronic infections, including:—
  (a.) Chronic bronchitis.
  (b.) Bronchiectasis.
  (c.)
(c.) Chronic appendicitis.
(d.) Rectal carcinoma with infection.
(e.) Prolonged cystitis.

The diameters of the reactions occurring in the groups of acute and chronic infections, and the non-infectious group are given in diagrams 42, 43 and 44 respectively. After allowing for the variations of normal range with age the percentage of reactions falling within, below and above the normal range for these three groups are given in diagrams 45 and 46. Figures corresponding to these graphs are given in tables 21 and 22.

Section 13. THE TYPE OF THE REACTION IN RELATION TO CERTAIN SPECIFIC INFECTIOUS DISEASES.

Diminution in tuberculin skin sensitivity in measles and others of the exanthemata has been reported frequently, and although only a limited number of such conditions were available the observations made in connection with them have been recorded.

The diameters obtained in the different groups of cases are seen in diagram 47 and Table 23. Diagram 48 shows the percentage incidence of reactions in relation to the normal range for measles and for the combined group of all other specific infectious diseases.

The cases of scarlatina, measles and chicken pox were/
were all tested during the eruptive phase, those of diphtheria after some days of treatment but while still infective, and the cases of pertussis when the convalescent period had been entered but with spasmodic cough still a prominent feature. The patients suffering from paratyphoid fever were tested before and after agglutination reactions had been obtained, and the cases of erysipelas during the acute inflammatory stage.

As the possibility of complete loss of tuberculin skin sensitivity had to be considered twenty cases of measles, ten each of scarlatina and diphtheria, and five each of chickenpox and whooping cough, all of which had failed to react to a first test were again tuberculin tested some weeks later. In every case a negative response to the second test was obtained.

Section 14. THE TYPE OF REACTION IN RELATION TO FEVER.

Loss of the power of the skin to react to tuberculin has been reported in cases with pyrexia but other factors known to modify the tuberculin skin reaction are present in a high percentage of cases with fever. It was considered possible therefore, that alteration in the skin sensitivity of the cases reported was not necessarily attributable to fever.

In order to study the question, cases were chosen in which a temperature of a hundred degrees Fahrenheit or more was recorded on two occasions on the day of tuberculin/
tuberculin testing, and on each succeeding day until the nature of the reaction was finally noted. Cases were selected from among those suffering from pneumonia, acute rheumatism, pyelitis, mastoiditis and septic surgical conditions. The sizes of the reactions obtained are indicated in table 24 and diagram 49. These observations modified by exclusion of anaemic and undernourished cases are given in the same table and in diagram 50, and the percentage incidence of reactions in relation to normal in the corrected and uncorrected groups, in diagram 51.

Section 15. THE TYPE OF REACTION IN RELATION TO PHYSIOLOGICAL EVENTS IN THE FEMALE LIFE.

Pregnancy, parturition, lactation and menstruation were studied as they all involve some temporary alterations in the distribution of the blood throughout the body and are associated with a varying amount of increased physical strain. It was considered that such fluctuations in bodily function might exert a modifying influence upon the tuberculin skin reaction.

The women selected for the series were physically robust and, as judged by clinical examination, in good health. Pregnant cases embraced all periods of gestation from seven months to term, women tested during the forty-eight hours succeeding delivery were considered as evidencing the effect of the immediate strain/
strain of parturition, while the examples of lactating mothers were all tested after there had been a free flow of milk for a minimum period of five days. Menstruating women were tuberculin tested on the third day of the menstrual flow.

The diameters of the reactions obtained in this group are given in diagram 52 and their relation to normal range in table 25. Diagram 53 shows the percentage incidence of the reactions of the combined group in relation to the normal range.

Table 26 gives the size of skin reactions obtained in the left arm of menstruating women and the reactions obtained in the opposite arm two to three weeks later in the same women. Where diminution in diameter occurred there was also lessening of intensity in colour and nodularity.

Section 16. THE TYPE OF REACTION IN RELATION TO ANAESTHESIA.

It was thought that the interference of normal bodily function following anaesthesia might result in alteration in the intensity of tuberculin skin reactions, and it is considered by certain French workers (19) that this does occur.

Individuals showing no clinical evidence of tuberculous infection were selected and were tuberculin tested the day before anaesthesia, while under the/
the influence of the anaesthetic or during the twelve hours following administration of the anaesthetic. Only cases undergoing minor operations were included in the series. In most instances the children under twelve years of age had ether following ethyl chloride induction but the adult group included examples of chloroform, ether, spinal and rectal anaesthesia. All adults who were tuberculin skin tested gave positive reactions.

Table 27 shows the relation to the normal range of the reactions obtained in this group, and also gives the percentage incidence in relation to the normal range of the combined observations for all age periods. The observations are given in graphical form in diagrams 54 and 55.

Section 17. THE TYPE OF REACTION IN RELATION TO A HISTORY OF HOUSEHOLD CONTACT.

The occurrence of large reactions in individuals with a history of recent contact with tuberculous infection has been reported by several workers and the material of the present investigation provided an opportunity to investigate this aspect of the subject.

In over four hundred cases a careful enquiry was made as to any clinically tuberculous, household infection with which the patient had been in contact. Those/
Those individuals over twelve years of age with such a history were grouped according as:–

(a.) Contact was of recent date, i.e. where known contact with a definite possible source of infection had occurred within the twelve months preceding tuberculin testing.

(b.) Contact was of distant date, i.e., where the last known contact with a definite possible source of infection had occurred at least five years prior to tuberculin testing.

In the case of children with a history of exposure to open household infection it was not possible to differentiate between contact of recent and distant date.

Cases of severe anaemia, syphilis, those which had been long confined to bed and those showing great emaciation were eliminated (See Sections 7, 8, 9, 10, 38, 39, 40 and 41). The sizes of the reactions obtained in the corrected groups are given in diagrams 56 and 57 for individuals of twelve years of age or more, and children under twelve years respectively. Tables 28 and 29 show the numbers in relation to the normal range. Diagram 58 dealing with those over 12 years of age, gives the percentage incidence of results in relation to normal range for cases with exposure of recent date, and cases with exposure of distant date: diagram 59 provides a comparison between the percentage incidence of results in relation to normal in healthy children and children with a history of contact.
Section 18. REACTIONS IN WHICH COLOUR AND/OR NODULARITY
AND/OR SIZE VARIED DISPROPORTIONATELY.

There were only a few cases in the entire series in which diminution in the size of the diameter of a reaction below the normal range, was not accompanied by a corresponding lessening in the nodularity and colour intensity. Vice versa increase in the size of the reaction was customarily accompanied by increased severity of the other properties. Exceptions to these findings have been considered under the following headings:—

(1.) Diminished colour -normal diameter and nodularity.
(2.) Diminished nodularity - normal diameter and colour.
(3.) Diminished colour and nodularity - normal diameter.
(4.) Diminished diameter - normal colour and/or nodularity.
(5.) Hyperaemia marked relative to diameter and nodularity.
(6.) Nodularity marked relative to diameter and colour.
(7.) Nodularity and colour both marked relative to diameter.

The prominent features concerning cases included under each of the above headings are given in table 30.
Section 19. NEGATIVE REACTIONS OCCURRING IN CLINICALLY NON-TUBERCULOUS ADULTS.

Among the one thousand and thirty-four individuals twenty-one years of age or over who were submitted to the tuberculin skin test, two of the five who failed to react to the tuberculin skin test were clinically non-tuberculous. The details in connection with these cases are given in table 31.
PART 3.
RECORD OF OBSERVATIONS.

(B.) Clinically Tuberculous Individuals.

Section 20. THE COMPLETE SERIES OF CASES OF CLINICAL TUBERCULOSIS.

Details are given in table 32 of those cases of clinical tuberculosis in which there occurred corresponding parallel variations in the colour, nodularity and size of the tuberculin skin reaction.

The table is subdivided into the following major columns:

(1.) Column I - gives the age of the patient.

(2.) Column II - indicates whether tuberculous infection has seriously interfered with the patient's health over a long period or for a relatively short time. Estimation of this was necessarily very approximate in the case of adults, but careful enquiry as to when the earliest suggestive symptoms were first noticed, made it possible to determine with reasonable accuracy whether a symptomatically recognisable condition had been present for a matter of many years or only of months. Cases in which the patient's information was indefinite or unsatisfactory were not dealt with in this connection. Details concerning children were usually reliable, being obtained from the parents or general practitioner previously attending the case.

The/
The following symbols have been employed in column II:

**Y** - indicates the presence of recognisable symptoms for one year or more.

**M** - indicates the presence of recognisable symptoms for two to twelve months.

**W** - indicates the presence of recognisable symptoms for a period of eight weeks or less.

(3.) Column III - indicates the extent of the tuberculous infection determined by clinical, radiological, histological or bacteriological methods or as found at autopsy. This column is divided into subsidiary columns. Asterisks in the appropriate columns indicate the extent of the tuberculous process.

(4.) Column IV - summarises the clinical picture and deals especially with the physical and physiological states of the individual, and any tendency towards improvement or decline in the patient's condition. Clinical features present in an individual are indicated by asterisks in the appropriate columns.

(5.) Column V - gives details concerning the tuberculin skin reaction. The maximum diameter is recorded and the latter "N" signifies that the size and intensity of the reaction are normal, while reactions diminished or increased in size and intensity are indicated by the signs "-" and "+" respectively.

Section 21. THE TYPE OF THE REACTION IN RELATION TO PROMINENT FEATURES IN THE PATIENT'S GENERAL CONDITION.

The frequency with which certain features in the patient's general condition were encountered/
encountered in association with variations in the intensity of the reaction suggested the possibility of some relationship.

Attention was paid to the occurrence, separately or conjointly, of certain of these features and groups were formed of cases in which they occurred. Individuals were classified according to the presence of:

(1.) A good colour - suggestive of excellent health.
(2.) Anaemia - of such severity as to be associated with distinct pallor of the skin and mucous membranes.
(3.) Excellent nourishment.
(4.) Emaciation - whether of long or short duration.
(5.) Progressive gain in weight - over at least three consecutive weekly weighings.
(6.) Progressive loss in weight - over at least three consecutive weekly weighings.
(7.) Average physical strength - included those assisting in the domestic work of the ward and not subjected to any restriction of activities.
(8.) Extreme physical weakness - included those bedridden cases, exhausted by the slightest movement and requiring constant skilled nursing.
(9.) Excellent appetite - Evaluation of those depend-
(10.) Abnormally poor appetite) ed upon reports obtained from the ward sisters.
(11.) Normal temperature - maintained over a minimum period of two weeks, with readings taken on five occasions each twenty-four hours.

(12.) Pyrexia - included those showing a rise of temperature of not less than one and a half degrees Fahrenheit above normal at some time each successive day over a minimum period of five days.

Additional groups were formed of those:-

(13.) not confined to bed.

(14.) confined to bed for more than four weeks.

(15.) with a long history. (Table 32 Column II).

Those included were: -

a. Age eighteen months or under with a history of one month or more.

b. Age one and a half to twelve years with a history of three months or over.

c. Age twelve years and over with a history of twelve months or more.

(16.) with a short history. Included those not in Group 15 above.

The number of skin reactions occurring within, above and below the normal range of size are given for/
for each of the above groups in tables 33, 34 and 35. Where three or four noteworthy characteristics were present in a given case, this case was included in the tables corresponding to all three (or four) headings. The almost invariable presence of many of these features made it impossible to study separately the relationship between any single one of them and the type of tuberculin skin reaction. An excellent appetite was customarily associated with good nourishment and colour in an active patient, in the same way that anaemia and emaciation commonly occurred in bedridden individuals with a poor appetite. The individuals of these two groups were regarded as exhibiting normal physiological function on the one hand and depressed physiological function on the other. They were considered collectively and the observations in connection with them appear in diagram 60 and table 36. Table 37 gives details of reactions obtained in cases of pulmonary infection before and after successful treatment.

Section 22. THE TYPE OF THE REACTION IN FATAL CASES OF TUBERCULOSIS.

Diminished tuberculin skin sensitivity has been recognised as occurring a short time before death. In many cases included in this investigation death was inevitable and the tuberculin test was carried out at periodic intervals during the remainder of life.
The size of the reaction obtained was noted and the colour and the nodularity of the reaction in each case were found to show corresponding, proportionate variations. The observations made are given in table 38 and the figures in connection with the time of appearance of the maximum reaction are given in table 39.

Section 23. THE TYPE OF THE REACTION IN RELATION TO DIFFERENT CLINICAL FORMS OF TUBERCULOUS INFECTION.

The different clinical forms of tuberculous infection have been variously reported in the literature as being associated with greater or less degree of severity of the tuberculin skin reaction.

In this section there have been included all those cases of clinical tuberculosis in table 32, with in addition a few cases in which details of the localisation of infection and of the severity of the reaction were noted, but in which other observations were not recorded. Only those cases have been considered in which colour, nodularity and size of the reaction showed parallel variations.

The cases have been grouped according to their clinical classification and the diameters of their reactions are given in diagrams 61 to 70 inclusive. The number of diameters in relation to normal range for different age periods are given in table 40:
table 41 and diagram 71 give these observations in percentage form. In table 42 the same observations have been divided into groups representing so-called "Surgical Tuberculosis" (infection of glands, bones and joints), and other forms of tuberculous infection. The age periods of, from birth to twelve years, and of twelve years and upwards were selected: diagrams 72 and 73 give the percentage incidence of diameters in relation to normal.

Section 24. A COMPARATIVE STUDY OF THE TYPE OF THE REACTION IN CLINICALLY TUBERCULOUS AND CLINICALLY NON-TUBERCULOUS INDIVIDUALS.

The added value which would be attached to the tuberculin skin reaction if it were possible to interpret the degree of activity of the underlying infection prompted this investigation.

Material was drawn from the following three groups:

(1.) Healthy individuals giving a positive reaction. These consisted of those forming the series in Section 1.

(2.) Hospital patients, other than the clinically tuberculous, giving a positive reaction. These included the cases of acute and chronic infections, the non-infectious conditions of Section 12 and the specific infectious diseases of Section 13, after correction for anaemia, malnutrition, cardiac insufficiency,
insufficiency, prolonged confinement to bed, syphilis and depression of physiological function (See Sections 7, 8, 9, 10, 38, 39, 40 and 41). Cases of measles were not included.

(3.) Hospital patients with clinically recognisable tuberculous infection. These consisted of all the cases in table 32 (See Section 20). In this group individuals were not eliminated on account of anaemia and/or malnutrition where these conditions were considered to be directly attributable to the tuberculous infection. On the other hand cases of pulmonary tuberculosis and tuberculous meningitis, tuberculin tested five days or less prior to death were excluded on the grounds that the almost, if not completely moribund condition of these cases was not a particular characteristic of the tuberculous infection but was, on the other hand, analogous to the state of physiological depression corrected for in the preceding group of clinically non-tuberculous hospital patients.

The diameters obtained in the clinically tuberculous group before and after correction are given in diagrams 74 and 75. Diagram 76 shows the diameters of the reactions in the corrected group of clinically non-tuberculous patients. The percentage incidence of reactions in relation to the normal range in all three groups, healthy individuals, clinically tuberculous and clinically non-tuberculous hospital patients are shown in table 43 and diagram 77. In table 44/
there are given the arithmetical means of diameters obtained for each age period in the above three clinical groups and the corresponding curves are seen in diagram 78.

Section 25. THE TYPE OF THE REACTION IN RELATION TO

THE SEASON OF THE YEAR.

The necessity for studying this question was referred to in Section 3. Clinically tuberculous cases were investigated along the same lines as the clinically non-tuberculous individuals and were divided into the same seasonal groups.

The sizes of the reactions obtained in each seasonal group are given in diagrams 79 and 80 for children and older individuals respectively, and diagrams 81 and 82 give the corresponding percentage incidence of the reactions in relation to the normal range. Tables 45 and 46 form the basis of diagrams 79 to 82 (inclusive).

Section 26. THE TYPE OF THE REACTION IN RELATION TO

ANAESTHESIA.

This subject has already been investigated in Section 16 in connection with clinically non-tuberculous individuals.

A number of clinically tuberculous children who underwent operations were tuberculin tested while under the influence of the anaesthetic. The majority of/
of these children were suffering from one of the "surgical" forms of tuberculosis, and in every instance the anaesthetic employed was ether following ethyl chloride induction.

The diameters obtained in this series are given in diagram 83 and the percentage incidence in relation to the normal range in diagram 84. The corresponding figures are given in table 47.

Section 27. REACTIONS IN WHICH COLOUR AND/OR NODULARITY AND/OR SIZE VARIED DISPROPORTIONATELY.

Only isolated cases were met with among clinically tuberculous individuals in which the reaction did not show variations in colour, nodularity and diameter corresponding in degree. These have been considered under the following headings:

(1.) Diameter small in relation to colour and nodularity.

(2.) Pallor marked (or reaction purple in colour); diameter and nodularity normal.

(3.) Colour and nodularity diminished; diameter normal.

The main features coming under each of the above headings are given in table 48.

Section 28. NEGATIVE REACTIONS OCCURRING IN CLINICALLY TUBERCULOUS INDIVIDUALS.

Among the two hundred and fourteen clinically tuberculous individuals tested three failed to react/
react to the tuberculin skin test. The details in connection with these cases are given in table 49.

Section 29. REACTIONS ABOVE THE AVERAGE IN SIZE IN CLINICALLY NON-TUBERCULOUS SUBJECTS WHO LATER BECAME CLINICALLY TUBERCULOUS.

The details of nine cases of particular interest are given in table 50. These cases were all admitted to hospital with vague complaints and although in eight of them at the time of first examination evidence of tuberculous infection was not found, tuberculin skin reactions above the average in size were obtained in them all. The presence of tubercle bacilli was proved in all at a later date. The ninth case was one in which a tuberculous condition had been previously suspected but never confirmed, and eventually an extensive tuberculous infection was revealed at autopsy.
PART IV.

DISCUSSION.
PART 4.
DISCUSSION.

Contents.

Sections 30 & 31. Preliminary.

Section 32. The type of the reaction in relation to age.

Section 33. The type of the reaction in relation to sex.

Section 34. The type of the reaction in relation to the season of the year.

Section 35. The type of the reaction in relation to the condition of the skin.

Section 36. The type of the reaction in relation to disease of the vessels.

Section 37. The type of the reaction in relation to blood pressure and pulse volume.

Section 38. The type of the reaction in relation to prolonged confinement to bed.

Section 39. The type of the reaction in relation to anaemia.

Section 40. The type of the reaction in relation to malnutrition.

Section 41. The type of the reaction in relation to certain clinical groups.
Section 42. The type of the reaction in relation to respiratory conditions.

Section 43. The type of the reaction in relation to infection.

Section 44. The type of the reaction in relation to certain specific infectious diseases.

Section 45. The type of the reaction in relation to fever.

Section 46. The type of the reaction in relation to physiological events in the female life.

Section 47. The type of the reaction in relation to anaesthesia.

Section 48. The type of the reaction in relation to a history of household contact.

Section 49. Reactions in which colour and/or nodularity and/or size varied disproportionately.

Section 50. The type of the reaction in relation to prominent features in the general condition of clinically tuberculous individuals.

Section 51. Changes in the type of the reaction in fatal cases of tuberculous infection.

Section 52./
Section 52. The type of the reaction in relation to different forms of clinical tuberculosis.

Section 53. A comparison of the type of the reaction in clinically tuberculous and clinically non-tuberculous individuals.

Section 54. Cases in which a tuberculin reaction of increased intensity preceded the development of clinically tuberculous infection.

Section 55. The diminished reaction.

Section 56. The increased reaction.

Section 57. Variations in intensity of the reaction in the same individual.

Section 58. Failure to react.

Section 59. The importance of bodily function.

Section 60. The importance of age.
Section 30. The observations made in a study of the variations occurring in the tuberculin skin reaction in association with a number of different conditions have been given in Part 3. The variations studied were limited to those occurring in properties readily appreciable during the routine examination of skin areas submitted to tuberculin testing, as it was considered that in this way conclusions would be arrived at having an essentially practical bearing on the subject. Observations were made concerning variations in colour, nodularity and size of the skin reactions obtained.

The occurrence of a positive reaction pointed to the presence of tuberculous infection in an individual, and positive reactors in the investigation belonged to two main groups viz.

(1.) Cases clinically non-tuberculous, in which positive skin reactions were the only indication of the presence of tuberculous infection.

(2.) Cases clinically tuberculous, in which pathological, bacteriological or radiological evidence of tuberculous infection was obtained.

Included in each of the above groups were cases representing/
representing all age periods of child and adult life, and while in the second group all clinical forms of tuberculous infection were considered, in the first group the positive skin reaction was associated with all types of illness and disease as well as normal health.

The need for study along the lines forming the basis of this thesis is indicated by the extensive literature on the subject and by the inconclusive and contradictory results arrived at by so many workers. Diminution in tuberculin skin sensitivity has been attributed to many different factors but confirmation is lacking of a large number of reports in this connection. Variations in reactions have been found not only in different individuals but also in the same individual, and this fact explains the many attempts made to establish some connection between the intensity of the tuberculin reaction and various factors connected with either the underlying infection, or with the individual's general condition. So long as there remain neither proved nor disproved, so many findings in connection with alterations in tuberculin sensitivity, some doubt must exist as to the dependability and full significance of the results obtained with skin tests. Were all recorded modifying factors consistently to exert their influence, the results of tuberculin surveys would not show the percentages of positive/
positive reactors that have been reported. A case in point is the finding of only five non-reactors among one thousand and thirty-four adults in the unselected series given in table 1.

A positive skin reaction is undoubted evidence of tuberculous infection but the question as to what significance, if any, is to be attached to variations in the intensity of the reaction has remained unsettled up to the present time.

It is with this problem that the present thesis is mainly concerned.

Section 31.

Dickey (20) and McCain (54) have remarked upon racial predisposition towards severe tuberculin skin reactions. In the present investigation the material consisted of entirely British stock. Subjects of Jewish and Irish extraction were excluded.

Baldwin (3) has pointed out that the intensity of the reaction may vary in different skin areas. The test in this investigation was invariably carried out on the flexor surface of the forearm.

Pirquet (73) considered the intensity of the reaction varied with the strength of tuberculin employed. Old Tuberculin (undiluted) prepared by Parke Davis and Co. Ltd. was used throughout this investigation.

Smith (81) maintains that the actual amount of fluid/
fluid introduced into the skin determines the severity of the reaction. The multiple puncture instrument was used in all the tests of this investigation thus ensuring uniformity in the quantity of undiluted tuberculin introduced into the skin.

Section 32. THE TYPE OF THE REACTION IN RELATION TO AGE (See Section 1).

It was noted in Section 1 that a particular range of size within which the majority of reactions fell, existed for each age period. This is demonstrated in diagram 1. This constancy in results, using only carefully selected material, was of definite significance and allowed of the determination of arbitrary "normal ranges" for each age group.

The progressive displacement to the right of the normal range as a whole with each succeeding age period up to that for twenty to twenty-five years, points to a tendency for the tuberculin reaction to increase in size and intensity during the first twenty-five years of life. A tendency to reduction of intensity after that age is indicated by the displacement of the normal range of size to the left for the period twenty-five years and over. Confirmation of these findings is obtained from the curve of arithmetic mean of diameters which rises uninterruptedly to a maximum at a point corresponding to the age period twenty to twenty-five years and thereafter falls/
falls during the remainder of life (diagram 5). Although there is a reversal of the shift of the normal range in the later years, the range remains to the right of that for the years of childhood. Also, the curve of mean diameters, although falling after the age of twenty-five years, does not fall to the levels associated with the age periods from birth to five years and from five to twelve years. The tuberculin reaction skin of later years therefore was less marked than that of early adult life but of greater intensity than the reaction obtained in childhood.

It is evident that age is an important factor in its influence on the intensity of the tuberculin skin reaction, a fact previously drawn attention to by Dickey (20). His observations however were confined to children, and although stating that the size of the reaction shows a gradual increase up to the age of six he does not discuss the question in connection with older subjects. Heimbeck's (34) belief that lessening in the size of the reaction occurs in old age is only partly confirmed by our observations: the reaction of later years, although less in size than that of early adult life, was found to be greater than that met with in children. Krause (45) considers that of those infected with tuberculosis, children give more violent reactions than adults. In particular circumstances this may be true of clinically tuberculous/
tuberculous (See Section 53) cases but was not found to be true of those healthy individuals included in this investigation in whom a skin reaction was the only evidence of tuberculous infection (Section 1).

The conclusions arrived at are:

1. Age influences the type of the tuberculin skin reaction.

2. The intensity of the tuberculin skin reaction in infected individuals increases with age up to a maximum in early adult life and thereafter lessens but not to the degree of intensity found in childhood.

Section 33. THE TYPE OF REACTION IN RELATION TO SEX.

(See Section 2.)

It was to be expected that the great majority of the reactions in both sexes in the group of healthy individuals (Section 2: Group A) would fall within the normal range. Diagrams 6, 7, and 8 and table 4 show that this occurred. Although there were a few more reactions above average size among the males than among the females, the fact that in both sexes over ninety per cent of reactions fell within the normal range, indicates that sex does not influence the tuberculin reaction. Among children of both sexes below twelve years of age only one reaction out of a total of fifty-six fell outside the limits of normal. These findings agree with those of Dickey (20) in connection with children, but differ from those of Cummins/
Cummins and Evans (17) who consider that among healthy clinically non-tuberculous subjects more marked skin reactions are met with in females than males.

In the second group studied, consisting of clinically non-tuberculous hospital patients (Section 2: Group B) fifty-five per cent of the reactions in males and fifty per cent in the case of females were of normal size, and thirty-nine per cent were below the normal range of size in each sex.

Thus, irrespective of whether the individuals were in good health or suffering from surgical or medical ailments a very close correspondence existed between the two sexes in the incidence of reactions in relation to normal range and it was concluded that sex does not influence the type of tuberculin reaction.

Section 34. THE TYPE OF THE REACTION IN RELATION TO THE SEASON OF THE YEAR.

(See Sections 3 and 25.)

The seasonal variations of tuberculin reactions recorded in the literature differ according to the age of the individuals concerned. Hamburger (28) and Peyrer (68) find that children give stronger reactions in spring than in autumn, and Schnippenkötter (79) finds reactions among adults less intense in winter and early spring than during other seasons of the year.

The seasonal groups into which the material of the/
the present investigation was divided. corresponded with those employed by Hamburger and Peýrer in connection with children, and Schnippenkötter in connection with adults. No evidence was obtained in support of the opinions of these workers.

Tables 5, 6, 45 and 46 and diagrams 12 to 16 (inclusive) and 79 to 82 (inclusive) show no significant seasonal variation in the type of reaction in relation to normal in children or adults, drawn from either the clinically tuberculous (Section 25) or clinically non-tuberculous group. (Section 3).

It was concluded that the tuberculin skin reaction is not subject to seasonal variation.

Section 35. THE TYPE OF REACTION IN RELATION TO THE CONDITION OF THE SKIN.

(See Section 4.)

Slater and Jordan (80) suggest that increased reactions such as they found in younger subjects may be explained by the "tender skin" of the individuals tested. This appears to be unlikely however considering that a progressive increase in the size of the reaction has been shewn to occur during the first twenty-five years of life. (Section 1).

The figures in table 7, and diagrams 17 and 18 dealing with individuals selected on account of the unhealthy state of their skins, show that the distribution of the reactions in relation to the normal range did not differ appreciably from that of an unselected/
unselected group of cases of the same age.

The condition of the skin therefore was not found to exert any influence upon the nature of the tuberculin reaction.

Section 36. THE TYPE OF THE REACTION IN RELATION TO DISEASE OF THE VESSELS. (See Section 5.)

The distribution of the reactions in diagrams 19 and 20 shows that there was a tendency for the reactions in this group to fall within the lower limits of normal or actually below them. This tendency was only slight however, and disappeared after further correction of the results by eliminating cases showing general physical debility which could not be directly related to the condition of the vessels, and which was disproportionate with age. (Diagrams 19 and 20, and table 8). The percentage of over seventy of reactions within the normal range for this corrected group indicates that the intensity of the tuberculin reaction is not directly subject to modification by the presence or absence of disease of the vessels.

Section 37. THE TYPE OF THE REACTION IN RELATION TO BLOOD PRESSURE AND PULSE VOLUME. (See Section 6.)

Diagrams 21, 22 and 23, and table 9 give the observations concerning the tuberculin reaction in individuals whose blood pressure and pulse volume were noted. Correction for other modifying factors (See/
Table 9 shows that small reactions occurred most often in individuals with low recorded blood pressures, irrespective of whether the diastolic or systolic reading was considered. On the other hand increased reactions were as common in individuals with a low systolic blood pressure as with a high reading. The figures in table 9, and diagrams 21, 22 and 23 indicate however, that no definite relationship exists between tuberculin sensitivity and blood pressure or pulse volume.

**Section 38. THE TYPE OF THE REACTION IN RELATION TO PROLONGED CONFINEMENT TO BED.** (See Section 7).

Only isolated cases satisfying the conditions necessary for inclusion in this group were met with in the younger age periods, but these, in giving rise to reactions below the normal range shared a tendency present in the larger group of individuals over fifty-five years of age. (Diagrams 24 and 25 and table 10).

Diminution in the size of the reaction occurred in over seventy per cent of the series after all cases with any other known modifying factors had been excluded (See Sections 8, 9, 10, 15, 39, 40, 41 and 46). No reference to previous study of the question is available, but Krause (47) suggests that anything depressing normal bodily function may diminish tuberculin/
tuberculin sensitivity. Such depression occurred in varying degree among those confined to bed in the present investigation and it was concluded that confinement to bed does result in reduced skin sensitivity to tuberculin.

Section 39. THE TYPE OF THE REACTION IN RELATION TO ANAEMIA.

(See Section 8.)

Diagrams 26 and 27 and table 11 indicate a tendency for diminished reactions to occur among the selected cases of anaemia. Diagram 28 and table 12 which include both severe anaemias and individuals with normal blood pictures, reveal the existence of a definite relationship between the intensity of the skin reaction and the blood count. The nearer the blood count approached normal figures the larger was the skin reaction, and conversely, the fewer the number of red blood cells per cubic millimetre the less marked was the skin reaction.

The variations in the size and severity of the tuberculin reaction accompanying gross changes in the blood picture which were taking place in individual patients, are shewn in diagrams 28 and 29 and tables 13 and 14. These indicate that as anaemia increased during the last weeks of life in malignant cases the skin reaction progressively diminished in size. On the other hand, as increasing response to treatment/
treatment took place in the primary anaemias the skin response to tuberculin tests increased in severity, a finding which was analogous to that of Krause (47) who, in an anaemic child previously negative to tuberculin tests, obtained a positive skin response following transfusion.

Thus anaemia, whether primary or secondary results in depression of tuberculin skin sensitivity. Parallel variations occur in the size of the reaction and the red blood count, the one decreasing or increasing (to the upper limit of normal) with the other.

Section 40. **THE TYPE OF THE REACTION IN RELATION TO MALNUTRITION.** (See Section 9.)

The contrast between the observations in well nourished individuals and those with impaired nutrition (Table 15 and diagrams 31 and 32) is striking. In the latter four out of every five reactions were diminished in size and no single one was above the average size. Where nourishment was good the great majority of reactions were of normal size and there were in addition instances of increased skin sensitivity. It was probable that the modification of reactions in the under-nourished group was partly attributable to co-existing anaemia, but as judged by the findings in Section 39 the anaemia was not of sufficient severity in any of the cases to account for the extent of diminution of the reactions.

The/
The correctness of this assumption is borne out by the figures in table 16 showing the disproportion between the increased skin sensitivity and alteration in blood count.

From the observations made by other workers the weight of evidence is in favour of impaired nutrition tending to depress tuberculin skin reactions. Andrus (1) finds a greater frequency of well marked reactions in under-nourished than in well-nourished cases, but Rominger (78), Krause (34) and Baldwin (3) consider exactly the reverse to be the case. Our own observations also disagree with those of Andrus and show that malnutrition depresses skin sensitivity.

Section 41. THE TYPE OF THE REACTION IN CERTAIN CLINICAL GROUPS.

(See Section 10.)

(A.) From the uncorrected observations in diagrams 33 and 34, and tables 17 and 18 the following facts are apparent:—

1. A certain percentage of the results fell below the normal range in each clinical group.

2. The clinical groups in which reduction in size of the tuberculin reaction predominated were:

   (a.) Anaemia.

   (b.) Malnutrition.

   (c.) Syphilis.

   (d.) Malignancy.

   (e.) Influenza.

(3.)
(3.) The clinical groups in which approximately the same percentage of reactions fell below as within normal range were:

(a.) Cardiac Insufficiency.

(b.) Cerebral Damage of Vascular Origin.

(B.) From the observations after correction for co-existing modifying factors in diagrams 35, 36, 37 and 38, and tables 17 and 18, the following facts are evident:

(1.) Correction resulted in the elimination only of cases with diminished reactions.

(2.) Diminished reactions remained in the majority in the following groups:

(a.) Anaemia.

(b.) Malnutrition.

(c.) Syphilis.

(d.) Cardiac Insufficiency.

(3.) Although well nourished, several of the cases in the group of diseases of the central nervous system, which were eliminated on account of prolonged confinement to bed necessitated by ataxia or paresis, had reactions below the average in size.

(4.) Correction in the groups of cerebral damage of vascular origin, and of malignancy resulted in reactions of normal and increased size predominating in contrast with the predominance of diminished reactions in the uncorrected table. This finding emphasises/
emphasises the importance of the factors corrected for, and at the same time indicates that malignant conditions and cerebral conditions of vascular origin do not of themselves modify tuberculin skin sensitivity.

(5.) Asthma is not associated with alteration in tuberculin skin sensitivity: this is in keeping with the findings of Bray (7).

Study of the nature of the tuberculin reaction accompanying various clinical conditions thus demonstrates the frequent occurrence of diminished tuberculin skin sensitivity in the following types of case:

(a.) Anaemia.
(b.) Malnutrition.

These have already been discussed in Sections 39 and 40.
(c.) Syphilis.

Similar findings, but in connection with cases showing secondary manifestations of the disease, are recorded by Lelong (22).

(d.) Cardiac Insufficiency.

Burhans (9) suggests that the diminution in intensity of the reactions commonly met with in massive tuberculosis may be due to cardiac failure.

(e.) Influenza.

Bloomfield and Mateer (6) report the frequent loss of skin reactivity in this condition.
Section 42. THE TYPE OF THE REACTION IN RELATION TO

RESPIRATORY CONDITIONS.
(See Section 11.)

The observations in tables 19 and 20 and diagrams 39 to 41 (inclusive) show:—

(A.) in the pneumonia group:—

(1.) no appreciable difference between the incidence of small reactions among those tested during high fever and those tested when the temperature had fallen permanently to normal.

(2.) an absence of diminished reactions in cases recovering rapidly, in contrast with the high proportion of small reactions in cases running a long course or developing complications.

(3.) the constant presence of extreme physical exhaustion in cases with depressed tuberculin sensitivity.

(B.) in the group of respiratory conditions other than pneumonia:—

(1.) no marked incidence of either small or large reactions after correction for other factors such as anaemia, syphilis, prolonged confinement to bed, malnutrition and cardiac insufficiency (See Sections 38, 39, 40 and 41).

Loss in part or in whole of tuberculin skin sensitivity in pneumonia has been reported by Nobécourt and Forgeron (64) and Rolly (76) but the observations made/
made in the present investigation show that depression of skin sensitivity, where it occurred, was related more to the general physical and physiological state of the patient than to the actual presence of a pneumonic process. Table 20 demonstrates that diminution in the size of the skin reaction occurred where extreme exhaustion had resulted from a particularly severe infection or from the development of complications. The typical pneumonia with its seven days' fever and dramatic improvement with the return of the temperature to normal, occurring in an individual of average physique, was not associated with lessened intensity of skin response to tuberculin. It was concluded therefore, that:

(1.) Partial depression of the tuberculin skin reaction may occur in cases of pneumonia where exhaustion and debility are extreme. The effect of a patient's poor physical condition upon the tuberculin reaction is the same whether it is his normal state or whether it is the result of the pneumonic infection.

(2.) When diminished reactions occur in cases of respiratory disease other than pneumonia they are due to the presence of other known modifying factors (Sections 7, 8, 9, 10, 15, 33, 39, 40, 41, 44 and 46).

Section 43./
Section 43. THE TYPE OF THE REACTION IN RELATION TO INFECTION IN GENERAL.  
(See Section 12).

Diagrams 42 to 46 (inclusive) and tables 21 and 22 demonstrate the close similarity in the observations made in connection with the three groups of acute infections, chronic infections, and non-infectious conditions after correcting for other modifying factors.

Burhans (9) has advanced the view that depression of the tuberculin reaction may occur in all acute infections, but our observations not only indicate that infection itself does not modify tuberculin sensitivity, but that acute infections are not associated with any greater frequency of small reactions than chronic infections.

The results of correcting for anaemia, malnutrition and extreme physical exhaustion show that the presence of these conditions accounts for depression of tuberculin sensitivity where it occurred.

It can be stated therefore, that:

(1.) Syphilis alone of the forms of chronic infection studied, tends to modify the tuberculin skin reaction. (See Sections 10 and 41).

(2.) The presence or absence of infection does not effect the type of the tuberculin skin reaction.

Section 44./
Section 44. THE TYPE OF THE REACTION IN RELATION TO CERTAIN SPECIFIC INFECTIOUS DISEASES.

(See Section 13).

The observations in connection with this section are given in diagrams 47 and 48 and table 23.

Among the adults included in the section only three gave small reactions, all of which occurred in the diphtheria group. Two of these three were critically ill and extremely weak at the time of testing and one of them died five days later.

Among the children no modification of the size of the reactions occurred in the scarlatina and chickenpox groups. Only a moderate number of cases of measles were tested and of the positive skin reactions obtained, half the number fell below the normal range of size. Of the convalescent cases of whooping cough three skin reactions were undersized but all three occurred in cases in which a prolonged, severe capillary bronchitis had left the patient weak and emaciated. Skin reactions obtained in the diphtheria group came within the normal range of size in every case.

Modification of tuberculin skin sensitivity in measles was first noted by von Pirquet in 1908 (75) and has come to be recognised as an established fact, Koch (43), Krause (46, 47), Krause and Willis (48) and Lesné and Coffin (51) having confirmed the original/
original finding. The fact that fifty per cent of the positive reactions obtained in the present series showed diminution in size is in keeping with the accepted belief concerning the desensitising effect of measles. Bloomfield and Mateer (6) found loss of sensitivity in diphtheria, and Nobécourt and Forgeron (64) consider that the same occurs in whooping cough. In the present investigation depression of tuberculin skin sensitivity in these conditions was not the general rule, but only took place where the infection had greatly interfered with the general health of the individual. There was a complete absence of diminished reactions in cases of scarlet fever and paratyphoid infection which does not agree with the views of Rolly (76) who finds diminished reactions in scarlatina, and of Baldwin (3) who finds the same in both scarlet and typhoid fever. It should be noted that in none of our cases was the condition severe. Erysipelas and chicken-pox are not referred to in the literature; diminution of skin sensitivity did not occur in these conditions.

The number of individuals suffering from each of the specific infectious diseases was limited, but allowed of the following general conclusions being arrived at:-

(1.) The specific infectious diseases studied do not modify the tuberculin skin reaction in/
in adults or adolescents.

(2.) The specific infectious diseases studied, with the one exception of measles, do not modify the tuberculin skin reaction in children.

(3.) Extreme physical exhaustion, intense toxaemia and marked emaciation resulting from infectious diseases tend to diminish the intensity of the tuberculin skin reaction in children.

(4.) Small tuberculin skin reactions occur with noteworthy frequency during the eruptive phase of a severe infection of measles in children with a coincident tuberculous infection.

Section 45. THE TYPE OF THE REACTION IN RELATION TO FEVER.

(See Section 14).

Krause (46) and Smith (81) consider that diminution in the size of tuberculin reactions occurs in cases where high fever is a prominent feature. Confirmation of this was lacking in the pneumonia group of the present series (Section 42), where depression of skin sensitivity was found to be related rather to the patient's physical and physiological state than to the presence or absence of fever. This is borne out by the observations made in all the clinically non-tuberculous cases with pyrexia (Diagrams 49, 50 and 51, and table 24) after correction for other modifying factors (See Sections 7, 8, 9, 10, 38, 39, 40 and 41). These cases showed no/
no noteworthy incidence of reactions falling outside the normal range.

In the clinically tuberculous group, a relatively large number of diminished reactions occurred in pyrexial cases (Table 34.). These reactions all occurred in individuals who were extremely weak, who had been confined to bed for a long time, and who were anaemic and/or in an emaciated condition. Table 33 shows that after eliminating these cases no relationship existed between pyrexia and tuberculin sensitivity.

Fever therefore does not modify the tuberculin skin reaction.

Section 46. THE TYPE OF THE REACTION IN RELATION TO PHYSIOLOGICAL EVENTS IN THE FEMALE LIFE. (See Section 15).

Diminution in the size of the skin reaction, although not constant in its occurrence, was found in a large proportion of women who were pregnant, lactating or menstruating, or who had recently given birth to a child (Diagrams 52 and 53 and table 25). This is in agreement with the findings of Nobécourt and Paraf (65), Krause (47, 49), and Krause and Willis (48) in connection with pregnancy, and those of Coulaud (11) and Thrap-Meyer (84) in connection with menstruation. The temporary nature of the alteration in the skin reaction, when it occurred, is/
is shewn in table 26, and was previously observed by Thrap-Meyer (84).

Taking into account the work of other investigators and the fact that the women tested in the present series represented normally healthy individuals, it was concluded that temporary depression of skin sensitivity to tuberculin occurs in a large proportion of cases of pregnancy, parturition, lactation and menstruation.

Section 47. THE TYPE OF THE REACTION IN RELATION TO ANAESTHESIA.

(See Sections 16 and 26).

The observations made are given in diagrams 54, 55, 83 and 84, and tables 27 and 47.

Of those individuals given an anaesthetic in whom the tuberculous infection was not clinically detectable, eighty-five per cent of the reactions fell within the normal range of size. The more marked type of reaction to be expected in cases of "surgical tuberculosis" (Section 52) was not interfered with, and over eighty per cent of the reactions in these cases were above the average in size and intensity.

Decressac and Jacquelin (19) record loss of skin sensitivity to tuberculin in a high percentage of individuals tested after operation. They find ether to be the anaesthetic causing greatest depression of reactivity. The fact that the present group of cases showed/
showed no diminution in tuberculin sensitivity cannot be explained by a difference in the form of anaesthesia employed as ether was used in the great majority of the individuals. It is possible that the contradictory observations made by Decressac and Jacquelin on the one hand, and by us on the other, may have its explanation in differences in the clinical status of patients tested. Were any of the modifying factors, discussed elsewhere (Sections 38, 39, 40, 41, 44 and 46) present in a proportion of the French series of cases they would explain the discrepancy.

The observations given in tables 27 and 47 allow of only one conclusion, namely that anaesthesia does not influence the tuberculin skin reaction.

Section 48. THE TYPE OF THE REACTION IN RELATION TO A HISTORY OF HOUSEHOLD CONTACT.

(See Section 17.)

From diagrams 56 and 58 and table 28 it is seen that in individuals over twelve years of age the majority of the reactions obtained were of a size falling within the normal range, irrespective of whether exposure to contact had been recent or not. Actually the distribution of reactions in relation to the normal range of size for this group closely resembled that found in all clinical conditions other than those considered as exerting a modifying influence (Table 18 and diagram 38).
The sizes of the reactions in adolescents and young adults of the series did not differ from those in healthy individuals with no history of recent exposure to infection.

In contrast, among children under twelve years of age, three in every four of those with a definite history of home contact gave tuberculin skin reactions of greater intensity than the average. (Table 29 and diagrams 57 and 59). Similar findings are recorded by Dickey (20).

The conclusions arrived at are, therefore:

(1.) Children who have been exposed to home contact, but in whom no evidence of tuberculous infection other than a positive tuberculin skin reaction can be demonstrated, give more marked skin reactions than children with no such history of exposure.

(2.) No relationship exists between the severity of the tuberculin skin reaction in adolescents or adults and a history of contact.

Section 49. REACTIONS IN WHICH COLOUR AND/OR NODULARITY AND/OR SIZE VARIED DISPROPORTIONATELY.

(See Sections 18 and 27.)

(A.) Considering table 30 of clinically non-tuberculous individuals, groups 1 - 4 (inclusive) represent instances of disproportionate diminution of one or more of the properties of the skin reactions. Of the thirty-six included, twenty-two were over the age of fifty years and had in common that they were each/
each associated with one or more of the following clinical features:

(a.) Anaemia.
(b.) A positive Wassermann reaction.
(c.) Terminal cardiac insufficiency.
(d.) Prolonged confinement to bed.

Of those under fifty years of age, there were three suffering from primary anaemia, four were recovering from severe forms of pneumonia, while two were cases of diabetes mellitus associated with great emaciation and dehydration. Prolonged confinement to bed was a feature in three cases, one a chronic alcoholic with a positive Wassermann reaction, another a woman with femoral thrombosis, and the third a case of complete cardiac failure with anasarca. In one individual the tuberculin test was carried out immediately prior to a violent haematemesis, while another case was completely exhausted and emaciated as a result of a chronic intestinal infection. Unimpaired general health was noted in only one individual — a boy aged nineteen years admitted for herniotomy.

Groups 5 - 7 represent cases in which a tendency to increase above the normal was not shared by all the properties of the reaction. The combined groups include thirteen cases. Only two of these were above the age of fifty-five years and nine were less than fifty years of age. Of these last nine cases the general/
general physique and appearance were noted as excellent in seven. These seven included two cases of rheumatoid arthritis bedridden for a number of years, a man suffering from acute rheumatism who had been in bed eight weeks, three individuals recovering from severe abdominal operations and one instance of convalescent pneumonia. Considerable weakness and exhaustion were present in two cases of recovering pneumonia, and poor nourishment was a prominent feature in a boy suffering from hysteria as well as in a case of hemiplegia aged seventy-five years. The remaining two cases were characterised by pronounced cardiac failure, in the one instance associated with chronic bronchitis and in the other with cancer of the lung and a positive Wassermann reaction.

Consideration of the cases occurring in groups 1 - 4 emphasises the almost constant existence of one of the following:

(a.) Anaemia.
(b.) Malnutrition.
(c.) Cardiac insufficiency.
(d.) Prolonged confinement to bed.
(e.) A positive Wassermann reaction.
(f.) Extreme physical exhaustion.

In Sections 39, 40, 41, 38 and 50 these same conditions have been shewn to be commonly associated with tuberculin reactions in which size, nodularity and colour were proportionately lessened. In the individuals/
individuals comprising groups 1 - 4 the above conditions are seen to have influenced the tuberculin reaction by modifying one or more but not all the properties of the reaction.

At least one of the above conditions was present in nine of the thirteen cases included in groups 5, 6 and 7. The general appearance of the remaining five was good, but of these, four were in some degree weakened, three having just undergone severe operations and another having passed through a pneumonic crisis. In these cases modification of the tuberculin reaction was of the nature found in groups 1 - 4 and is to be explained in the same way.

(B.) The details given in table 48 (Section 27) of clinically tuberculous individuals in whom one or two, but not all the properties of the reaction showed disproportionate diminution, show that in each of the individuals concerned several of the following features were present:

(a.) Anaemia.
(b.) Emaciation.
(c.) Prolonged confinement to bed.
(d.) Progressive loss in weight.
(e.) A moribund state.

Depression of physiological function was a characteristic of each case, and this is in agreement with the views of Kolmer (44) concerning the occurrence of atypical/
atypical skin reactions in the terminal stages of tuberculous disease, and also with the reports by Marriette and Fenger (61) in connection with the "pale reactors" they encountered in sanatorium patients.

The observations made in connection both with those clinically non-tuberculous and those clinically tuberculous, lead to the same conclusion. The conditions which commonly result in proportionate diminution in the intensity of the colour and nodularity and in the size of the tuberculin skin reaction occasionally modify only one, or at most two of these properties of the reaction.

Section 50. THE TYPE OF THE REACTION IN RELATION TO PROMINENT FEATURES IN THE GENERAL CONDITION OF CLINICALLY TUBERCULOUS INDIVIDUALS. (See Sections 20 and 21).

Among the noteworthy points in tables 33, 35 and 36 are:-

(A.) (1.) No reaction fell below the normal range of size in any case in which there was noted: -

(a.) Healthy colour (51 cases),

or (b.) Good nourishment (42 cases),

or (c.) A normal active existence (31 cases),

or (d.) Normal physiological function (41 cases).

(2.) Only one reaction fell below the normal range of size in each of the following groups: -

(a.)/
(a.) Twenty cases showing progressive gain in weight,

and (b.) Forty-nine cases with a markedly good appetite.

(B.) (1.) The incidence of the reactions below the average range of size in the individual groups was as follows:

(a.) Anaemia ... 89 cases .. 33.7%
(b.) Emaciation ... 58 cases .. 45.7%
(c.) Bedridden ... 65 cases .. 38.5%
(d.) Extreme weakness 96 cases .. 36.5%
(e.) Marked physiological depression ... 43 cases .. 44.3%
(f.) Progressive loss of weight ... 99 cases .. 29.8%
(g.) Poor appetite 65 cases .. 37.0%

(C.) (1.) There was a greater incidence of diminished reactions in cases with a long clinical history than in those with a short history.

After exclusion of cases showing anaemia or emaciation, or patients long confined to bed and extremely weak the tendency for small reactions to occur in cases with a long history disappeared. This is shewn in table 35.

(D.) (1.) Reactions above the average in size were in excess of those within normal range in the following groups:

(a.)/
(a.) Healthy colour (51 cases).
(b.) Good nourishment (42 cases).
(c.) Physically strong (47 cases).
(d.) Progressive increase in weight (20 cases).
(e.) A normal active existence (31 cases).

These observations draw attention to the vital importance of anaemia, impaired nutrition and depression of physiological function in their effect upon the tuberculin skin reaction. The presence of some or all of these conditions would explain the diminished skin sensitivity frequently recorded in certain types of cases. In this connection miliary tuberculosis (30, 83, 31 and 20), advanced adult tuberculosis (16) and tuberculous meningitis (30, 83, and 20) have all been found associated with either diminution in, or loss of skin tuberculin reactions. Such cases all represent terminal stages of tuberculous infection which are accepted as being accompanied by varying degrees of prostration, anaemia and emaciation, all clinical features which have been shewn (Sections 39, 40 and 49) to lessen tuberculin skin sensitivity. The failures to react met with by von Pirquet (75) in moribund cases further stress the relationship between depression of physiological function and the intensity of tuberculin skin sensitivity. In the same way, the loss of sensitivity during the last week of life reported by Krause (46), Sutherland (83), Dickey (20)/
and others is explained by the depression of bodily function present in the terminal stages of all fatal diseases.

Although the factors mentioned above exert their influence throughout life they do not do so to the same extent at all ages. This is shewn in tables 33, 35 and 36. In the groups of anaemia, emaciation, confinement to bed, extreme weakness, progressive loss in weight, poor appetite and depression of physiological function the following facts are evident:

(1.) In each group for the age period from birth to twelve years, the reactions within the normal range of size greatly exceeded in number those below the normal range.
(2.) In each group for the age period twelve years and upwards the reactions within the normal range of size were definitely fewer in number than those below the normal range.

In the seven groups of good colour, good nourishment, active existence, physiological activity, physically strong, increasing weight and good appetite it is seen that:

(1.) in each group for the age period from birth to twelve years, the reactions above the normal range of size greatly exceeded in number those within the normal range.
(2.) in each group for the age period twelve years and upwards the reactions above the normal range of/
of size were definitely fewer than those within the normal range.

The conclusions arrived at therefore, are:—

(1.) Lessening in the size and severity of the tuberculin skin reaction in cases of clinically recognisable tuberculous infection occurs where one or more of the following features are present:—

(a.) Anaemia.
(b.) Emaciation.
(c.) Prolonged confinement to bed.
(d.) Depressed physiological function.
(e.) Extreme physical weakness.
(f.) Progressive loss in weight.

(2.) Diminution in the size of the tuberculin reaction in clinically tuberculous cases is more likely to occur in those above than in those below the age of twelve years.

(3.) Tuberculin skin reactions of increased intensity in clinically tuberculous cases are common in children under twelve years of age where anaemia, emaciation, depression of physiological function and progressive loss of weight are not features of the case.

(4.) Tuberculin skin reactions of increased intensity only rarely occur in adults with clinically recognisable tuberculous infection.

Section 51.
Section 51. CHANGES IN THE TYPE OF REACTION IN FATAL CASES OF TUBERCULOSIS. (See Section 22).

Of the twenty cases included in table 38 in which repeated tuberculin tests were carried out, seventeen showed diminution in the size of the reaction and four showed no alteration in size. Of the last four, two at the first time of testing showed an already minimal response, and two, with a relatively marked skin response, died suddenly following violent convulsions before extreme emaciation and absolute weakness had become prominent features of the disease. The four remaining cases were tested only once and all during the last seven days of life and three of the four gave minimal reactions.

Table 38 also brings out the fact that in all of the seventeen cases in which diminution in the size of the reaction occurred diminution first took place during the last two weeks of life, seven between the seventh to fourteenth days, eight between the fourth and second days, and two during the last forty-eight hours prior to death.

Experience with the multiple puncture test has shown that normally the maximum reaction is obtained within forty-eight hours (13) and appearance of the maximum reaction after that period is to be considered as delayed. Among the twenty-seven cases included in table 39 all the delayed reactions occurred in individuals/
individuals who were tested during the last week of life, and of the fourteen tested during the last week of life nine patients gave delayed reactions. Burhans (9) found a similar delay in advanced tuberculous infection. This is of importance in that it explains many of the results of tests falsely recorded as negative in fatal forms of tuberculosis. The apparent absence of a skin response in such cases is not due to the fact that tuberculin skin sensitivity is completely lost but is the result of death occurring prior to the recognisable development of a delayed reaction.

Modification of tuberculin skin reactions therefore sometimes occurs in the terminal stages of fatal tuberculosis, and takes the form of:

(a.) diminution in the severity of the reaction as shown by lessening of size, and of intensity of colour and nodularity.

(b.) delay in the appearance of the reaction.

These modifications become more pronounced with the nearer approach of death. That the changes in the reactions are allied to the extreme physical exhaustion and depression of physiological function is shewn by their occurrence only in the final stages of subacute illness, as seen in the majority of cases of tuberculous meningitis and by their absence in cases dying suddenly before emaciation, dehydration or weakness have become pronounced.
Section 52. The Type of the Reaction in Relation to Different Clinical Forms of Tuberculous Infection.

(See Section 23.)

Table 41 shows that in the complete series of cases of clinical tuberculosis under twelve years of age, cases with reactions above the normal range of size formed the largest group, and among those over twelve years of age the largest group was composed of cases with diminished reactions.

From Table 42 it is seen that in cases other than those termed "surgical tuberculosis", ninety-two per cent of the reactions in those under twelve years of age were evenly distributed between the groups of average and increased size. In those over twelve years of age, ninety-two per cent of the reactions were either of average or diminished size.

Only a very few cases of "surgical tuberculosis" over twelve years of age were tuberculin tested and the percentage figures based upon them have to be regarded with caution. However, the same tendency exists for increased reactions to occur with greater frequency in those below than in those above the age of twelve years (Table 42.).

Increased size characterised eighty per cent of the reactions in the age group from birth to twelve years, and thirty-three per cent in those over twelve years of age in the cases of "surgical tuberculosis", as/
as compared with the corresponding percentages of forty-four and eight among cases other than surgical (Table 42).

Among the surgical cases there were no diminished reactions in those under twelve years of age and only seventeen per cent in older individuals, whereas in the corresponding age groups of the cases other than surgical eight per cent and fifty-one per cent were below the normal range of size.

These facts indicate the tendency for more marked reactions to occur in cases of so-called "surgical tuberculosis" than in other types of tuberculous infection - a fact already noted by Dickey (20) and Hart (31).

From table 41 it is seen that reactions increased in size constituted eighty-four per cent (all under twelve years), seventy per cent, seventy per cent and sixty-seven per cent of the results obtained in all cases of tuberculous joints, bones, glands and skin respectively. For children under twelve years of age only, the corresponding figures for the first three named conditions were eighty-four per cent, seventy-five per cent and seventy-eight per cent. In this connection Dickey (20) and Hart (31) both found heightened skin sensitivity in cases of tuberculous joint and bone involvement. In all the clinical groups among children of the present series, at least thirty-six per cent of the reactions were above the normal range of size.
For the complete series including all ages, the greatest incidence of diminished reactions occurred in cases of pulmonary tuberculosis, miliary tuberculosis and tuberculous meningitis. These findings are in agreement with those of Happ and Casparis (30), Hart (31), Dickey (20), Krause (46), Kolmer (44) and others. Among children under twelve years of age however, this high incidence of diminished reactions was not found in cases of pulmonary infection although for children, as for the entire series, cases of meningitis and extensive miliary spread provided the greatest incidence of lessened skin sensitivity with percentages of fourteen and ten respectively.

Comparing the frequency of diminished reactions in children with those in the complete age series, it is seen that for each clinical condition it was very much less in the case of the former.

From the above it is concluded:

(1.) Heightened tuberculin skin sensitivity occurs much more frequently in cases of so-called "surgical tuberculosis" than in other forms of tuberculous infection.

(2.) Diminution of tuberculin skin sensitivity occurs most frequently in cases of tuberculous infection of the lungs or meninges, or where miliary spread has taken place.

(3.) Diminution of tuberculin skin sensitivity is/
is of very much less frequent occurrence in those under twelve years of age than in older individuals.

Section 53. A COMPARISON OF THE TYPE OF THE REACTION IN CLINICALLY TUBERCULOUS AND CLINICALLY NON-TUBERCULOUS INDIVIDUALS. (See Section 24).

Table 43 and diagrams 74 to 77 (inclusive) bring out the following facts:

(A.) In the age period from birth to twelve years of age:

1. Seventy-three per cent of reactions were above the average size among those with clinically recognisable tuberculous infection.

2. Only three per cent of reactions were below the average size among clinically tuberculous individuals after elimination of moribund cases.

(B.) In the age group twelve years of age and upwards:

1. The percentage of reactions above the average size was very slightly greater in the clinically tuberculous group than in the clinically non-tuberculous group.

(C.) (1.) Reactions above the average in size occurred with much greater frequency in the first twelve than in the later years of life.

2. Reactions below the average in size occurred with very much less frequency in the first twelve/
twelve than in the later years of life.

Those of the observations in connection with children confirm similar findings by Dickey (20). Cummins (16) found that diminished reactions in adults were more commonly associated with clinical tuberculosis than with what he termed the latent forms of infection but our observations in table 43 indicate that no particular modification of the skin reaction characterises clinically tuberculous or clinically non-tuberculous adult cases.

The term "active tuberculosis" is commonly used in the literature to indicate clinically recognisable infection, and conversely, clinically recognisable infection is frequently taken to imply activity. In this connection King (40) and Ustvedt (86) are of the opinion that no relationship of practical value exists between active infection and a large skin reaction. Similarly Austrian (2) does not consider that the "clinical status" of an individual with reference to tuberculous infection is indicated by the nature of the tuberculin reaction. Holmes (38) finds that increased skin response to tuberculin occurs in association with active infection, and, in so far as activity is indicated by the demonstration of tubercle bacilli, our observations agree with those of this worker in their application to children but not to adults.
Diagram 78, based on the figures of table 44, demonstrates that the relationship applies only to children. This diagram shows that the curves of mean diameters of reactions in the groups of clinically tuberculous and clinically non-tuberculous individuals coincide during adolescence and active adult life. On the other hand the mean diameter of the skin reaction throughout childhood is greater in clinically tuberculous cases than in clinically non-tuberculous cases, and the difference between the two lessens with increasing age.

It is concluded therefore that clinically tuberculous children as a group give tuberculin reactions of greater intensity than tuberculous children whose infection is not clinically recognisable.

Section 54. CASES IN WHICH A TUBERCULIN REACTION OF INCREASED INTENSITY PRECEDED THE DEVELOPMENT OF CLINICALLY TUBERCULOUS INFECTION. (See Section 29).

Considerable importance is to be attached to the skin reactions of increased intensity occurring in all nine cases included in table 50.

In five of these cases medical advice was first sought on account of apparently trivial complaints - slight rickets in one; a painless limp in another; in the third, an infant, failure to thrive; while the symptoms of the fourth and fifth children were those of/
of an ordinary dyspepsia.

Manifest serious disease was present in two children, one a case of rheumatic pericarditis and the other a case of alveolar pneumonia. Neither in the history nor in the results of a careful examination of any of these children was there anything directly pointing to the presence of tuberculous disease. In the case of the child admitted to hospital on account of an extensive purpura the presence of physical signs suggestive of an old lung lesion raised the question of a pulmonary focus but did not explain the skin condition. The last child was recommended for admission to hospital as a case of hysteria, the practitioner having satisfied himself as to the absence of organic disease.

Clinically the only point in common in these cases was the occurrence of a tuberculin skin reaction of increased intensity. Eight of the nine cases were dead within four months of tuberculin testing, four dying from generalised tuberculous infection while in the other four, active tuberculous infection was shewn at autopsy to be a contributory factor in causing death. Early tuberculous disease of the spine was revealed by X-ray examination in the remaining case.

Such findings favour the view that the listlessness, the anorexia, the failure to thrive and similar symptoms appearing in the histories of these children were in reality "the finger prints of tuberculous toxaemia"/
toxaemia" (21) so often emphasised by Philip (69, 70).

Philip has stressed the important relationship that may exist between such vague events in the child's early history and a positive tuberculin reaction. The observations in table 50 confirm Philip's views, and in addition they show that the test has an unrealised value in that a reaction of increased intensity indicates the presence of infection which threatens to become overwhelming.

Section 55. THE DIMINISHED REACTION.

Where skin sensitivity was diminished the colour, nodularity and size of the reaction were all lessened in degree in the majority of cases, but in a few irrespective of whether the underlying tuberculous infection was clinically recognisable or not, one or more, but not all these properties of the reaction were less marked (Sections 18, 27 and 49).

Tuberculous infection may be active although not demonstrable other than by tuberculin tests, but in the majority of the cases where the presence of the organism is proved, activity of the infection can be assumed. Positive reactors of the clinically non-tuberculous group included all forms of unrecognisable infection, but as a group can be considered as representing a less active form of tuberculous infection than the clinically tuberculous cases. Diminished reactions occurred in both groups of cases (Sections 24/
24 and 53) and therefore cannot be explained by the degree of activity of the infection. In support of this is the fact that among clinically tuberculous cases depression of sensitivity was not related to the length of time that symptoms had been present (Sections 21 and 50). Small reactions occurred among those dying only a few weeks after the onset of symptoms as well as among those never critically ill, but with a long history of infection.

Cases of clinical tuberculosis with small skin reactions all showed marked constitutional disturbance in the form of anaemia, emaciation or great physical exhaustion and they had all been confined to bed for a prolonged period (Sections 21 and 50). Similar findings were made in connection with positive reactors among the clinically non-tuberculous individuals. In these last a close relationship was demonstrated between diminished intensity of the reaction and anaemia, impaired nutrition and confinement to bed whether these conditions occurred separately or together (Sections 7, 8, 9, 38, 39 and 40). Where they occurred together, depression of physiological function was necessarily present in some degree and the same was true where one of them existed alone when of sufficient severity.

Depression of physiological function therefore, is associated with the main factors so constantly found/
found co-existing with diminished skin sensitivity apart from the recognisability or otherwise of the tuberculous infection. Further evidence in favour of this view was obtained in the observations made in connection with cases of cardiac insufficiency (Sections 10 and 41). Interference with normal physiological function in these individuals had resulted from prolonged impairment of circulation, and, in the absence of other modifying factors small skin reactions were commonly, although not constantly met with.

The striking clinical feature of influenza is the extreme physical and physiological depression present in convalescence and, the fact that reduced sensitivity was met with in every case tested (Sections 10 and 41) emphasises the relationship existing between tuberculin sensitivity and normal bodily function. The observations made in connection with the specific infectious diseases (Sections 13 and 44) lead to similar conclusions. A few small skin reactions were encountered but in each instance the patient's condition was critical, either on account of the severity of the infection or as the result of serious complications.

The same is true of the diminished skin reactions found in connection with physiological events in the female life (Sections 15 and 46). Menstruation, pregnancy and lactation all involve alterations in the distribution of the circulating blood, while with parturition/
parturition there are the additional factors of great physical strain and considerable loss of blood. In these conditions metabolism undergoes temporary re-adjustment and physical vitality is lowered: the changes which occur are essentially normal physiological events and the alteration in tuberculin reactivity is related to the temporary modification of bodily function. The intimacy of the relationship is shewn by the way in which, where depression of sensitivity was found during menstruation tuberculin reactivity regained its normal intensity during the intermenstrual phase (Sections 15 and 46). The increased sensitivity which followed clinical improvement in the cases of pulmonary tuberculosis (Sections 21 and 50) and primary anaemias (Sections 10 and 39) is strictly analogous. In all these conditions restoration of normal bodily function was accompanied by a return to normal of tuberculin skin sensitivity.

A contrast with the cases involving temporary changes in physiological balance is provided by the individuals with malignant disease (Sections 8, 10, 39 and 41) and those dying of miliary and pulmonary tuberculosis (Sections 22 and 51) where metabolism progressively lessened until bodily function finally ceased. As long as life existed in the body metabolic processes were continuing to take place, and the protracted dying days of such individuals consisted in/
in the gradual failure of these processes. The tuberculin reaction provided a measure of the body's decline: its increasing delay in appearance (Sections 22 and 51) and diminishing intensity (Sections 22 and 51) mirrored the decline of metabolism thus further demonstrating the close relationship existing between tuberculin skin sensitivity and physiological function.

Small reactions were also met with in cases of syphilis and measles (Sections 10, 13, 41 and 44). All the cases of spirochaetal infection were examples of tertiary syphilis. As none of them had at any time had antispecific treatment the disease in each instance had pursued its course unchecked and visceral involvement was characteristic. Even where cardiac damage was not detectable, disease of the vessels was gross and evidence of impairment of either renal or hepatic function was present in most of the individuals. Although the selected cases were not emaciated or anaemic their tissues lacked healthy tone, and the effect of the syphilitic poison was most evident in the lowering of general health which necessarily followed impaired function on the part of the various organs concerned in metabolism. There was an absence of vitality and vigour in these individuals and this sluggishness had its counterpart in the smallness of the skin reactions they gave. Tuberculin reactions have been shewn not to be subject to modifications attributable/
attributable to local conditions of the skin or peripheral vessels (Sections 4, 5, 35 and 36), and in the absence of such an explanation the diminished skin sensitivity is accounted for by the general toxic depression of bodily function in these individuals.

In the selected cases of arterio-sclerosis the frequent occurrence of extreme debility was noted (Sections 5 and 36) and the debilitated individuals in the series gave a high proportion of diminished skin reactions. Where sclerosis was marked but debility absent, tuberculin sensitivity was unimpaired. Diminished reactivity therefore is not directly attributable to the state of the vessels, but where, in the absence of any specific poison as in the syphilitic cases, metabolic processes have been interfered with by the arterial condition, depression of sensitivity occurs.

Fever was shewn not to interfere with skin response to tuberculin (Sections 14 and 45) and therefore does not explain the lessened reactivity encountered in measles. Measles is an infection of short duration and of only mild severity. Its danger lies in the possible sequelae. Children recovering from an attack of measles are liable to contract other infectious conditions. Of still greater significance is their liability at a later date to betray clinical evidence of tuberculous disease. Measles/
Measles in particular appears to lessen a child's ability to keep an already existent tuberculous infection within unrecognisable bounds. It is possible therefore that, even in the absence of any marked constitutional upset measles taxes a child's resources more than is outwardly apparent, and that there is greater interference with physiological processes during the eruptive phase of the disease than appearances suggest. Such a state of affairs would explain the occurrence of diminished skin sensitivity. Any considerable metabolic upset is necessarily of short duration as convalescence is rapid and this is in keeping with the transient nature of the lessened skin reactivity. That the factor modifying the tuberculin reaction in measles is related to the extent of interference with bodily function is borne out by the case of rubella reported by Koch (43) in which loss of sensitivity was found, and by the absence of alteration of the skin reaction in cases of attenuated measles (43). In his case, Koch attributed the unusual loss of sensitivity to the exceptional severity characterising the infection.

Section 56. THE INCREASED REACTION.

The majority of reactions above the average size occurred in cases clinically tuberculous (Sections 24 and 53). Among children the clinically tuberculous subjects as a group gave larger reactions than those/
those clinically non-tuberculous. These facts are significant in that they indicate that the intensity of the tuberculin reaction is not solely dependent upon physiological function, but is also related to the nature of the underlying infection.

The observations made concerning improving cases of pulmonary tuberculosis (Sections 21 and 50) are important in this connection. The intensity of the skin reaction in these individuals increased following satisfactory response to treatment. Active convalescence in these patients implied a body metabolism approaching normal, despite the presence of a potent infection under some measure of control.

Increased reactivity was an almost constant feature in cases of pleural effusion and in those included under the term "surgical tuberculosis" (Section 23 and 52). Although not physically robust, the great majority of these individuals had been living an active existence to within a few hours of entering hospital. Pallor was present in a few and some showed milder degrees of malnutrition, but their general health was not actually poor. Tuberculous infection in these individuals became clinically manifest for the first time while their physiological activities were still those of a healthy person.

The cases of tuberculous meningitis tested two to three weeks before death (Sections 22 and 51) come into/
into the same category. Apparently in normal health one day, they were admitted to hospital the next for some vague complaint such as vomiting or headache. At the time of admission the general constitutional upset was no greater than that often resulting from definitely trivial ailments, and examination revealed no evidence of a tuberculous process. Increased in size, the tuberculin reactions in these cases were obtained while physiological function was still normal despite the presence of a tuberculous infection which was to prove rapidly fatal.

The same was true of the cases detailed in table 50 (Sections 29 and 54). The child with purpura, the girl with hysteria, the boy with a limp and the dyspeptic children were all living a normally active life: all showed increased sensitivity to tuberculin and in them all severe tuberculous infection was demonstrated at a later date.

Increased tuberculin sensitivity in all these groups of cases was associated with two prominent features. Firstly the individual's health was such as to allow of average physical and physiological activities, and secondly, tuberculous infection of an immediately threatening nature was present. A large reaction therefore has a definite significance - it reveals the presence of tuberculous infection, and also indicates a danger of the individual's resistance/
resistance to the infection being overcome. Kolmer (44) quotes Krause as saying: "the patient is as resistant as the shell of his tubercle". The severe tuberculin reaction indicates that that resistance is at breaking point. Proof of this is seen in the prognostic value of the large reaction in the cases included in table 50. In the absence of clinical evidence of tuberculous infection, the increased tuberculin sensitivity gave warning of the danger underlying the patient's trivial initial symptoms. Of the eight cases which came to autopsy the tuberculous process was the primary factor causing death in four, and a contributory factor in the remaining four. In all eight cases death occurred within a few months of tuberculin testing.

The large skin reactions found in a high percentage of children with a history of household contact (Sections 17 and 48) further explain the significance to be attached to heightened sensitivity. It is accepted that danger not only of infection but of a severe form of infection, is increased by the factor of constant exposure. This danger is greatest in the case of children. The possibilities of the initial infection becoming speedily localised and serving a protective function are lessened: the chances that the first infection will be extensive and even overwhelming are increased. Even should a child acquire an initial protective infection, continual household exposure/
exposure involves a constant risk of any existing protection being overcome. In the natural course of events the position of the child constantly exposed to infection is one of peculiar precariousness. His infection must almost inevitably be extensive, and his resistance to generalised spread under continuous and increasing strain. Both clinically and pathologically the tuberculous process in such individuals resembles that found in the children in table 50 in whom infection had assumed threatening proportions in the absence of a known history of contact. Heightened tuberculin sensitivity was characteristic of both groups of cases and was therefore, a warning of the immediate danger attached to the existing tuberculous infection.

Section 57. VARIATIONS IN INTENSITY OF THE REACTION IN THE SAME INDIVIDUAL.

Variations in the intensity of the tuberculin reaction occurred in a number of individuals. Sensitivity was depressed in a large proportion of menstruating women, but not during the intermenstrual phase (Sections 15 and 46). Small skin reactions were given by anaemic patients and undernourished individuals, but reactions normal in size were obtained in these subjects following improvement in their condition (Sections 8, 9, 39 and 40). On the other hand skin sensitivity lessened progressively in cases dying of malignant/
malignant conditions (Sections 8 and 39). In all these individuals the tuberculous process remained clinically unrecognisable and the variations of skin reactivity cannot be related to changes connected with the tuberculous infection.

Among clinically tuberculous cases reactions became increasingly smaller during the last few days of fatal illness (Sections 22 and 51), but became larger in individuals successfully treated for pulmonary infection (Sections 21 and 50). The severity of the infection and the intensity of the reaction did not correspond. As in the clinically non-tuberculous individuals, the tuberculin skin sensitivity varied with the physical and physiological activities of the individual (Sections 21 and 50).

A "secondary reaction" was only once met with in the present investigation. In children a positive reaction was never obtained where there had been no response to a previous test. Five adults failed to react to tuberculin, and four of these remained persistently negative to further tests (Sections 19 and 28). The fifth, a case of severe pernicious anaemia gave a weak positive reaction after two weeks in hospital (Section 8) by which time any general sensitising influence of the first test may be assumed to have disappeared. The second test was carried out on the opposite arm to the first so that there was no question/
question of increased local sensitivity due to the initial test. It was shewn that this patient's power to react to tuberculin became manifest and later increased as his general physical condition improved.

It was also found that age was accompanied by variations in the intensity of the tuberculin reaction (Sections 1 and 32), and it is evident that alteration in the processes of bodily function, occurring either as the result of normal physiological events or as the result of illness, account for alterations in the tuberculin sensitivity of an individual.

Section 58. FAILURE TO REACT.

Three adults with proved tuberculous infection failed to give a skin reaction to tuberculin (Section 28). All three cases were in a critical condition, showed extreme exhaustion, were definitely anaemic and had been confined to bed for a long period. These factors have already been shewn to interfere with bodily function (Sections 7, 8, 9, 10, 38, 39, 40 and 41), and the complete loss of tuberculin sensitivity in these cases was a result of the disorganisation of metabolic processes.

Two clinically non-tuberculous adults were persistently negative to tuberculin tests (Section 19). One of these was a man in whom a chronic dysenteric infection had resulted in extreme emaciation and dehydration and who died a few days after the carrying out/
out of the tuberculin test. The other was a man of advanced years who was healthy apart from some deformity of his extremities resulting from long standing rheumatoid arthritis.

The occurrence of these non-reactors is striking considering the almost universal sensitivity met with in adults (Section 1). Assuming tuberculous infection to have taken place at some time, the absence of skin sensitivity is adequately explained in the case of dysentery by the individual's almost moribund condition. There was nothing in the clinical state of the patient suffering from rheumatoid arthritis to explain the non-appearance of a positive reaction, and the question arises as to whether sensitivity to tuberculin had been present at any time. The incidence of reactors in the series given in table 1 increased uninterruptedly from birth to the period in adult life when ninety-nine per cent (99.4%) of individuals reacted to tuberculin. This does not favour the view that loss of tuberculin sensitivity occurs in normal health as an accompaniment of the extinction of tuberculous infection. Krause (46) does not consider that all adults are infected and it is probable that the patient with rheumatoid arthritis had never acquired tuberculous infection and had therefore never been sensitive to tuberculin.

Negative responses were also obtained in two individuals/
individuals who at other times reacted positively to tuberculin (Sections 8 and 39). The one was a case of pancreatic carcinoma which although giving a skin reaction on three previous occasions, was persistently negative during the last week of life. The other was the case of pernicious anaemia referred to in the previous section; a non-reactor at the time of admission, tuberculin sensitivity developed during the time the patient was in hospital and was present at the time of discharge. In both, absence of tuberculin skin sensitivity occurred at the period when depression of physiological processes was greatest.

This depression of bodily function accounts for the isolated instances occurring among adults in whom tuberculin reactions were not obtained, with the exception of the one case in which tuberculous infection was not shewn ever to have existed.

Section 59. THE IMPORTANCE OF BODILY FUNCTION.

Consideration of the factors concerned in increase, decrease, and disappearance of tuberculin skin sensitivity reveals the importance of normal bodily function. Interference by disease of normal physiological processes resulted in diminution of sensitivity irrespective of whether the individuals were clinically tuberculous or clinically non-tuberculous (Sections 8, 9, 10, 13, 18, 22, 23, 24, 27, 28, 39, 40, 41, 44, 49, 50, 51, 52, 53, 55). Conversely small/
small reactions did not occur in the presence of normal metabolism (Sections 1, 15, 21, 22, 23, 32, 46, 50, 52, 54). When account is taken of the fact that variations in the acid base equilibrium of the body influence the nature of the tuberculin reaction (4) it is evident that factors dependent upon the physiology of the individual and not necessarily in any way connected with the presence of a tuberculous process, explain alterations in skin sensitivity. Balint and Weiss (4) report lessening of skin response to tuberculin where there is displacement to the alkaline side of the reaction of the blood, and the increase in the alkali reserve recorded by Dautrebrande and Davis (18) in extensive tuberculous disease of the lungs would explain the "cachexia reactions" often associated with this condition.

The extent of metabolic upset necessary for interference with the tuberculin reaction is considerable. There was no diminution in the size of the reaction in a certain number of anaemic and undernourished individuals. The same was true of a number of cases admitted to hospital on account of recent coma arising from acidosis, uraemia and intracranial haemorrhage. The metabolic changes associated with anaesthesia given for minor operations did not modify skin sensitivity (Sections 16, 26 and 47). On the other hand diminished reactions were met with in several individuals tested during/
during the post-operative period following gastro-enterostomy (Sections 18 and 49). It was considered that in these cases the combined effects of prolonged anaesthesia, operative shock, starvation and recumbency had sufficiently altered bodily metabolism to lessen skin reactivity.

Any influence exerted upon the tuberculin skin reaction by variations in physiological function should be apparent not only in connection with variations following on ill health, but also with those resulting from normal bodily growth and decline in the course of the life cycle.

The energy requirements of an individual provide a measure of physiological function. Table 51 gives the caloric requirements of an average healthy individual at different ages and these are plotted in the form of a curve in diagram 85. This curve shows that the energy requirements of an individual rapidly increase up to the period of adolescence and early adult life and thereafter decline. In diagram 85 there is also given the curve of arithmetical mean of diameters obtained in healthy positive reactors. The ordinate of this curve increases up to the age period twenty to twenty-five years, and afterwards decreases in the same way as that of the curve of caloric requirements. The tuberculin skin reaction increases in size and intensity with the energy intake, and both reach their maximum/
maximum between the ages of twenty and twenty-five years. As the prime of early manhood is passed, diminution of skin sensitivity accompanies the lessening needs of bodily function.

From these findings the conclusion is arrived at that changes occurring in bodily function, whether as the result of disease or of normal physiological events, influence the intensity of the skin response to tuberculin.

Section 60. THE IMPORTANCE OF AGE.

It has been shown that the intensity of the tuberculin skin reaction is subject to variations with age (Sections 1 and 32). The potency of factors decreasing or increasing tuberculin sensitivity is also related to age. The incidence of reactions of increased intensity among contact children was high, and among adult contact cases low (Sections 17 and 48). Heightened sensitivity was characteristic of cases clinically tuberculous as opposed to those clinically non-tuberculous among children, but not among those over twelve years of age (Sections 24 and 53). Clinical tuberculosis in association with unimpaired physiological function gave rise to increased reactivity in eighty-five per cent of cases under twelve years of age, but in those above that age reactions of normal size were twice as common as those of increased intensity (Sections 21 and 50). These observations/
observations show that heightened tuberculin skin sensitivity, although not occurring exclusively in childhood, is very much more common below than above the age of twelve years.

Exactly the reverse held for diminished sensitivity. Depression of physiological function almost invariably led to decreased skin reactions in clinically tuberculous cases over twelve years of age, but where present in children it exerted a similar effect in only eight per cent of cases (Sections 21 and 50). Also, the three instances of failure to obtain a skin response to tuberculin in clinically tuberculous cases all occurred in adults (Sections 28 and 58).

Tuberculin tests have always been recognised as having a particular value in their application to children. Although a positive reaction in infancy and the earlier years of childhood has been considered significant, the value of the tests has been mainly in the fact that an absence of response ruled out the presence of tuberculous infection. Hitherto even the value of a negative reaction has been limited on account of the variety of factors recorded as interfering with tuberculin skin reactivity. Our observations show that desensitising factors only rarely modify the tuberculin skin reaction in children. They also demonstrate that the influence of factors heightening sensitivity is more pronounced in those below than above the age of twelve years.
The likelihood of obtaining false negative responses, therefore, is least in tests carried out on children. Large reactions having a certain ominous significance regarding immediate danger occur almost exclusively among children.

The tuberculin test therefore is especially sensitive, and has a particular significance in its application to children.
PART V.

SUMMARY AND CONCLUSIONS.
PART 5.
SUMMARY AND CONCLUSIONS.

1. Variations in the intensity of the tuberculin skin reaction are related to:
   (a.) the normal development and decline of bodily function,
   (b.) depression of bodily function associated with:
       (1.) Prolonged confinement to bed.
       (2.) Anaemia.
       (3.) Malnutrition.
       (4.) Cardiac insufficiency.
       (5.) Syphilis.
       (6.) Influenza.
       (7.) Measles.
       (8.) Physiological events in the female life.

2. Tuberculin skin reactions attain their maximum reliability in children owing to the relative infrequency in the early years of life of the conditions found to modify skin reactivity to tuberculin.

3. A severe tuberculin skin reaction occurring in a child is an indication of impending failure of local or general resistance to tuberculous infection.
PART VI.

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