

THESIS WRITTEN BY SINCLAIR REID WILSON, M.B., Ch.B., Glasgow,

for the M.D. Glasgow

on

" A STUDY OF PULMONARY TUBERCULOSIS IN CHILDREN "

with an appendix on

" THE TREATMENT OF PULMONARY TUBERCULOSIS IN CHILDREN
WITH SANOCRY SIN " .

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SECTION I. - Introductory.

The problems of Pulmonary Tuberculosis in Children, from the diagnostic standpoint, would be practically eliminated if the bacillus of Tuberculosis could be demonstrated in the sputum or in any of the other excreta of the body, normal or abnormal. Children, however, have very little expectoration, and what little they do have they usually swallow, so that the opportunity of bacteriological examination of sputum, so useful in the case of adults, is denied us when we come to examine the disease process in children. We know that the child has a cough, and, from our physical examination, we can hear that much pulmonary excretion may be taking place, but this gives us only false hopes of coming to a definite diagnosis of the child's pulmonary condition, and we would hide our confusion and say rather that there is a catarrhal condition of the bronchi and air passages which might or might not be of a tubercular character. Then it is that the parent tells us that the child has been losing weight, has very little appetite, and is listless and apathetic, and, with all our detective instincts aroused, we discover possibly that one or another of member of the family has died of "consumption". This

adds considerably to our bias in favour of a definite diagnosis, and we repeat our examination with the balance of evidence going strongly against the child. With greater finesse in our percussion, then, we probably decide that there is some glandular enlargement at the root of one or both lungs, and ultimately we consider ourselves justified in declaring a diagnosis of Pulmonary Tuberculosis. In spite of ourselves, however, or because we are still endeavouring to be completely honest with ourselves, doubts often assail us, and we would be happier if the decision could be made more easily, either by means of our physical examination alone, or by the aid of the numerous tests which have been developed, both in laboratory and at the bedside.

It is generally agreed that congenital tuberculosis is rare; and Hebert (1) says that "during the first two years of life, the number of deaths from pulmonary tuberculosis is relatively high, and the disease is usually fatal". This would lead to the inference that the infection in infancy is very virulent and widely distributed, and were the infection suddenly to take place among the young of a susceptible tribe, the fatality would probably approach a hundred per cent, and the tribe might be in danger of annihilation. Cummins (2) gives this interesting comparison between "primitive"

and "civilised" peoples :-

"Primitive tribes are highly susceptible to tuberculosis, because in the absence of tubercle bacilli, they have never been obliged to protect themselves against that organism. Civilised peoples are highly protected against tuberculosis because, in contact with the tubercle bacillus, they have elaborated protective substances against that organism".

It would appear therefore that, as Hebert (1) puts it, "Childhood is the period of infection", and the number infected is probably much greater than a general survey of children would lead one at first to expect. The children of this country, and of civilisation generally, whose ancestry has been in long-continued association with the tubercle bacillus, are blessed with a certain amount of resistance against the organism, and the fight they have to sustain varies in degree with the quantity of infection to which they are exposed. As age increases up to five years their resistance seems to increase very greatly, because, according to Hebert (1) "the number of deaths from pulmonary tuberculosis between 5 and 12 is much lower than at any other period of life". Nevertheless, it seems reasonable to suppose that, all along, the children are liable to small infections from time to time, which will undoubtedly cause a more or less severe reaction in their general constitutional condition, whether the infection is of the pulmonary type or of

Any other type which may occur in the body.

We can look at the child's progress, then, as a series of waves, mounted on a straight line, the waves representing these reactions to periodic infections, and the straight line representing the periods when resistance has been raised and the antibodies are sufficient to meet any attack which may be launched by the organism. The ideal is to maintain the resistance at as high a level as possible, for as long as possible, the liability to infection being so general and widespread, and so to increase the power of the body to deal with these infections as they occur in the later stages of life.

This ideal demands a prolonged supervision over the children who are deemed to be tuberculous, and it is surely necessary to have no doubt in the mind of the supervisor as to which child is suffering, and which is not suffering from tuberculosis. Therefore, if by greater skill in diagnosis, aided by the correlation of various tests, we could come to a more definite knowledge of the state of the children's health, we might be able to make some classification which would help us in our treatment, and give us greater assurance when we come to make a prognosis.

SECTION IIHistorical Sketch.

The story of the plagues in Egypt, as told in the Book of Exodus (3), is a descriptive glorification of the God of the Israelites, who were a clean-living, open-air tribe, and at the same time a denunciation of a civilisation, which lived in a slothful luxury, supported by slaves, which was concentrated in a dense population, and which was comparable in many ways to every civilisation which has existed in the world we know. It is true that Moses, the author of this most engrossing history, has speeded up the actual occurrence of these plagues, and, just as he depicted the creation of the Universe as taking place within six days with a certain amount of production for each day, he has found it more attractive and impressive to allot, by special instruction from the Almighty, certain days for the advent of the ten destructive pestilences, which so crippled the Egyptian tyrants, that the Israelites were allowed to leave the country. The interest, for me, is greatly enhanced when I read that at one time the animals are stricken with a "murrain", so that horses, oxen, sheep and cattle are destroyed, at another time both men and animals are infested with lice, and that, finally, the first-born of every house of the Egyptians is destroyed and the

first-born of all the cattle at the same time. This last plague makes me think that an acute tuberculosis must have carried off a tremendous number of Egyptian children, and the fact that the cattle also suffered simultaneously appears to me to add strong proof that tuberculosis was the cause. As soon as a population becomes unwieldy and congested, the stagnation of circulation, human or animal, leads to acute destruction of the excess, in an effort to bring back to normal the balance of growth.

Plagues, in various forms and of different degrees of severity, have been recorded in many of the histories of the human race. It was the custom of the ancients, however, to associate calamities with displeasure of their Gods, and diseases with demons which possessed their sufferers, and it is interesting to read of the amulets they wore as a protection against these malignant external influences, and of the prayers they offered up for their self-preservation. The following prayer, according to Neuburger's "History of Medicine" (4), was frequently used by the Babylonians :-

"Wicked Consumption, villainous Consumption, Consumption which never leaves a man, Consumption which cannot be driven away, Consumption which cannot be induced to leave, Bad Consumption, in the name of Heaven be placated, in the name of Earth I conjure thee !"

Tuberculosis, the same we know and try to understand, has been known evidently for thousands of

years. Hippocrates (460 - 370 B.C.) has described the disease, clearly and minutely; and he has called it "phthisis". He was familiar with the friction of a dry pleurisy, and with moist râles which he compared to "the noise of boiling vinegar". In his medical aphorisms (Book 5) he says that "consumption most commonly attacks persons who are between the ages of eighteen and thirty-five", and again "when a consumptive person has attacks of diarrhoea, a fatal issue may be anticipated". Inasmuch as he was the greatest of the physicians, the most critical of observers, so did the Asclepion at Cos, where he practised, become one of the greatest sanatoria of Greece, and the pattern of the medical schools of the world.

Celsus, and Aretaeus of Cappadocia, about the time of the birth of Christ, Galen (131 - 201 A.D.) and the Arabian physician, Avicenna (980 - 1037 A.D.) all knew the disease which we now call pulmonary tuberculosis, and they have described as accurate a clinical picture of the tuberculous patient as it is possible to read. They saw the wasting, the hectic flush, the consuming fever of phthisis, and they knew the significance of the persistent cough, with spitting of mucus, of pus, or of blood.

Probably the next advance in the observations on this dire disease, called so aptly by Osler "the

captain of the men of death", was made by Fracastoro of Verona (1483-1553 A.D.) (see the "Growth of Medicine" p. 389, by Albert Buck) who "ranks very high among the physicians of the first half of the sixteenth century for his valuable contributions to our knowledge of internal pathology". Evidently this Italian described the germ theory of diseases very clearly in a treatise written in 1546, in which he divides the infectious diseases into three classes :- (1) Those which infect only by contact; (2) Those which not only infect by contact, but at the same time leave behind a centre or focus of infection - in which category he places tuberculosis, elephantiasis, and similar diseases; and (3) Those which infect not only by direct contact, or through the agency of a residuary centre or focus of infection, but also those which are capable of spreading their infective elements over wide areas, - for example, the pestilential fevers, certain ophthalmias, variola, etc.". Speaking of tuberculosis, which Fracastoro calls "phthisis", "it is astonishing", he says, "for how great a length of time the virus of this disease retains its infective power".

It must be agreed, then, that the infectious nature of tuberculosis has been admitted for centuries. The commencement of the pathological study of tubercle probably dates from 1782, when an English physician, Thomas Reid (5), called attention to the granulations

and tubercles, which increase in size, become purulent in their centres, and eventually go to form large abscesses in the lungs. Boyle, a French physician (1810) described acute military tuberculosis as a general disease, not confined to the lungs, which is "probably identical with scrofula". Laennec (1781-1826) laid the real foundation of the pathological study of tubercle; Villemin (1865) demonstrated the inoculability of tubercle and caseous material; Pasteur about the same time laid the foundation stone of the edifice of Bacteriology; and Koch (1882) at last showed that the infective agent in tuberculosis was the Tubercle Bacillus, (6) a definite, specific organism, pathogenic to man and certain animals, all but omnipresent, and almost unlimited in its numbers.

The story of tuberculosis, I think, and of diseases generally, has been a gradual study through thousands of years of the macroscopic to the microscopic; and, more recently, from the microscopic back to the macroscopic again. Out of it there has emerged the theory of infectivity, and by this time the number of infective agents has become legion. One of these agents is the Bacillus of Tuberculosis, and its locus operandi appears to be wherever civilisation has spread its influence. This very bacillus, like the atom of the physicists, is itself undergoing the scrutiny of further microscopic examination, and, even as I write,

I come from reading a short notice, ("Observer", for 23rd March 1930) regarding the present researches of Calmette, who has discovered a pre-bacillary state of the Tubercle Bacillus. The bacillary atom would appear to have electrons in its structure, which can pass through a filter, and can traverse the tissues of the placenta. What this research means to the bacteriologist it is impossible to predict, because what may be proved of one unicellular organism may have to be applied to them all, and the text books of bacteriology may have to add another chapter, involving a general principle, in an attempt to come nearer still to the ultimate causes of pathological processes.

This research of Calmette's appeals to me further in that it renders the possibility of infantile infection with tubercle much greater, and, although I have written above that congenital tuberculosis is rare, I cannot but feel that the potential bacillus may be present often at birth, its activities being only delayed for a shorter or longer period. Thus do we of necessity return from the ultramicroscopic to the macroscopic, and see the disease process itself, whether in the form of an acute miliary tuberculosis of infants, or later in the more chronic lymphatic disease of childhood. It must be admitted that infection, as we must call it, either before or after

birth, is very widespread, and has been so for many, many years, but it must be understood that infection with the tubercle bacillus is a different thing from tuberculosis. As Fishberg (7) puts it (in his "Pulmonary Tuberculosis") :- "Tuberculous disease is always preceded by infection, but infection with the tubercle bacillus is not invariably followed by disease."

Other cases of definite physical signs in the lungs, the examination of the sputum being negative.

The children were drawn chiefly from various classes of a city population, and in many cases there was a history of tuberculosis in the family, the father or the mother had undoubtedly the disease and had been a patient in the hospital several years before.

(b) Clinical Examination.

SECTION III.Scope of the Thesis.

The work embodied in this Thesis includes the physical examination of upwards of a hundred children, whose ages range from five to fourteen years, who were subjected also to radiological examination, and upon whom Blood Sedimentation Tests, Polynuclear Counts, and Tuberculin Tests were done. About a dozen were selected, whose faeces were examined for tubercle bacilli, in the hope of obtaining a definite bacteriological diagnosis, but it must be declared at once that, in spite of the fact that the children chosen had definite physical signs of activity in the lungs, the examination of the faeces was in all cases negative.

The children were drawn chiefly from the working classes of a city population, and in the large majority there was a history of tuberculosis in the family, either on the father's or the mother's side, and occasionally the children were born of parents who themselves had been patients in the children's sanatorium years before.

(a) Physical Examination :-

In children this requires great care, and often it is extremely difficult to say that there is anything abnormal in the chest. Percussion in the interscapular region must be delicate, in order

to elicit variations in dullness from the normal, or differences between each lung; but the information supplied, coupled with even slight abnormality in the respiratory murmur, will often tell us that some thickening exists at the hilus, and that some enlargement of glands has taken place in the tracheo-bronchial lymphatics. To quote Riviere (8) "We speak of 'Tuberculosis of Thoracic Glands' or 'Hilus Tuberculosis' as the earliest stage of tubercle in childhood. The resulting disease runs a different clinical picture (from that of the adult) on account of the prominence of the lymphatics at this end of life". Doubtless, then, the disease process tends to spread along the framework of the lung, in the lymphatics, and results in a chronic interstitial fibrosis, ulceration very, very rarely occurring at this period of life. Hebert (1) says :- "Chronic interstitial fibrosis is the commonest of the chronic pulmonary diseases of children, whereas fibrocaseous tuberculosis, for which it is liable to be mistaken, is rare..... It probably favours the implantation of T.B." But now, however, even if it is decided that some glandular enlargement is present, it must not be concluded that this glandular condition is tuberculous, because, the lymphatic system in childhood being relatively so much more active than in the adult, it is much more liable to engorgement from any slight upset of the normal metabolic balance.

With moist sounds in the lungs, superimposed on the above findings, particularly if these sounds are persistent, the diagnosis becomes much more definite of Pulmonary tuberculosis. But, as the signs, even then, are often indeterminate, because of this fine gradation which exists between normal and abnormal, it is frequently impossible to classify cases as + or — . Hence I have found it convenient to make the following classification, as determined by physical examination alone :-

- + = Positive tubercle.
 - ± = Doubtful, but most probably tuberculous.
 - ∓ = Doubtful, but most probably not tuberculous.
 - = Negative tubercle.
-

(b) X-Ray Examination :-

What has been said regarding the interpretation of the physical signs in children applies equally to the interpretation of the radiographs of the chest at this stage of life. The fine differences between the picture of a normal chest, showing the delicate framework of the child's lungs, and the "beading" or lymphatic thickening which takes place in that framework, are only too difficult at times of discrimination, and the decision cannot always be a dogmatic one, either in the positive or the negative. This gradation seems

to me to be constantly presenting itself when I am faced with the diagnosis of pulmonary tuberculosis in children. The shadows due to enlargement of glands in the mediastinum present the same problem which arises when percussion reveals some root-thickening, and the corroboration of the findings in an X-Ray film simply tells us that there are glands in the tracheo-bronchial lymph-stream which are capable of engorgement, the ultimate, underlying cause of which may or may not be tuberculosis. The reading of X-Ray photographs in children, then, appears to demand as great a care as the interpretation of physical signs, and, in spite of an extended practice, I have considered it necessary to adopt a classification similar to that which I have already described, thus :-

+ = Positive tubercle.

± = Doubtful, but most probably tuberculous.

∓ = Doubtful, but most probably not tuberculous.

- = X-Ray signs negative.

(c) Blood Sedimentation Rates :-

It has been found that, in blood, which has been citrated to prevent the formation of clot, the red corpuscles fall at a rate which varies according to the protein-content of the blood serum. Fahraeus (9) has shown that the rate is slow in a

solution of albumen, more rapid in globulin, and very much increased in pure fibrinogen. The cause of an increase of fibrinogen, and consequently of the haemagglutinins, in the blood, is a breakdown of the tissue proteins, and, as tissues are broken down to a greater or lesser degree in tuberculosis, it may be inferred that the Blood Sedimentation Rate (B.S.R.) ought to be of some value in the diagnosis of the condition. It must, however, be remembered that tuberculosis is not the only disease process in which the tissue proteins are burnt up at a rate increased above the normal. Any infective condition in which the body finds itself will be accompanied by some tissue breakdown and therefore by an increase in the B.S.R. Fahraeus found that the rate was increased "in all kinds of infection, most distinct when accompanied by high fever, in many cases of malignant tumour, and in certain species of psychoses" .

As applied particularly to tuberculosis, the test has been extensively used by Westergren (10) in Stockholm, who gave the following figures after an examination of 340 male patients (adults) suffering from the disease :-

1. Clear fluid column of 3 mm. is normal.
2. " " " " 4 - 6 mm. is doubtful.
3. " " " " 7 - 12 mm. is probably pathological.
4. " " " " over 12 mm. is certainly pathological.

Westergren's method, which I have employed in this study, is as follows :- 0.4 c.c. of a 3.8% solution of sodium citrate is drawn up into a 2 c.c. syringe. Blood is taken from the patient's vein, in the arm, to fill the syringe up to the 2 c.c. mark. The blood is well shaken in the syringe to ensure good mixing. It is well to note that air drawn into the syringe with the blood may spoil the result, so that a clear flow of blood from the vein is desired. This citrated blood is then drawn up to the mark 0 in a special pipette, 1 m.m. in bore, which is graduated from 0 to 200 m.m. from above downwards. When the blood has been drawn up into the pipette, the lower end is sealed, and the pipette placed upright in a rack. Readings, of the level of the red blood corpuscles, are taken at the end of one hour and at the end of two hours. The sum of the first added to half the second, divided by 2, will give the average hourly rate of sedimentation of the red blood corpuscles.

As it seemed to me that a few points must almost certainly be conceded to children, I have classified my results into four groups, whose rates are :-

- | | | | | |
|-----|---------|---|------------------------|---|
| (1) | 0 - 5 | = | normal or | — |
| (2) | 5 - 10 | = | doubtful or | + |
| (3) | 10 - 15 | = | doubtful or | ± |
| (4) | over 15 | = | definitely positive or | + |

This classification follows, in kind, that already adopted, and therefore ought to be useful when an attempt is made to correlate the results.

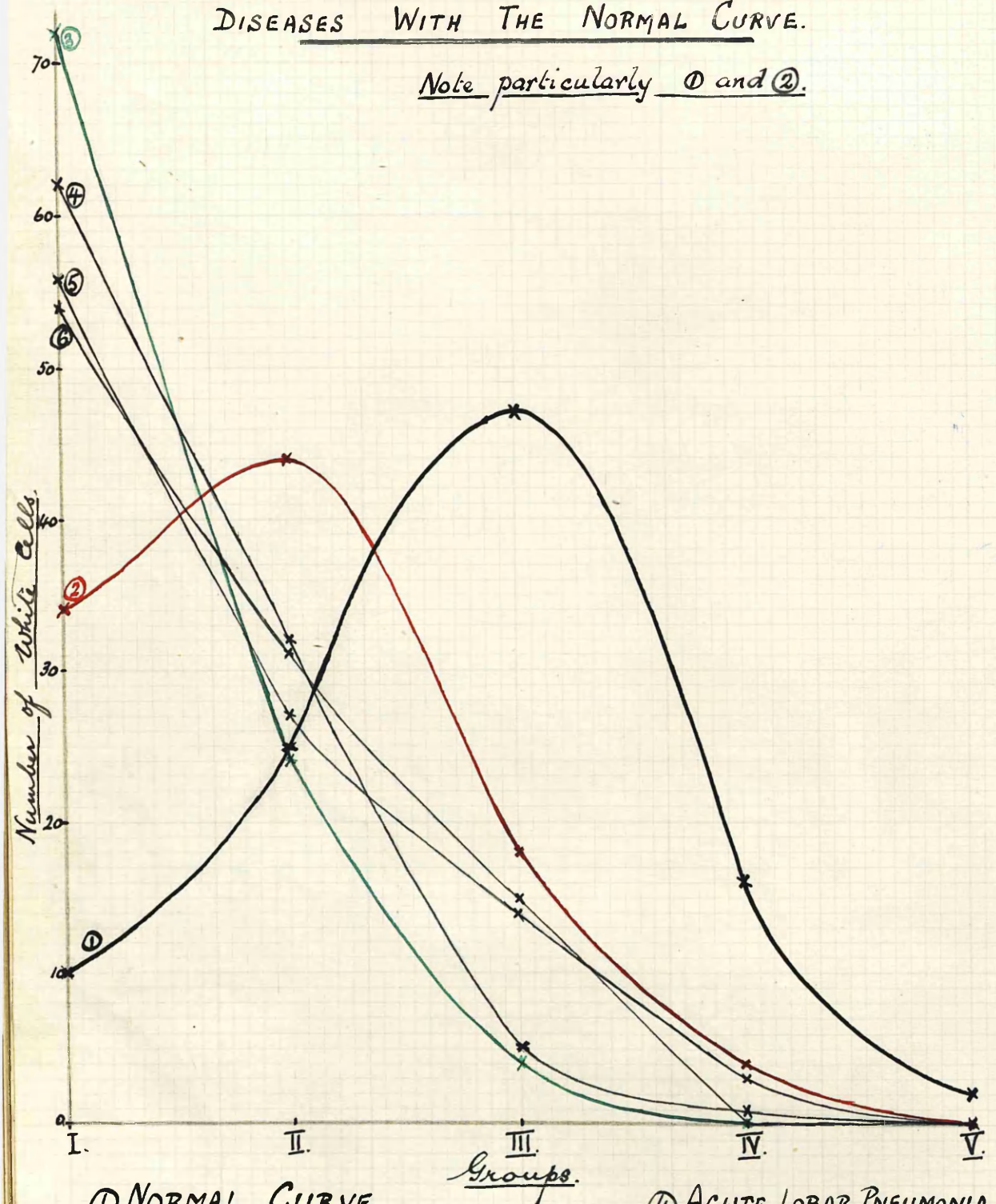
(d) Polynuclear Counts :-

The life of the Polymorphonuclear leucocyte has been keenly studied by W.E.Cooke (11) who modified the original Arneth count (12) by developing a much simpler classification. The count consists in examining a hundred polymorphs, and counting the number of lobes in the nucleus of each. From the time of the birth of the polymorph until it dies, the nucleus would appear to shape itself into lobes, from one up to five, according to the stage of its development. From an extensive examination of "normal" blood films, Cooke decided that the average polynuclear count was as follows :-

- (1) With 1 lobe = 10.
- (2) " 2 lobes = 25.
- (3) " 3 lobes = 47.
- (4) " 4 lobes = 16.
- (5) " 5 lobes = 2.

GRAPH COMPARING POLYNUCLEAR CURVES OF VARIOUS DISEASES WITH THE NORMAL CURVE.

Note particularly ① and ②.



① NORMAL CURVE.

10 · 25 · 47 · 16 · 2.

② PULMONARY TUBERCULOSIS.

34 · 44 · 18 · 4 · 0.

③ MEASLES

72 · 24 · 4 · 0 · 0

④ ACUTE LOBAR PNEUMONIA.

62 · 32 · 5 · 1 · 0.

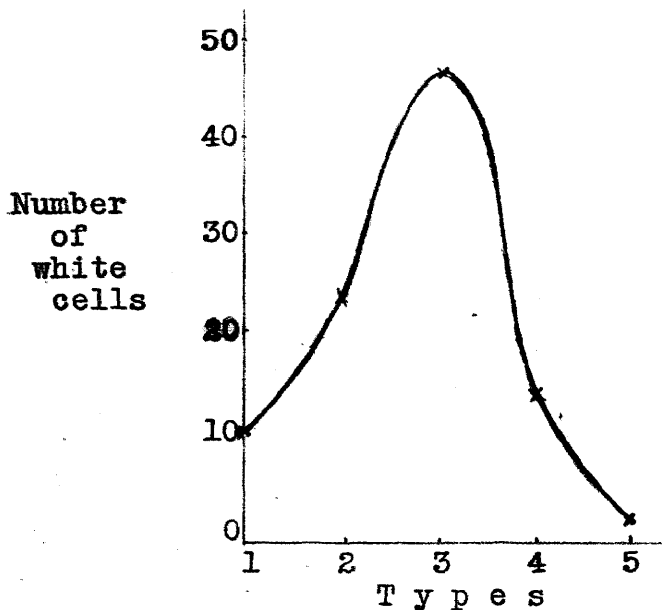
⑤ CEREBROSPINAL FEVER.

56 · 27 · 14 · 3 · 0.

⑥ TYPHOID FEVER.

54 · 31 · 15 · 0 · 0.

This can be represented graphically to give the polynuclear curve, thus :-



Variations from the normal can be readily compared, when the figures are plotted to form a graph, and I have taken the figures from Cooke for diseases such as Typhoid Fever, Measles, Cerebrospinal Fever, Acute Lobar Pneumonia, and Pulmonary Tuberculosis, and in the accompanying figure the general displacement of the curve to the left is well demonstrated, showing that, when the blood-forming tissues are overworked, a much larger number of one-lobed nuclei make their appearance in the blood.

Allow me to quote from Cooke :-

"The count is not prophetic. It is an index of marrow reaction, and the amount of dislocation (of the curve towards the left) depends upon the severity of the toxæmia which is present at the time the blood is taken".

In conclusion, he says :-

"We must impress on the reader that the polynuclear count must not be used to replace any other method. Nothing can take the place of a careful clinical examination, the count merely completes the picture of the disease and is a pointer to the way the disease is progressing."

I have done this test, primarily to see if it is of service in the diagnosis of pulmonary tuberculosis in children, and secondarily to see if it can be correlated with (a) the Blood Sedimentation Rate, and (b) with the other examinations already described. The Blood Films were made at the time when the blood was taken for the B.S.R., and stained in the usual way with Giemsa's stain. I found it convenient to count with the aid of peas, dropping a pea into one of five saucers, according to the number of lobes seen in each nucleus. This permits of greater concentration on microscopic detail, without removing the eye from the eye piece.

It is obvious that the figures given as the normal count may show tremendous variations, and an average number is desirable to use as an index of normality. An average can be struck by adding up the total number of lobes present in the count and dividing this total by a hundred, that is, the number of cells examined. This number, so obtained, is called the weighed mean (W.M.) and, according to Cooke, an excellent criterion of normality is when the W.M. is not less than 2.4 . It is also stated that when the W.M. is under 2, we have a definite index of a disease

process, existing at the time of blood examination. From these figures it is feasible to construct a classification, on the lines already described, which may be summarised as follows:-

(W.M.)	Weighed Mean under 2	= +
"	" 2 and under 2.2	= ±
"	" 2.2 and under 2.4	= -
"	" 2.4 and above	= -.

(e) Tuberculin Tests :-

The story of Tuberculin is packed with stormy dissensions, and, during the last 30 years, the tuberculin tests have been censored and condemned, praised and passed, by a myriad of workers in the specialty of Tuberculosis. The test, elaborated by Von Pirquet, has been performed by many other observers, and variable results have been obtained, and, when compared with the reactions following the intradermal or subcutaneous injection of tuberculin, the results would appear to have been of still greater divergence. Nevertheless, Calmette (13) has said that "In the present state of our knowledge we ought to consider as suspect every healthy individual who gives a positive reaction to tuberculin", and he would apparently recommend this test as an index during

a patient's lifetime of the need for continuing or stopping his surveillance, because although the patient may be perfectly fit, "without any perceptible warning, his dejecta or certain of his glandular secretions may harbour bacilli." This, from a practical standpoint, may not be of any value, as the clinical examinations of such a suspect would, I believe, be sufficient evidence for or against him, but the fact that a great worker against Tuberculosis should favour the tuberculin reaction as an aid in the supervision of his patients is in itself sufficient stimulus to use the reaction, if possible, as an aid in diagnosis.

Much, has, however, been said against the use of tuberculin. Sir James Kingston-Fowler (14), after denouncing tuberculin as a remedy, says of it in diagnosis :- "The test may do definite harm..... When reliable, the use of these tests is fraught with grave danger, and that, when not fraught with grave danger, they are unreliable." And Dr. Noel Bardswell (15) says that "In my opinion the test is not a means whereby the existence or absence of tuberculous disease can be determined. Neither, when a tuberculous lesion is present, does the test give any information as to its activity." Professor Hamburger, of Graz, (16) denounces the Pirquet reaction as very deceptive and liable to many errors, because it depends on (1) the instrument used and the depth of the scratch, (2) the

Diagram to show Quantitative
PIRQUET Reaction.



To face page 23.

time allowed for the tuberculin to react; (3) the potency of the tuberculin; (4) the repeated, or the single-test, which brings in the complication due to protein-sensitivity; (5) the time of year at which the test is done.

It is evident, then, that the use of tuberculin has been under the severest criticism, and I felt bound to put this test to the proof, and try to determine its value in diagnosis. I have remembered the views of the great authorities who believe that, with a positive Pirquet, infection with Bacillus tuberculosis has taken place, and with a negative Pirquet an absence of tuberculosis cannot be inferred. I have adopted the quantitative method of doing the Pirquet test, using dilutions of 16%, 64%, and 100% of old tuberculin, and taking normal saline as my control. The scarifier used was of the ordinary type, suitable for vaccinating purposes. The arrangement of the scars was as seen in the accompanying figure, the control being at the top, and the increase in strength of the tuberculin occurring from above downwards. Two drops (of each dilution, and of normal saline) were put on the skin, which was first carefully cleansed, and the scarification was done through the fluid. This was allowed to "stand" for 3 or 4 minutes, when any excess of fluid was carefully taken up by a wisp of cotton wool. The reactions were observed on the first, second, third, and eighth

days. The reading of the reactions presented me with the same problem which the reading of all my tests has already done, the question of gradation of reaction again cropping up, and consequently the undoubted need to classify them accordingly. I have classified the reactions thus :-

- (1) $+$ = Positive to tuberculin, where a definite erythema occurred, which, if excessive, might be even $++$.
- (2) \pm = Probable positive. Required usually on first and second days, the reaction being still doubtful.
- (3) $\bar{+}$ = Probable negative. Required for the same reason as in (2).
- (4) $-$ = Negative to tuberculin, no reaction whatever having occurred.

The comparison with the scarification through normal saline proved that the latter made a good control, and the reaction to trauma could itself be thus easily estimated. As this reaction to trauma must always be remembered in the reading of skin tests, the scarification was performed as lightly as possible to reduce trauma to a minimum, and as evenly as possible, so that the indispensable trauma might be equal in all respects.

As a more complete examination of the reactions to Tuberculin, I then performed the intradermal test, again quantitatively, on those cases who gave a negative response to the Pirquet test as already performed. This test was done in a manner similar to

that employed in doing a Schick test, 0.2 c.c. of the dilutions of tuberculin being injected into the substance of the skin itself, in order to produce a wheal. The dilutions of old tuberculin were $\frac{1}{10}$, $\frac{1}{100}$, and $\frac{1}{1000}$ and the three injections were done at the one sitting, so that the amount of tuberculin given at once to these cases was 0.0222 c.c., which would have been too much as an initial dose to give to an average child, but which, in children who showed no sensitivity to tuberculin as shown by the Pirquet test, was, I considered, perfectly safe. This was proved to be the case, no greater disturbance than a slight rise in temperature on the day following the injections occurring in two of the children.

The intradermal test gave me further information in regard to tuberculin reactions in diagnosis. The readings of these reactions were taken on the first, second, third and eight days, and the same classification used which has already been described :-

An erythema whose area was equal to the size of the wheal produced by the injection was considered positive, the average diameter of this area being 1 c.m. (+). An erythema with a diameter of 2 c.m. was read as ++, with an area of 3 c.m. as +++, and occasionally it was necessary to go as high as ++++. The doubtful reactions (\pm and $\bar{+}$) were again seen, chiefly on the 1st and 2nd days, and were those in which a certain amount of redness occurred at the site of injection, but the area had a

diameter less than 1 c.m. Then those cases which showed nothing abnormal at the site of injection were read as negative (—).

Then finally, I took 17 cases, of my most recent admissions, and performed on them the Intradermal test alone, modifying the procedure in the following way :- An intradermal injection of 0.2 c.c. of $\frac{1}{1000}$ old tuberculin was done, and a control of 0.2 c.c. of normal saline for comparison was done at the same time. This was examined daily for three days, and the reactions noted. The negative cases were then given on the fourth day an intradermal injection of 0.2 c.c. of $\frac{1}{100}$ old tuberculin, another injection of normal saline being given again. These were read daily for three days, and the test repeated on the negative cases, this time using 0.2 c.c. of $\frac{1}{10}$ tuberculin. Here it may be noted that, for accuracy, two syringes should be employed, the one for the tuberculin injections, the other for the saline, as the slightest amount of tuberculin in the saline will give a false result. I am inclined to think that this method of performing the tuberculin test is probably the best, because the amount of tuberculin given at each injection is accurate, and the commencement with 0.2 c.c. of $\frac{1}{1000}$ is perfectly safe, and will scarcely be capable of causing any general disturbance or any focal reaction.

SECTION IV.

(A) Results, with criticism.

(B) Correlation of Tests.

A. Following the classification which I have described in the last section, I have been able to construct the following tables of results :-

(a) Results of Physical Examination of 116 Children :

+	= 62,	which expressed as a percentage	= 53.5%	} = 73.4%
±	= 23,	" " " "	= 19.9%	
∓	= 15,	" " " "	= 12.9%	} = 26.6%
-	= 16,	" " " "	= 13.7%	

(b) Results of X-Ray Examination of 109 Children :

+	= 58,	which expressed as a percentage	= 53.2%	} = 74.3%
±	= 23,	" " " "	= 21.1%	
∓	= 22,	" " " "	= 20.2%	} = 25.7%
-	= 6,	" " " "	= 5.5%	

(c) Results of Blood Sedimentation Tests on 108 Children :

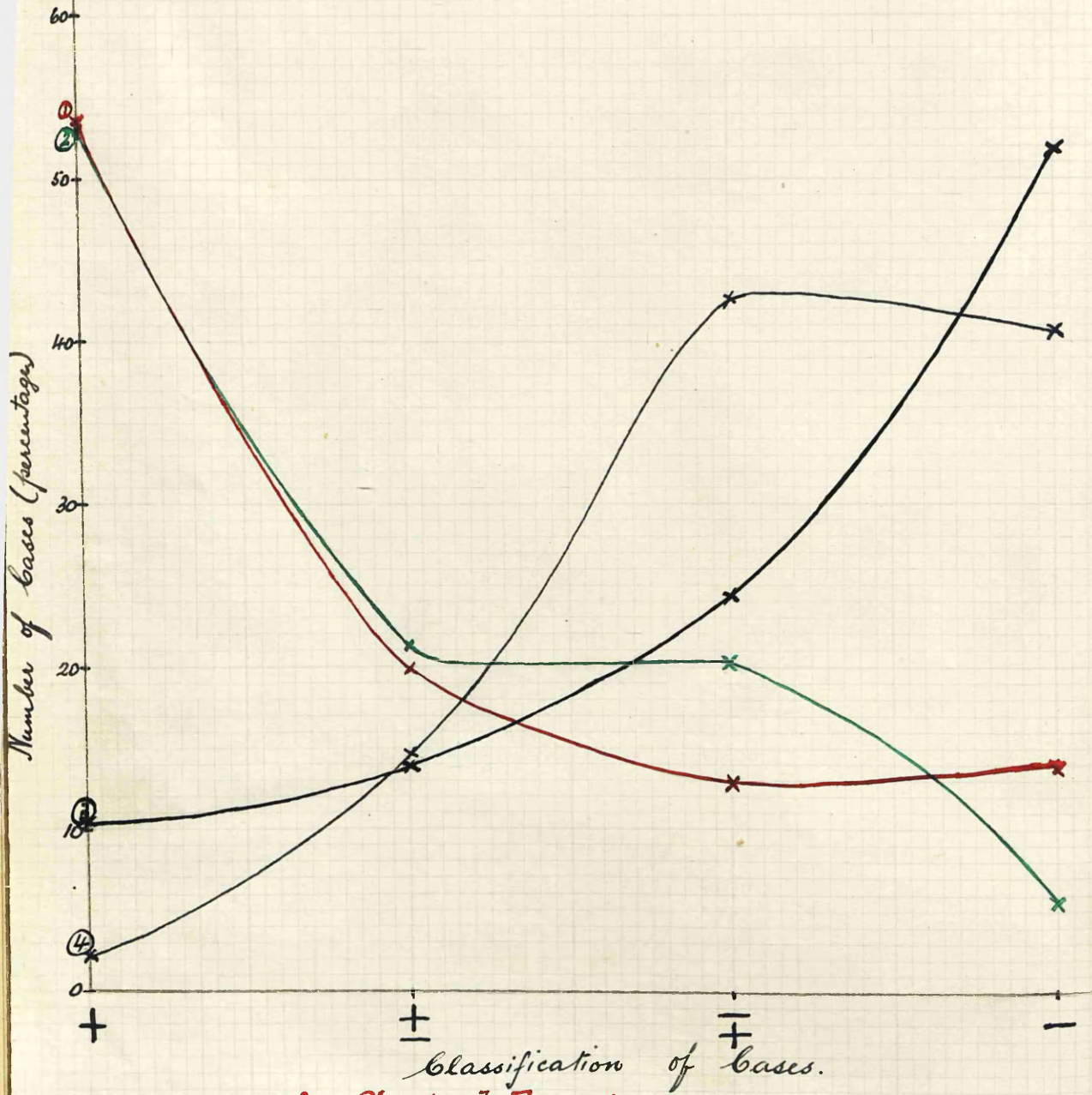
+	= 11,	which expressed as a percentage	= 10.2%	} = 24.1%
±	= 15,	" " " "	= 13.9%	
∓	= 26,	" " " "	= 24.1%	} = 75.9%
-	= 56,	" " " "	= 51.8%	

(d) Results of Polynuclear Counts on 89 Children :

+	= 2,	which expressed as a percentage	= 2.2%	} = 16.8%
±	= 13,	" " " "	= 14.6%	
∓	= 38,	" " " "	= 42.7%	} = 83.2%
-	= 36,	" " " "	= 40.5%	

I have represented these results in the form of a graph, from which it is easily seen how the Curves for Physical Examination and X-Ray Examination closely

GRAPH TO SHOW CORRELATION OF TESTS.



- ① By Physical Examination. }
- ② By X-Ray Examination. }
- ③ By Blood Sedimentation Test }
- ④ By Polynuclear Count Test. }

approximate, while those for the Blood Tests are also more or less in accord with each other. It is to be noted, however, that the directions of these two sets of curves are opposed. This, no doubt, is to be expected, because, as an index of tissue-breakdown, the blood tests will only reveal those cases where there is some definite destruction of tissue, at the time when the blood is taken, and, as we are dealing rather with a condition the chief feature of which is a fibrosis, we find that the results of blood examination and physical examination do not run parallel. It will be of considerable interest, in a later section, to study in more detail those cases in which the Blood Tests would point to active disease, and see how far the results of the Blood Tests compare with the other findings.

After an average period of sanatorium treatment of 4 to 6 months, the following results were obtained, as determined by physical examination :-

Cases Improved :

+	becoming	±	=	11	} = <u>36</u> , which is <u>32.4%</u>
+	"	±	=	6	
+	"	-	=	6	
±	"	±	=	7	
±	"	-	=	2	
±	"	-	=	4	

Cases not Improved :

-	becoming	±	=	0	} = <u>10</u> , which is <u>9%</u>
-	"	±	=	0	
-	"	+	=	1	
+	"	±	=	1	
±	"	+	=	3	
±	"	+	=	5	

Cases, whose classification remained the same, = 64,
or 57.7%.

Deaths = 1, due to $\left\{ \begin{array}{l} \text{Pneumonia} \\ \text{Bronchitis} \\ \text{Cardiac Failure} \end{array} \right.$ that is 0.9%

Of the 64 cases, whose classification remained unaltered :-

15	were	classified	—	} = <u>40</u> , or <u>34.5%</u> of the children examined.
6	"	"	≠	
10	"	"	±	
30	"	"	+	

There were, therefore, 40 children, who were definitely or almost certainly, on admission, considered to be tuberculous, who remained so even after prolonged treatment in the sanatorium. Adding this number to those in whom physical signs became positive, i.e., 9%, we arrive at the conclusion that 43.5% of the children, who are admitted to sanatorium between the ages of 5 and 14 years, may be sent out with signs in their chests of definite disability, of such an extent that, when the period of adolescence begins, they commence it with a tremendous handicap, and they doubtless comprise the majority, or at least a large percentage, of the cases who develop the acute destructive signs of adolescent and adult phthisis. I think these figures go to show the potentiality of tubercle in children, the immense importance of our estimates of the tuberculous process in children, and a definite reason for the prophylaxis against phthisis which should be begun in childhood and

maintained for many years after the child has been classified as an undoubted positive. The general improvement in physical signs is obvious from the figures already given, and this gradual clearing of these signs justifies the treatment even over so short a period as six months. But the impression I have received is that, given a longer period of sanatorium regime, extending over years, the percentage of improvement would go still higher, with the result that the material which goes to provide much of the adolescent tuberculosis would be greatly diminished.

(e) Tuberculin Tests :-

(1) The results of the Quantitative Pirquet Tests, which were performed on 89 children, may be summarised in the following table :

	Day of Examination	Dilutions of Old Tuberculin.		
		16%	64%	100%
<u>Positives</u> +	1st day	21	35	46
	2nd day	29	33	36
	3rd day	27	33	36
	8th day	21	29	36
<u>Doubtful Positives</u> +	1st day	10	8	4
	2nd day	2	7	7
	3rd day	3	6	7
	8th day	7	6	4
<u>Doubtful Negatives</u> +	1st day	13	14	21
	2nd day	4	6	13
	3rd day	3	3	6
	8th day	3	4	5
<u>Negatives</u> -	1st day	45	32	18
	2nd day	54	43	33
	3rd day	56	47	40
	8th day	58	50	44

(2) On 45 of these children, who gave negative or doubtful negative reactions to the Pirquet test, I did the Intradermal test, with the following results :-

	Day of Examination	Dilutions of Old Tuberculin.		
		$\frac{1}{1000}$	$\frac{1}{100}$	$\frac{1}{10}$
<u>Positives</u> + (including ++ and +++)	1st day	17	20	31
	2nd day	6	9	23
	3rd day	5	5	10
	8th day	5	6	8
<u>Doubtful Positives</u> ±	1st day	0	4	5
	2nd day	1	5	3
	3rd day	1	1	3
	8th day	0	1	2
<u>Doubtful Negatives</u> =	1st day	12	12	6
	2nd day	7	9	4
	3rd day	0	6	12
	8th day	0	1	3
<u>Negatives</u> -	1st day	16	9	3
	2nd day	31	22	15
	3rd day	39	33	20
	8th day	40	37	32

(3) Out of 17 children, upon whom I did not perform the Quantitative Pirquet Test, but who were subjected to Intradermal Injection alone, I obtained the following results :-

Dilution of O.T.	Classification	1st day	2nd day	3rd day
$\frac{1}{1000}$	+	8	8	8
	±	0	0	0
	=	2	0	0
	-	7	9	9

Of these 9 children who gave negative results to $\frac{1}{1000}$, I obtained the following results to $\frac{1}{100}$:-

Dilution of O.T.	Classification	1st day	2nd day	3rd day	
$\frac{1}{100}$	+	5	2	2	} Doubtfuls & Negative.
	++	1	4	4	
	+++	1	0	0	
	++++	2	3	3	
	-				

Of the 7, negative or doubtful to $\frac{1}{100}$, I obtained the following results with $\frac{1}{10}$ intradermally :-

Dilution of O.T.	Classification	1st day	2nd day	3rd day
$\frac{1}{10}$	+	6	2	2
	++	1	0	0
	+++	0	0	0
	++++	0	5	5
	-	0	5	5

From the Quantitative Method of performing the tuberculin tests, no matter whether by the scarification of the skin, or by the Intradermal Route, it is to be noted that the reaction to tuberculin is a quantitative reaction. It is also to be observed that the reaction to tuberculin has a variable period for its occurrence, for its persistence, and for its disappearance. The acuteness of the reaction appears to vary according to the strength of the tuberculin used, full strength tuberculin tending to cause a sudden reaction on the first day, which is not maintained on the second, whereas 16 % tuberculin would appear to take longer for the full height of the reaction to be reached.

The condition of the reactions on the second and third days appears to me to be about the same, therefore I think it reasonable to take the reading on

the second day as being the most just.

This very variation in time and acuteness of reaction to tuberculin puts the test into quite a different category from, say, the Schick test in which the reaction to the toxin is more definite in degree, in extent, in period and in estimation and inference. A positive Pirquet does not denote a lack of immunity against tuberculosis; it signifies a sensitivity to tuberculin, due to some previous infection with the bacillus of tuberculosis, and this sensitivity may be quickly or slowly developed, or may even be latent.

I think it may be said also, from the above readings, that the tuberculin reactions are more definitely positive or negative when the test is performed by the intradermal method. This is doubtless due to the fact that the trauma in the scarification method is greater than that of the other; and the readings of a Von Pirquet are therefore liable to be more clouded and doubtful than the readings of the intradermal reaction. The subcutaneous method probably causes the least trauma of all, but it is not so safe as the intracutaneous method, as the reaction is general rather than local; so that the intradermal method appeals to me as being the method of choice of performing a tuberculin test. Another reason for the complete adoption of this method, is that the amount of tuberculin given at each injection can be accurate to

at least a thousandth part of a c.c., whereas the amount in Von Pirquet's method is indefinite. To commence the intradermal test with a dilution of $\frac{1}{1000}$ is safe, and the reactions are much more definite than those of the scarification test.

The fact that out of 45 cases who were negative to Pirquet's test, 23 were definitely positive when the test was repeated on them by the intradermal method, points very distinctly to the greater efficiency of the latter in estimating a sensitivity to tuberculin.

Now, taking the number positive on the second day to 100% Old Tuberculin (Pirquet), i.e., 36, and adding this to the number positive on the second day to $\frac{1}{10}$ Old Tuberculin (intradermal), i.e., 23, we may conclude that 59 out of 89 children were definitely positive in their reaction. This is 66.3%.

Taking now the figures for the 17 cases, on whom the intradermal test alone was done, we find that 12 gave a positive, and 5 a negative result. The positives, therefore, by this method, are 70.6%.

As there were 10 doubtful positives among the 89 children, it might be suggested that the figures are very nearly equal; but to obtain as high a percentage of positives using both Pirquet test and Mantoux test, the latter on the negatives of the former, as by using the Mantoux test alone, appears to me to wipe out the value of the Pirquet test altogether.

The only objection to the Intradermal Test is the necessity for the repeated injection, and the possible oversensitisation of the patient to tuberculin, with the result that second or third injections might give excessive reaction. I must say, however, that I did not see any evidence of this increased sensitivity in these cases, although the number is too small, I admit, to allow me to dogmatise. What I maintain is that the Intradermal test is safe, more definite in estimation and therefore a clearer index of tubercular infection.

Having proved - what is generally accepted - that the number of cases infected is greater than the number of children who are suffering from a tubercular process, I am willing to agree with Hamburger and say that

Tuberculin tests vary :-

- (1) according to the method employed.
 - (2) according to the amount of tuberculin used.
 - (3) according to the strength of the tuberculin.
- and (4) according to the time allowed for the reaction to occur.

I cannot say whether the time of year has anything to do with the results of the tuberculin tests, but this is a point of minor importance, and probably would also vary tremendously in the results of different observers.

SECTION IV. (B)

We are now able to make a composite table of the results, as follows :-

Classification	Physical Examination	X-Ray Examination	B.S.R.	Polynuclear Count	Tuberculin Tests	
					Pirquet	Intra-dermal
+	53.5	53.2	10.2	2.2	66.3	70.6
±	19.9	21.1	13.9	14.6	11.3	0
+	12.9	20.2	24.1	42.7	4.5	0
-	13.7	5.5	51.8	40.5	17.9	29.4

It is obvious at a glance that the Blood Tests, both B.S.R. and Polynuclear Count, do not give us much help in our estimate of tuberculosis in children. The reason, probably, is that, in children, there is not a marked destruction of tissue; in fact, there is, in a great majority under treatment at a Children's sanatorium, a definite increase in weight, regular and sustained, only a very small number remaining stationary in this respect; and, again, the pathological process is one which does not usually affect the lung parenchyma. Westergren's results were obtained from adults, in whom one is dealing with an entirely different clinical condition, where there may be caseation, fibrosis, or a mixture of both, with more or less active destruction of lung tissue. But, as the exact nature of the tissue breakdown, in children, cannot be indicated by the blood picture, I

feel that these tests, from a diagnostic point of view, are rather of haematological interest than of practical value.

It is to be observed, however, that the Blood Sedimentation Rate and Polynuclear Count are comparable; so that the effect of a change in metabolism makes itself felt both on the red cells and on the white cells, as well as on the vehicle of these cells, the blood serum. The importance of the protein content in the serum, emphasised by Fahraeus and others, is no doubt diminished, when one remembers that any toxin or antitoxin, which may be circulating in the blood-stream, attaches itself to the protein, and may therefore become the more important of the causes for change in the behaviour of the blood cells. The amount of antitoxin (for example), natural or acquired, varies with every infective process, and therefore the change produced in the blood-protein must vary as a sequel. The amount of toxin introduced into the blood-stream, either autogenetically or from the outside, also varies both materially and in virulence; so that again the protein element in the serum must of necessity be altered. As the toxin of tuberculosis is only one of many, which may all have a similar effect, though varying in degree, I cannot see how reliance can be placed on these blood tests in the formation of a definite diagnosis. However, I submit that, for comparison, the tests when done at intervals on the same

patient, may be of definite value, but that the labour involved does not justify their general use.

Physical Examination and X-Ray Examination give more or less parallel results, which is gratifying to both physician and radiologist. It justifies the work of both, but although it places X-Ray Examination in the front line of our corroborative tests, it emphasises the reminder that X-Rays must not be used to replace Physical Examination, which of necessity is the first and last of our tests in the diagnosis of tubercle.

Tuberculin tests tell us which patients have been infected with Tubercle Bacilli. This number (of definite infections) is greater than that of any of the other tests. Of what significance is this fact? Is it of service in our prognosis?

From my data I am enabled to construct the following table, in comparing Physical Examination with Tuberculin results, and I have put the doubtfuls into the class to which they are the more prone :-

- (1) Physical Examination \blacklozenge & Tuberculin test \dagger = 59
- (2) Physical Examination $-$ & Tuberculin test $-$ = 11
- (3) Physical Examination $+$ & Tuberculin test $-$ = 18
- (4) Physical Examination $-$ & Tuberculin test \dagger = 21

It is evident that the results on the same patient do not always agree, and, in the above table,

39 cases out of 109 disagree. This means that the tuberculin test does not prove the presence or absence of an active disease process. We may infer, however, that :-

In (1) the children have been infected with T.B., and are still showing signs of a tubercular process. The prognosis must be guarded, and the period of observation must be more or less long, though variable because of the change in physical signs which may take place.

In (2) there are neither physical signs of active disease (or disease, at all, in the lungs) nor signs of tubercular infection. These cases, - a minority - would bear a good prognosis, and their period of observation may be curtailed with safety.

In (3) there are signs of active disease in the chest, which, because of the tuberculin result, may be of non-tubercular character. On the other hand, the disease may be a tuberculosis, the infection with T.B. being recent, and the sensitivity to tuberculin being still undeveloped. Therefore the combination of positive physical signs and negative tuberculin test would require a careful prognosis, and the patients would need a much longer period of observation before a definite bill of health could be made out.

In (4) there has been a definite infection with T.B., probably at some previous date. The physical signs being negative, and some immunity therefore

having been developed against tubercle, the prognosis may be given more cheerfully, and the period of observation may again be reduced. Here, however, it must be remembered that the child may very quickly show physical signs of disease, if circumstances are in favour of another, and possibly greater, infection, or a reduction in his natural or acquired resistance.

Therefore, bearing these comparisons in mind, it is certainly of some service to us to know what a child's reaction is to tuberculin, and I submit that it is in prognosis that we obtain most help from the tuberculin test.

I hold, therefore, that, in the observation of children in a sanatorium, careful physical examination and X-Ray corroboration should be done regularly, and that every patient should be submitted to an intracutaneous test with tuberculin, the former for the purpose of estimating the extent and activity of the pathological process, the latter to assist in the making of a more reliable prognosis.

SECTION V. - Description of some Individual cases.

Case No. 11 (Margaret George, age 8) :-

This girl was admitted chiefly because she was not eating well, and was inclined to lose weight. Her general build was good, and, although she occasionally had spasms of coughing, it was not more than the dry, slightly croupy cough which is common enough in children of somewhat nervous temperament. Her mother said that she had not been sleeping well at home, and often spent restless nights.

Physical Examination :- Signs negative in both lungs. Second sound over mitral area was suspicious, not being quite pure. Heart rather rapid.

Blood Sedimentation Rate :- 17 - 50 = 21 (+).
(B.S.R.)

Polynuclear Count :- 56 - 34 - 10 - 0 - 0. Weighed Mean =
(W.M) 1.54 (+)

X-Ray Report :- Negative.

Tuberculin Tests :- (a) Pirquet = Negative.
(b) Intradermal = Negative.

The case is interesting because of the Results of the Blood Tests, both of which are positive. Whether the nervous condition of the patient has anything to do with the results of blood tests is difficult to decide, but Fahraeus says that the B.S.R. is increased in certain psychoses, and therefore one might suspect that fear of a needle-prick could have an effect on the blood tension,



Margaret George.

Report - Negative.



Arthur Noon

Report - Negative.

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with the result obtained in this child. If the blood sedimentation were used as an index of pulmonary tuberculosis, this child must be considered a positive case, which is not borne out otherwise.

B.S.R. (repeated 3 months later) :- 15 - 48 = 19.50.

Polynuclear Count (repeated 3 months later) :-
20 - 36 - 34 - 10 - 0. W.M. = 2.34 .

This certainly shows an improvement, which could easily be attributed to the general increase in tone which took place in the child. Later physical examinations still proved negative, and the heart sounds became pure and of excellent quality. The child was able to be discharged in 3 to 4 months after admission.

Case No. 7 (Arthur Noon, age 7) :-

This boy was admitted for observation.

Physical Examination :- Negative.
Heart sounds good.
General condition
Satisfactory.

B.S.R. :- 2 - 5 = 2.25 (-).

Polynuclear Count :- 16 - 36 - 38 - 10 - 0. W.M. = 2.54 (-)

X-Ray Report :- Negative.

Tuberculin Tests :- (a) Pirquet = Negative.
(b) Intradermal = Negative.

All the corroborative tests went to strengthen the conviction that there was no tuberculosis present in this patient, and, after six weeks' observation, the child was able to go home, with a good prognosis.

Case No. 12 (Molly Neal, age 8) :-

This child had suffered from winter cough, which, in 1929, had persisted longer than usual, right through spring towards the summer. Her general condition was good, and she was well covered with healthy fat.

Physical Examination :- Except that the Respiratory murmur, which was quite clear, was fainter than usual in places, the signs were practically negative.

B.S.R. :- 2 - 9 = 3.25 (-).

Polynuclear Count :- 10 - 36 - 42 - 12 - 0. W.M. = 2.56 (-)

X-Ray Report :- Signs definitely positive in both lungs. Signs of old infiltration. (+).

Tuberculin Tests :- (a) Pirquet = Positive (+)

The Physical Signs remained practically negative in the two subsequent examinations, and the general condition was satisfactory; so that the child was discharged in 3½ months, with a good prognosis, but with a caution to the parent to keep the child under regular observation at the Tuberculosis Dispensary.

Case No. 28 (Ivy Purple, age 9) :-

This child was small for her age, and, though cough was not a prominent symptom, she was under weight, and had not shown any increase in weight for some months previous to admission to sanatorium.

Physical Examination :- In both lungs, the upper lobes were rather dull to percussion, and the respiratory murmur was harsh and



Ivy Purple.

Report - Signs definite
in Right and Left
Upper Lobes.
Exudative type.

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accompanied by both fine and coarse moist sounds. Chest movements were not good, and, though the heart sounds were normal, there was a slight tendency to cyanosis (+).

B.S.R. :- 6 - 16 = 7.00 ($\bar{+}$).

Polynuclear Count :- 24 - 34 - 34 - 8 - 0. W.M = 2.34 ($\bar{+}$)

X-Ray Report :- Signs definite in Right and Left
Upper Lobes. Exudative type (+).

Tuberculin Tests :- (a) Pirquet = positive (+).

A definite case of pulmonary tuberculosis in a child, which, because of the extent of the disease process, should be under sanatorium treatment for a prolonged period. The subsequent examinations, given shortly, were :-

On 30.7.1929 :- Signs still++ (chest drier, settling).

On 9.9.1929 :- Signs still++ (Right apex the seat of bronchial breathing. Still harsh Respiratory murmur through left lung).

On 2.10.1929 :- Signs +. (Fibrosis more marked, tendency to arrest).

The child was then taken home by the parent against advice, and I considered that four and a half months was too short a stay in this case. The gradual but certain improvement would have persisted, I have no doubt, and the ultimate arrest of the pathological condition could have been anticipated.

Case No. 46 (Jack Glen, age 13) :-

This boy had a history of cough, and periodic losses of weight, which had always been made up again, and had evidently not caused any delay in his physical development. He was well-built and fairly well nourished, in spite of the fact that his home conditions were not of the best. Mentally he was very active, and his disposition was of the kindest. He was not afraid of anything, and would have been willing to "rough it" in any campaign.

Physical Examinations :-

- (1) First Exam. : Râles and Rhonchi heard in both lungs, with slight dulness to percussion. Heart sounds good. (+).
- 6 weeks later (2) Second Exam. : Signs greatly improved, but still positive. Prolonged expiration at right apex.
- 6 weeks later (3) Third Exam. : Except for prolonged breath-sounds at right apex, signs were almost negative. Lungs quite dry, and respiratory murmur generally clear.

B.S.R. :- 2 - 6 = 2.50 (-)

Polynuclear Count :- 20 - 34 - 36 - 10 - 0. W.M.=2.36 (±)

X-Ray Report :- Definite disease of the adult type present in both lungs (+).

Tuberculin Tests :- (a) Pirquet = Positive (+).

The improvement in physical signs was rapid, and the general condition satisfactory, immunity being quickly regained to the tubercular process. This case, however, as the history pointed out, showed the grave danger of subsequent infections, which were readily to be expected in the lad's home-surroundings, where his



Jack Glen.

Report:- Definite
disease of Adult
type in both lungs.



Winifred Richmond.

Report:- Active adult
Disease, both upper
lobes being affected.

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resistance was not always supported to combat these. His natural build was sufficient to have kept him fit, if his opportunities for fitness had allowed him. The Grancher system would have made a man of him, with little or no disability in his chest.

Case No. 64 (Winifred Richmond, age 13) :-

This case, like the last, was of the active, adult type of disease. The family history was a poor one, and the father died of pulmonary tuberculosis while the child was an in-patient in the sanatorium. There was also a younger sister under my care at the same time, in whom the signs were not so extensive, and the pathological process not so deep.

General appearance was not robust. The complexion, except for the classical flush over the cheek bones, was pale; though in cold weather there was a marked tendency to cyanosis. Her temperament was built on deep affection and nervousness. There were periods of pyrexia, alternating with periods without fever, but cough was rather frequent, although sputum was very slight.

Physical Examination :- Right lung showed much Root Thickening, and active disease in the upper lobe. Left lung the seat of frequent crepitations and fine post-tussive râles. The Heart sounds were slapping in tone, but there were no accompaniments. (+).

B.S.R. :- 22 - 69 = 28.25 (+).

Polynuclear Count :- 28 - 32 - 34 - 6 - 0. W.M. = 2.18 (±).

X-Ray Report :- Active adult disease, both upper lobes being affected (+).

Tuberculin Tests :- (a) Pirquet = Positive (+).

This child was considered a suitable case for the administration of Sanocrysin, and she will be referred to again in the Appendix to this Thesis. It may be said here that her physical signs did not abate, and, six months after admission, though her lungs were slightly less moist, her temperature was febrile, and her general condition not improved.

The absolute correlation of tests is well shown in this child, and the tissue-breakdown, which was easily diagnosable by physical examination, was proved again by the blood tests, which, in the previous case (similar, but not of so advanced a degree) were of no support. This adult type of disease, I agree, seems to show a Blood Sedimentation Rate which is of some service; but the more typical condition exhibited by children does not produce an effect on erythrocytes and blood-protein to render the B.S.R. a valuable test in children generally. In the exceptional case, therefore, where signs of adult disease are present, the blood tests may be employed with some advantage.

The prognosis in this child was bad. Adding her own disability to poor family history, the persistence of fever and the undoubted prematurity of adolescent phthisis, the outlook was almost hopeless. Sanatorium treatment had to be prolonged indefinitely, and, if circumstances could have allowed it, a change of climate might have been considered.

Case No. 74 (George Townsend, age 13) :-

This boy had a history of an attack of acute bronchitis, as a child of five, which almost caused his death, but which, after recovery, left him with a "weak chest". There was a family history, negative for tuberculosis, and it was the persistence of the cough which eventually brought the child under the scrutiny of the Tuberculosis Dispensary. Routine physical examination there was almost enough to enforce an immediate admission to the Sanatorium.

The general build was good, being of the sturdy type; and his shortness of breath might, on first observation, have been due to a definite nasal obstruction, which had caused him to become almost a persistent mouthbreather. But exertion of moderate degree developed acute dyspnoea, and left the boy with flushed face for a considerable time after respiration had returned to his normal rate. It was therefore concluded that his nasal obstruction was of minor importance, and his chest condition the principal cause of his disability.

Physical Examination :- Definite dullness to percussion over both lungs, more so in the right. Prolonged expiration over both upper lobes, and moist sounds and rhonchi fairly general. Much bronchial catarrh. Also much nasopharyngeal catarrh, with adenoid enlargement.
Heart sounds normal and of good tone.

B.S.R. :- 17 - 55 = 22.25 (+).



George Townsend : 1st Report :- Dense fibrosis in
Right Lung. Active disease
Right and Left.

2nd Report :- Shows no change.



NOTE :- This case had
SANOCRY SIN, - see p. 75

To face page 49.

Polynuclear Count :- 26 - 40 - 30 - 4 - 0. W.M = 2.12 (\pm)

X-Ray Report :- Dense fibrosis in the right lung.
Active disease right and left (+).

Tuberculin Tests :- (a) Pirquet = Negative
(b) Intradermal = Negative (-).

Here we have a case, in which all the tests, except the tuberculin tests (both methods), are positive, and the inference to be drawn is that the boy was not infected with Tubercle Bacilli, although the signs were practically conclusive in all other respects. I think this is an example of the adult type of the disease, fairly frequent in sanatoria, which is classified T.B.—, occurring in a child, because the history is one of at least eight years, commencing with an acute attack, and developing as a chronic bronchitis. The tissue-loss is not necessarily great, the chief loss being that of elasticity, with subsequent replacement of elastic fibre by ordinary fibrous tissue. This fibrous-tissue replacement tends to spread, gradually and surely, and the disability produced is a physical one due to a fixation of lung substance, rather than a biological one due to the production of a toxæmia of either a tuberculous nature or of some lower or higher degree of virulence.

The Physical Examination and X-Ray report, six months later, were practically unchanged, and, as long as the lad did not exert himself beyond a certain limit, he was fit, and his breathing not at all laboured. With

care and persistent attention, his mouthbreathing was greatly reduced, but I advised an operation for the removal of his adenoids after his discharge from the Sanatorium. The prognosis I considered fairly good, with the warning that over-exertion must never be indulged in.

Case No. 85 (Raymond Scott, age 10) :-

This boy, an only child, came from a good home where every care was taken of his health. Although the parents were healthy, there was a history of tuberculosis in the maternal grandmother. The mother had developed the clinical thermometer habit, and she said that the boy had frequent feverish attacks, when it had been difficult often to assign a cause. A day or two in bed had usually been sufficient to bring things back to normal, and the diagnosis had frequently been given as Influenza. The more recent advent of a cough had made the suspicions of pulmonary tuberculosis more tenable, and the child was admitted to sanatorium for observation.

The child was fairly well nourished, and of good colour. He was not excitable, but rather early began to show signs of homesickness. He found it difficult to become one of a large family.

Physical Examination :- Percussion was clear over both lungs, but there were moist sounds generally through the left lung, and fine

post-tussive crepitations in the right apex.
The heart sounds were good.

B.S.R. :- 4 - 7 = 3.75 (-).

Polynuclear Count :- 18 - 34 - 38 - 10 - 0. W.M. = 2.30 (7)

X-Ray Report :- Fibrosis in the left lower lobe
and possible cavitation. Heart pulled towards
the left (+).

Tuberculin Tests :- (a) Pirquet = Positive (+).

After six weeks in the sanatorium, the child was taken home by his mother, who could not rest easy in mind when she thought of him being away for so long; so that the period of observation and the necessary sanatorium treatment were too early cut short. The signs, on discharge, were certainly improved, the right lung having become drier, but the left lung still the seat of active disease.

Cavity-formation is rare in children, and, although in this case it is not absolutely definite, the X-Ray signs are sufficiently strong to make one incline to the positive. At least, cavity-formation is a very possible feature of the child's further history, and I feel inclined to believe that the very advanced disease seen in adolescents, where sometimes huge cavities have existed without apparent symptom or disability, may result in such a case as this one, where the disease process, allowed to advance insidiously, is causing constant damage to lung tissue.

Sanatoria, if they are to continue in

existence, would, I feel sure, show greater justification for their existence and better results for the race, if they were chiefly for children; because, as it is agreed that the period of infection with tubercle is, in the very large majority, in childhood, so at this age may the crumbling also commence in the very tissue which is going to build the adult. The argument leads one to the consideration of home conditions, the building of open-air towns, and the considered balance of the reproduction of the race, and is therefore beyond this work; but, though the death rate from tuberculosis is lowest in this period which this Thesis is considering, I feel that there are many signs of the approaching nemesis in these very children who on the surface appear so healthy.

Childhood the "period of infection" is also the period for the stabilisation of the results of infection.

Case No. 86 (Shirley Riley, age 6) :-

This case, in short, was really one of unresolved pneumonia, a rather severe attack of lobar pneumonia having occurred about two months before admission to sanatorium. The child seemed to have good recuperative power, and, on admission, was well nourished and rather chubby. He had no pain, not even on deep breathing, and only occasionally did he

show signs of shortness of breath, when doing more than average exercise. He had, however, spasmodic attacks of coughing which made me suspicious of whooping-cough as a sequel to his pneumonia, and caused me to hesitate about retaining the child in the sanatorium. After a week's isolation, the cough had improved so much that I decided that further danger of a general B. Pertussis infection was very small indeed.

Physical Examination :- The percussion note over the left lower lobe was dull, and the breath-sounds were bronchial in type. Towards the apex of the same lobe many crepitations could be heard, and dry sounds in the rest of the lung. The right apex was also the seat of fine crepitations, but percussion was clear.

After two months the percussion note over the left lower lobe had cleared considerably, and the breathing was no longer bronchial in type. Two months later, there were still fine crepitations audible in right apex and in the apex of left lower lobe, but the physical signs were greatly improved, and the general condition satisfactory.

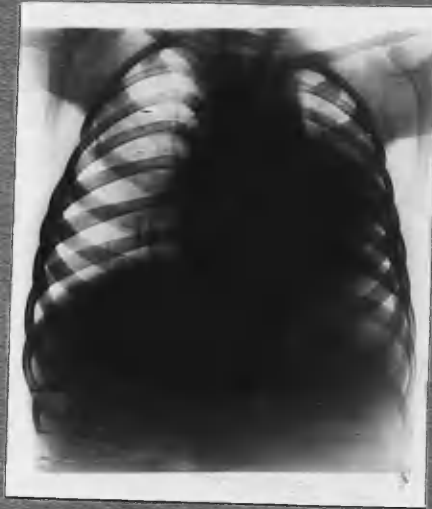
B.S.R. :- $3 - 7 = 3.25$ (-).

Polynuclear Count :- 16 - 26 - 46 - 12 - 0. W.M. = 2.54 (-).

X-Ray Report :- Pneumonic area likely in left lower lobe. (+).

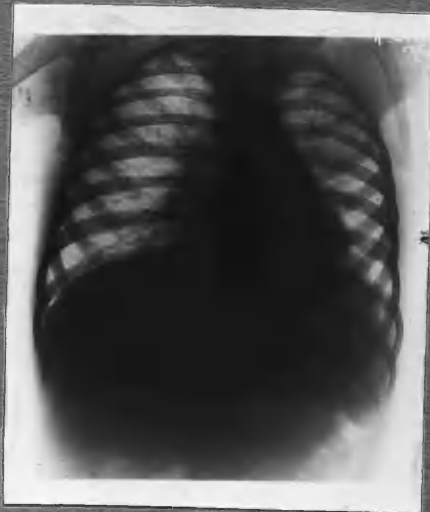
Tuberculin Tests :- (a) Pirquet = Positive (+).

Before discussing this, I shall describe the next case.



Shirley Riley

Report: Pneumonic
area likely in Left
lower lobe.



Kathleen Smith.

Report: Left lung is
not clear, being generally
hazy. Right lung looks
emphysematous. Heart
pulled towards the left.
Bronchitis or tubercular
disease.

To face page 54.

Case No. 91 (Kathleen Smith, age 6) :-

This child, on admission, was in fairly good condition generally, although she was suffering from a persistent cough, due to a bronchitis which had begun at the end of the summer and had gradually become worse as the winter advanced. She had no fever, and, as this condition maintained itself for several days after admission, I began to allow the child up gradually, from day to day, thinking that the bronchial catarrh, as in most of these cases of pulmonary tuberculosis in children, would steadily decrease and at last become dry.

Physical Examination :- Percussion in the interscapular space was slightly dull, and there was general bronchitis in both lungs. There was no appreciable difference between right and left lung, both on percussion and on auscultation. The heart sounds were good.

B.S.R. :- $8 - 15 = 7.75$ (\mp).

Polynuclear Count :- 20 - 32 - 42 - 8 - 0. W.M. = 2.18 (\pm).

X-Ray Report :- Left lung is not clear, being generally hazy. Right lung looks emphysematous. Heart pulled towards the left. Bronchitis or tubercular disease.

Tuberculin Tests :- (a) Pirquet = Negative. (—)
(b) Intradermal = Positive to 1/10, but, only just positive.

The temperature remaining afebrile, the child was gradually allowed up, more each day, until, a fortnight after admission, she was up all day, like the large majority in the sanatorium at the time. The only outward sign of catarrh was a rather severe nasal

discharge, but, otherwise, one would have inferred that the chest condition was steadily improving. Unfortunately, one day about six weeks after admission, the temperature began to rise, and the child had to return to absolute rest, having developed a definite pneumonia in the left lung, and a more acute bronchitis in the right lung. The outlook became grave - and the child died seventeen days after having been put back to bed. I gave the cause of death as (1) Pneumonia, (2) Acute Bronchitis, (3) Cardiac Failure.

This was the only death I had among my cases, definitely due to pneumonia and acute bronchitis. I could not truthfully say that death was due to Pulmonary Tuberculosis, the very slight sensitivity to tuberculin making an infection with tubercle bacilli somewhat doubtful, although distinctly probable. There was, certainly, a thickening in the left lung on admission, which, although the previous history was one of acute bronchitis and not of bronchopneumonia, may have been due to a definite lobular pneumonia on the left side, which did not clear up during convalescence. The blood tests would encourage the belief that some tissue-destruction was taking place (which, in the case previous to this one, was not evident); the sluggish tuberculin reaction would almost negative an infection with tubercle; and a period of six weeks of apyrexia would tend to support one in a hopeful outlook. Hence, it appears to me that, although the temperature

chart is in general a good indicator in the grading of sanatorium patients (both children and adults), there are a few cases, in whom the physical signs must be the first index in determining the period of absolute or modified rest on which they must be kept.

Note on the Relationship between Pneumonia and
Pulmonary Tuberculosis.

- (1) Pneumonia (and bronchopneumonia) is not likely to arise per se as the result of an infection with Tubercle Bacilli.
- (2) In a generalised tuberculosis, pneumonia might arise as a final complication in the general infection of the body.
- (3) In a case of unresolved pneumonia (or bronchopneumonia) tuberculosis of the damaged lung may easily arise, and a secondary pneumonia may take place on top of that which may be fatal. This type of case is therefore to be watched carefully, particularly if the tuberculin reaction is negative :- The special sensitivity may be sluggish in its development, or even clouded by the previous pneumonic infection. The case in which the tuberculin reaction is definitely positive would appear to have developed, in becoming positive, one definite immunity at least, and therefore a better chance of recovery.
- (4) Hence a careful consideration of physical signs in a case of unresolved pneumonia, and of the tuberculin sensitivity, may be useful in determining the period of rest, in spite of a normal temperature, required for the slow resolution of the pneumonic area. The tuberculin test, repeated at intervals if necessary, may help, as I have suggested previously, in the prognosis of the case.

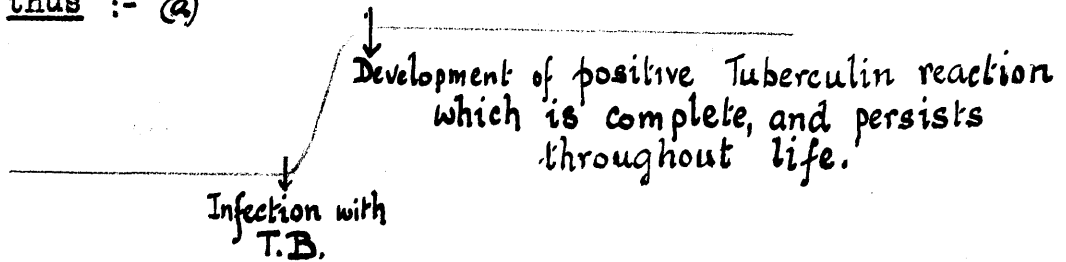
SECTION VI.Summary and Conclusions.

- (1) Tuberculosis has accompanied the human race for thousands of years. By this time a truce has almost been declared between mankind and the tubercle bacillus, the percentage of infections now approaching a hundred, but the percentage of affections being gradually reduced.
- (2) The infective agent may not be the tubercle bacillus as such, but some potentially bacillary organism, which is capable of passing through the tissue of the placenta into the blood stream, and thereafter the tissues, of the foetus, and which later develops, if circumstances allow it, into the B. Tuberculosis of Koch.
- (3) The result of infection may show itself in
 - (a) Acute military tuberculosis of infants, and death due to absolute or almost complete lack of immunity.
 - (b) Subacute or chronic lymphatic disease of childhood, with the development of fibrous tissue, which may or may not be subsequently absorbed.
 - (c) The production of an immunity against further infection with T.B., which may be long, lasting throughout a lifetime, or short, being insufficient to meet a superadded infection or a series of infections.
 - (d) The development of a sensitivity to tuberculin which varies in degree, in the period required for its occurrence, and the period of its persistence.

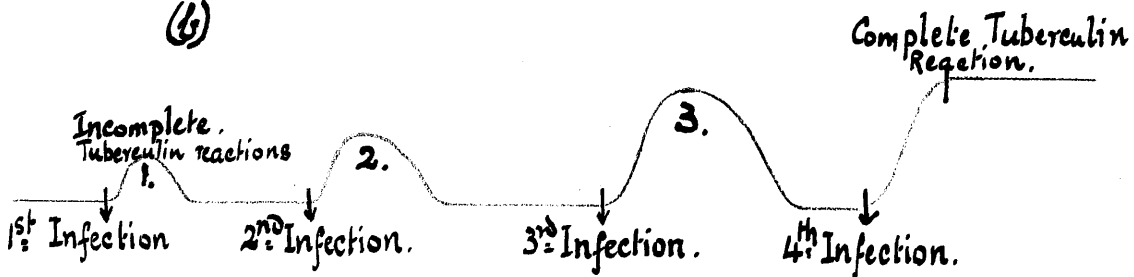
(4) It is feasible that complete tuberculin sensitivity is developed -

(a) at once.
or (b) as a cumulative process;

thus :- (a)



(b)



(5) For diagnosis in children, the tests to be relied upon are :-

- (a) Physical Examination.
- (b) X-Ray Photography.

(6) For prognosis in children, I suggest :-

- (a) Physical Examination
 - (b) X-Ray Photography
- } repeated at intervals.

and (c) The result of the tuberculin test as performed by the intradermal method.

The Intradermal, and not the Scarification, method is the method of choice for tuberculin testing.

(7) Blood Tests ((a) Sedimentation of Red Cells and (b) Polynuclear Count) may be of service in prognosis in a case which shows definite signs of adult disease; but otherwise these tests are

of little value in children

(a) would appear to me to be of greater value than (b).

(8) I think that infected children probably go to make up a large percentage of the cases of adolescent and adult phthisis, and that childhood is therefore the period for prophylaxis against phthisis. Any further decrease in the deathrate from tuberculosis must be expected only by prolonging the low deathrate which exists in the age period of 5 to 14 years. The deathrate among infants will only decrease at a very slow, almost imperceptible rate, because of the non-development of immunity at this early stage of life.

(9) It would appear to me that the case of unresolved pneumonia requires the greatest care in its treatment. The child shows a reactionary sluggishness which is deceptive because of its quietness. The affected lung is a potential focus of a tubercular process, and the sooner a positive tuberculin reaction and therefore a certain degree of immunity to tuberculosis, has developed, the greater seems to be the chance of recovery.

(10) The temperature chart is not absolutely infallible as an index of activity. The smouldering fire may suddenly burst into flame.

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and disappears from the analysis of the patient's condition. The temperature chart, therefore, would only be a guide to the physician's attention.

In a review of the history of medicine we are obliged to notice the failure of the medical profession to give any weight to the evidence which can give to a patient's condition a more reliable index of activity than the temperature chart. Nevertheless, because of the danger of a sudden burst of activity, we must at least say that the patient's condition is a danger to his health and that the physician should be on his guard against it.

A p p e n d i x.THE TREATMENT OF PULMONARY TUBERCULOSIS IN CHILDREN
WITH SANOCRY SIN.

-----ooooOoooo-----

Sanocrysin has been in use as a therapeutic remedy in Pulmonary Tuberculosis for the past six years, and its value, like that of so many drugs which have appeared and disappeared from the shelves of the physician, has been widely discussed by the very specialists who, themselves, would only too gladly find a "cure" for this dire disease.

In a perusal of the history of medicine, one is able in retrospect to assess the values of the remedies which the medical profession has employed, at a much truer figure than one can give to a remedy which appears in our midst and proclaims to us its insistent demands as a specific :- because we find this new remedy a mystery to us. Nevertheless, because of our eternal hope in things curative, we must at least try it out before we pass our judgment upon it, whether it be of service in our work, or a danger to our patients. And so we must utilise it without bias, without prejudice, and with an outlook open to all its possibilities.

Sanocrysin is the thiosulphate of gold combined with that of sodium; and it is readily soluble in water,

which makes its applicability in treatment much easier, particularly as an injection by the intravenous route. The novelty of this remedy is not, then, in its constituents, which have been known for hundreds of years, but rather in the combination of its constituents. Mollgaard (17), of Copenhagen, is responsible for the introduction of the remedy, and he was stimulated to a wide use of it, first by his experiments on animals and later by his employment of it in the therapeutics of human tuberculosis. He was careful, at the outset, to keep secret the formula of its composition, and so the stimulus of mystery was added to the stimulus of the drug itself, with the result that Sanocrysin has developed for itself a premier position in the auxiliary armamentarium of many European Sanatoria.

Gold - the precious metal - has been used in some form or another, at varying periods in the history of civilisation, to combat disease. From the sixth century to the thirteenth or fourteenth, the art of the alchemist was directed towards the transmutation of the baser metals into gold and silver, which were considered to add vigour to the healthy, and strength and recuperation to the diseased. This was described as the Black Art - this power of the alchemist over metals - and, although we may look askance at their "philosopher's stone", we must admit that out of it has grown the real science of chemistry and, later, the biochemistry of modern days.

The growth itself has been slow; and each generation, repeating the work and interests of the numerous generations before it, has raised to a place of importance many a man who, because of his association with a certain remedy, became famous in the assembly of the Asclepiads. It were a good thing to remind ourselves of this repetition, from generation to generation, and to note that, in general as well as particular item, we may only make progress in that imperceptible way called evolution. However, as we go on with our art, by giving a new name to an old remedy, we maintain that interest, which, as I have said, is the soul of our hopes in things curative.

"Clinical trial in tuberculosis, as experience has shown, is a ticklish affair" (18) - and here we have the expression of the wariness which awaits a new remedy. A long experience, stabilised by a balanced estimate of human progress, engenders a note of carefulness such as I have quoted; and I therefore admit a tendency to observe this wariness when I commenced the treatment of tuberculous patients with Sanocrysin. I had tried the drug in adults and read several criticisms of other workers among adults, before I began to treat children with it. As far as I know, only one article has appeared, giving any results in the case of children, and it states (19) in conclusion :- "Sanocrysin is well-tolerated in children, and most encouraging immediate

results have been obtained in children, suffering from pulmonary tuberculosis, who do not respond to routine treatment." Heaf was encouraged with his results, especially considering the unfavourable prognosis in children with positive sputum.

I therefore commenced the treatment, and carried it out on the following lines :-

The patients chosen were either from among those who had been under routine sanatorium treatment for some time, or, if more recently admitted, had a definite lesion in the lungs. The various tests, as described in the Thesis, were carried out, and, as soon as treatment was commenced, the patients were confined to bed, and daily examinations of urine were done. The injections of Sanocrysin, commencing with .05 gm. and increasing by .05 gm. with each successive dose, were given intravenously at intervals of seven to ten days, or in accord with the manner in which the children reacted to the drug. If there was any tendency to the development of an erythema or an albuminuria, the interval before the next injection was usually lengthened, and the succeeding dose was not increased. As far as possible, the maximum dose was .5 gm., and this was repeated until the total amount of Sanocrysin taken was about 3 gms.

I propose to give short descriptions of the individual cases, and then to summarise my results.

Case 1. (Gladys Sheffield - Age 10)

Physical Examination :- General condition not robust.
 Under weight : No increase for some time.
 Right upper lobe the seat of granular breath sounds, and suspicious of active disease.

X-Ray Report :- Suspect right upper perihilar region.

Blood Sedimentation Rate (B.S.R.) :- 2 - 4 = 2.00.

Polynuclear Count (P.C.) :- 16 - 46 - 34 - 14 - 0. W.M.=2.16.

Tuberculin Test :- Quantitative Pirquet = Positive.

Sanocrysin Treatment.

13.6.29 = 0.05 gm.
 20.6.29 = 0.10 gm.
 27.6.29 = 0.10 gm.
 4.7.29 = 0.15 gm.

Total = 0.40 gm.

Notes.

24.6.29 - Rash, present for 2 days.
 4.7.29 - Rash and headache, both quickly over.
 11.7.29 - Rash returned and markedly increased.
 Sanocrysin stopped.
 Congramine injected intramuscularly (3 injections given).
 22.7.29 - Now also a trace of albumin in the urine. Rash gradually decreasing. Skin on forearm thickened.

I considered it inadvisable to proceed further with the treatment in this case, both skin and kidneys showing a decided dislike to excrete the sanocrysin.

Case 2. (Irene Brown - Age 10)

Physical Examination :- General condition fairly good.
Right lung the seat of active disease, and left lung also suspicious.

X-Ray Report :- Small, active nodules in right and left lungs, chiefly in right.

B.S.R. :- 3 - 7 = 3.25

P.C. :- 14 - 48 - 32 - 6 - 0. W.M. = 2.30.

Tuberculin Test :- (a) Quantitative Pirquet = Negative.
(b) Intradermal Test = Positive to 1
10

Sanocrysin Treatment.

13.6.29 = 0.05 gm.
20.6.29 = 0.10 gm.
27.6.29 = 0.10 gm.
4.7.29 = 0.15 gm.
11.7.29 = 0.15 gm.

Total = 0.55 gm.

Notes.

13.6.29 - Slight flushing of face and neck.
12.7.29 - Slight rash on feet.
Hands also suspicious.
13.7.29 - Trace of albuminuria.
20.7.29 - Definite albuminuria.
27.7.29 - Still albumin in urine.
3.8.29 - Urine now clear.

An albuminuria, which persists for at least two weeks, is, in my opinion, sufficient index to stop the treatment, if damage to kidney tissue is to be avoided.

It is interesting to note that, in this case, the signs on physical examination improved steadily until, after a further six months, there were no signs of any active disease in either lung.



Before SANOCRYLIN.

14.6.1929

Irene Page.



After SANOCRYLIN.

9.11.1929.

Note: Certain amount of
improvement.

To face page 67.

Case 3. (Irene Page - Age 7)

Physical Examination :- General build puny, and cough a persistent feature. Rather nervous.

Both apices atrophied, right more than left. Active disease in both, but only slight on left side.

X-Ray Report :- Perihilar nodules in both - right definite and caseating, left only slight.

B.S.R. :- 4 - 7 = 3.75.

P.C. :- 19 - 39 - 36 - 6 - 0. W.M. = 2.29.

Tuberculin Test :- (a) Quantitative Pirquet = Negative.
(b) Intradermal Test = Positive to $\frac{1}{10}$.

Sanocrysin Treatment.

13.6.29 = 0.05 gm.
20.6.29 = 0.10 gm.
1.7.29 = 0.10 gm.
11.7.29 = 0.15 gm.
25.7.29 = 0.15 gm.
8.8.29 = 0.20 gm.
22.8.29 = 0.25 gm.
2.9.29 = 0.30 gm.
12.9.29 = 0.30 gm.
23.9.29 = 0.35 gm.
3.10.29 = 0.40 gm.
14.10.29 = 0.45 gm.

Total = 2.80 gm.

Notes.

23.6.29 - Erythema, lasting 5 days.
1.7.29 - Very slight reaction.
20.7.29 - No ill effects so far.
24.7.29 - Very faint erythema on legs.
22.8.29 - Vomiting occasionally, which comes on at no definite period.
2.9.29 - Sickness after injection.
12.9.29 - Sick again after injection.
22.9.29 - Note:- Injection done very slowly appears to reduce sickness.
14.10.29 - Sickness more delayed, but now more severe.
Albuminuria now developed.

In this case I lengthened the interval between the injections, and possibly this may have prevented some of the reactions which appeared so quickly in the first two cases. In spite of that, the drug must be given with care, and the dosage carefully controlled.

Both X-Ray signs and Physical signs were improved, though the general condition still remained poor.

Case 4. (Peggy Lord - Age 8)

Physical Examination :- General condition fairly good.
Respiratory expansion poor,
lungs filling badly. In left lung, upper lobe,
moist crepitations and fine post-tussive rales.

X-Ray Report :- Peribronchial infiltration, right and
left, with some nodular disease.

B.S.R. :- 4 - 11 = 4.75.

P.C. :- 15 - 40 - 35 - 10 - 0. W.M. = 2.40.

Tuberculin Test :- (a) Quantitative Pirquet = Positive.

Sanocrysin Treatment.

13.6.29 = 0.05 gm.

21.6.29 = 0.10 gm.

1.7.29 = 0.10 gm.

Total = 0.25 gm.

Notes.

23.6.29 - Rash, for 7 days.

2.7.29 - Rash and slight headache.

11.7.29 - Rash persists, chiefly
on legs and arms.

Contramine injected.

20.7.29 - Dermatitis sicca.

Trace of Albuminuria.

Pyrexia severe, persisting.

I considered it wise to stop the treatment in
this case. Pyrexia continued for some time, and later,
I began to put the child on graduated exercises, with good
results. Six months later, the left lung was dry, and
the physical signs had so much improved that the child was
discharged with a more hopeful prognosis.

Case 5. (Florence Leach - Age 9)

Physical Examination :- General condition fairly good.
Breath sounds were clear.
Percussion note slightly dull
over left apex behind. Signs almost negative.

X-Ray Report :- Signs very slight.
Fine nodules possible, but quite
indefinite.

B.S.R. :- 6 - 13 = 6.75.

P.C. :- 20 - 34 - 37 - 6 - 0. W.M. = 2.23.

Tuberculin Test :- (a) Quantitative Pirquet = Negative.
(b) Intradermal Test = Positive to $\frac{1}{10}$.

Sanocrysin Treatment.Notes.

1.7.29 = 0.05 gm.
11.7.29 = 0.10 gm.
25.7.29 = 0.15 gm.
14.8.29 = 0.20 gm.
30.8.29 = 0.25 gm.
12.9.29 = 0.30 gm.
23.9.29 = 0.35 gm.
3.10.29 = 0.40 gm.
14.10.29 = 0.45 gm.
24.10.29 = 0.50 gm.
1.11.29 = 0.50 gm.

No reaction.

No reaction.

Total 3.25 gm.

This case, - one with very little in the way of physical signs, and a distinctly doubtful case - took the treatment well. It is interesting to note that X-Ray Report six months later says :- "Very definite peribronchial infiltration in Left Lung: probable slight fibrosis in right lung."

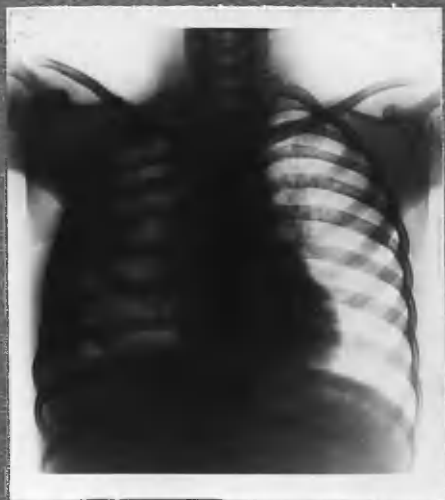
It is, I think, difficult to estimate the value of the drug in this case, which appears to me to have been very doubtful.



Before SANOCRY SIN.

30.4.1929

Edith Newbold



After SANOCRY SIN.

9.11.1929

NOTE:- Some X-Ray clearing.

To face page 70.

Case 6. (Edith Newbold - Age 10)

Physical Examination :- Child rather thin: of nervous temperament.

Right upper lobe dull to percussion, and respiratory murmur much reduced. Active disease in left upper lobe.

X-Ray Report :- Activity in both upper lobes. peribronchial infiltration very marked. Right pleura thickened.

B.S.R. :- 4 - 9 = 4.25.

P.C. :- 18 - 36 - 32 - 4 - 0. W.M. = 2.02.

Tuberculin Test :- (a) Quantitative Pirquet = Positive.

Sanocrysin Treatment.

1.7.29 = 0.02 gm.
11.7.29 = 0.05 gm.
and then by regularly
increasing doses to
1.11.29 = 0.50 gm.

Total = 3.27 gm.

Notes.

First injection satisfactory in spite of nervousness. To continue.
26.10.29 - Slight albuminuria.

This was a successful completion of the course, and the child improved greatly. At the end of the course, the temperature remained febrile for several days, and then gradually fell to normal. The X-Ray report showed that both lungs were much clearer, and the pleural thickening much reduced.



Before SANOCRY SIN
8.5.1929

Hilda Smart.



After SANOCRY SIN
9.11.1929

NOTE:- No appreciable
change.

To face page 71.

Case 7. (Hilda Smart - Age 12)

Physical Examination :- General condition good.

Girl is well-built, and gives the impression of robust health. The weight, however, has remained stationary since admission, and cough is rather troublesome.

Signs in chest are practically nil, except for prolonged expiration at both apices.

X-Ray Report :- Peribronchial infiltration right and left, with active nodules.

B.S.R. :- 15 - 23 = 13.25.

P.C. :- 35 - 41 - 23 - 1 - 0. W.M. = 1.9.

Tuberculin Test :- (a) Quantitative Pirquet = Negative.
(b) Intradermal Test = Positive to $\frac{1}{10}$.

Sanocrysin Treatment.

4.7.29 = 0.05 gm.

and regularly increasing doses to

1.11.29 = 0.50 gm.

Total=3.25 gm.

Notes.

19.7.29 - Very slight erythema.

There was very little reaction in this case to Sanocrysin, and the course was easily completed. The physical signs were unchanged, however, and the X-Ray findings still suggested active disease in both lungs. The general condition was excellent, and the child was taken home with a good prognosis.

Case 8. (Doris Swanson - Age 13)

Physical Examination :- General condition only fairly good. Face rather flushed, frequent tendency to cyanosis.

Right apex actively diseased, plus some fibrosis in both apices and upper lobes. Râles and Rhonchi both right and left.

X-Ray Report :- Active nodular disease of the adult type, both lungs.

B.S.R. :- 15 - 48 = 18.75.

P.C. :- 24 - 38 - 32 - 6 - 0. W.M. = 2.22.

Tuberculin Test :- (a) Quantitative Pirquet = Negative.
 (b) Intradermal test = Positive up to $\frac{1}{1000}$.

Sanocrysin Treatment.

14.10.29 = 0.05 gm.

and by regularly increasing doses to

2.1.30 = 0.50 gm.

Total = 3.25 gm.

Notes.

7.12.29 - Slight Albuminuria, not persisting.

Successful completion of course, with no serious complications. There was some improvement in the physical signs, but the disease was still active. There was slight clearing, from the X-Ray point of view.

Case 9. (May Wickwar - Age 9)

Physical Examination :- General condition fairly good.
Fibrosis at both apices, with active disease at right apex.

X-Ray Report :- Definite adult type of disease, right and left.

B.S.R. :- 2 - 7 = 2.75.

P.C. :- 16 - 28 - 44 - 12 - 0. W.M. = 2.52.

Tuberculin Test :- (a) Quantitative Pirquet = Negative.
(b) Intradermal Test = Negative.

Sanocrysin Treatment.

14.10.29 = 0.05 gm.

and by regularly increasing doses to

2.1.30 = 0.50 gm.

Total = 3.25 gm.

Notes.

3.1.30 - Slight sickness.

Another case in which the course was completed without any serious complication. The physical signs and X-Ray findings were only slightly improved, however, and the child was in a febrile state at the end of the course, which took some time to settle. The benefit of the drug doubtful in this case.

Case 10. (Nellie Topham - Age 13)

Physical Examination :- Not robust generally.
Percussion note dull over both upper lobes, and Respiratory Murmur harsh.
Enlarged bronchial glands.

X-Ray Report :- Definite disease in both lungs.

B.S.R. :- 8 - 20 = 9.00.

P.C. :- 16 - 34 - 42 - 8 - 0. W.M. = 2.34.

Tuberculin Test :- (a) Quantitative Pirquet = Negative.
(b) Intradermal Test = Negative.

Sanocrysin Treatment.

14.10.29 = 0.05 gm.
24.10.29 = 0.10 gm.
1.11.29 = 0.15 gm.
22.11.29 = 0.15 gm.
29.11.29 = 0.25 gm.
6.12.29 = 0.30 gm.
13.12.29 = 0.35 gm.
19.12.29 = 0.40 gm.

Total = 1.75 gm.

Notes.

7.11.29 - Rash on arms.
Fourth injection postponed.
24.12.29 - Rash again evident.
2.1.30 - Dermatitis sicca, persisting, on face, back and arms. Enough to stop Sanocrysin.

Course incomplete. A definite sensitivity to the drug showed itself after the third injection, and manifested itself again after the seventh. It suggests itself that the elimination of sanocrysin is variable in different children, and, whereas a weekly interval between injections seems to be safe in some, in others the interval should be at least ten days if complications are to be avoided. It also suggests itself that, the less robust the child, the less likely will it be that a complete course of sanocrysin will be tolerated.

Case 11. (George Townsend - Age 13)

Physical Examination :- Of good build and good bodily activity, but quickly becoming short of breath on average exertion.

Percussion note dull over right lung, which is seat of bronchial breath sounds and numerous rales and rhonchi. Left lung also fairly moist.

X-Ray Report :- Dense fibrosis right lung (old, unresolved pneumonia) with active disease right and left. Heart pulled towards the right.

B.S.R. :- 17 - 55 = 22.25.

P.C. :- 26 - 40 - 30 - 4 - 0. W.M. = 2.12.

Tuberculin Test :- (a) Quantative Pirquet = Negative.
(b) Intradermal Test = Negative.

Sanocrysin Treatment.

24.10.29 = 0.05 gm.

and by regularly increasing doses to

2.1.30 = 0.50 gm.

Total = 3.25 gm.

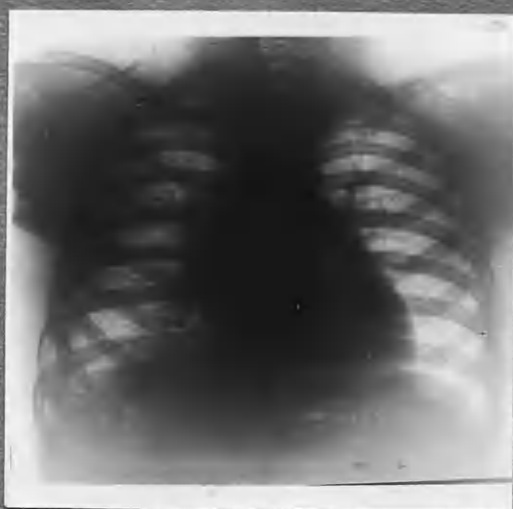
Notes.

16.11.29 - Slight rash on upper arms, not serious.

Course successfully completed, without complications.

The physical signs, however, and the X-Ray Report showed no appreciable change. The general condition, as one might have anticipated in any case, had improved.

NOTE :- See page 49 for X-Rays of this Case.



Before SANOCRY SIN.

20.9.1929

Raymond Paddison.



After SANOCRY SIN

22.1.1930.

NOTE:- X-Ray Clearing.

To face page 76.

Case 12. (Raymond Paddison - Age 12)

Physical Examination :- General condition good.
 Percussion note generally rather dull, and respiratory murmur reduced on the right side. No accompaniments to the breath-sounds, which were clearly heard.

X-Ray Report :- Pleural thickening on Right.
 Active disease on Left.

B.S.R. :- 27 - 45 = 24.75.

P.C. :- 22 - 40 - 32 - 6 - 0. W.M=2.22.

Tuberculin Test :- (a) Quantitative Pirquet = Positive all dilutions.

Sanocrysin Treatment.

24.10.29 = 0.05 gm.

and by regularly increasing doses to

2.1.30 = 0.50 gm.

Total = 3.25 gm.

Notes.

16.11.29 - Headache, feeling of nausea.

A successful case, and one which improved in general condition in a most satisfactory way. Percussion was still dull over the roots, but had become generally more resonant. From the X-Ray standpoint, the pleural shadow (right) had disappeared, and the lungs were much clearer.



Before SANOCRY SIN.
29.8.1929.

Walter Cockerill.



After SANOCRY SIN
22.1.1930

NOTE: MARKED CLEARING.

To face page 77.

Case 13. (Walter Cockerill - Age 11)

Physical Examination :- General condition only fairly good, and fatigue very quickly produced on exertion.

Both apices suspicious of disease. Prolonged expiration at right apex, and breath sounds not clear.

X-Ray Report :- Definite active, adult-type of disease in both subapical regions. Dense area on left may be consolidation or fibrosis.

B.S.R. :- 35 - 84 = 38.50.

P.C. :- 34 - 40 - 24 - 2 - 0. W.M. = 1.94.

Tuberculin Test :- Quantitative Pirquet = Positive all dilutions.

Sanocrysin Treatment.Notes.

24.10.29 = 0.05 gm.

and by regularly increasing doses to

2.1.30 = 0.50 gm.

Total = 3.25 gm.

10.12.29 - Faint rash on chest.
 19.12.29 - Faint rash, persisting.
 26.12.29 - Rash clear. Continue.
 5.1.30 - Nausea. No rash.
 8.1.30 - Vomited to-day. Slight pyrexia. Some albuminuria.

This case was definitely sensitive, though not to a very marked degree, to sanocrysin, and it was almost impossible to complete the course without the development of some complication - in the skin, or the kidneys, or the gastro-intestinal tract. Both physical signs and X-Ray report were improved, however, and it would appear that the drug justified its exhibition in this case.

Case 14. (Harold Farn - Age 10)

Physical Examination :- General condition fairly robust.

Percussion note dull over both roots, and respiratory murmur harsh in both lungs. Expiration prolonged in right apex.

X-Ray Report :- Evidence of only slight disease in right and left lungs.

B.S.R. :- 3 - 7 = 3.25.

P.C. :- 12 - 36 - 46 - 6 - 0. W.M. = 2246.

Tuberculin Test :- (a) Quantitative Pirquet = Positive all dilutions.

Sanocrysin Treatment.

24.10.29 = 0.05 gm.

and by regularly increasing doses to

2.1.30 = 0.50 gm.

Total = 3.25 gm.

Notes.

No reactions to note.

Course successfully completed without complications. There was a steady improvement in general condition, although physical signs and X-Ray Report were not much altered. It is to be noted, again, that a child of fairly good physique appears to tolerate the drug much more easily than one of poor general tone, in spite of the local signs in the chest.



Before SANOCRYGIN.

5.7.1929.

Arthur Marlow



After SANOCRYGIN.

25.1.1930.

NOTE: No improvement.

To face page 79.

Case 15. (Arthur Marlow - Age 10)

Physical Examination :- Of small build but good general tone.

Percussion note rather dull over both lungs, and fine post-tussive rales heard in the upper lobes.

X-Ray Report :- Right Root Shadow ++.
Left Root Shadow +.
Fine peribronchial infiltration right and left.

B.S.R. :- 13 - 30 = 14.00.

P.C. :- 12 - 48 - 34 - 6 - 0. W.M. = 2.34.

Tuberculin Test :- (a) Quantative Pirquet = Negative.
(b) Intradermal Test = Positive to $\frac{1}{10}$.

Sanocrysin Treatment.

24.10.29 = 0.05 gm.

and by regularly increasing doses to

2.1.30 = 0.50 gm.

Total = 3.25 gm.

Notes.

14.12.29 - Slight vomiting, not serious.

Satisfactory completion of course, without complications. The physical signs were improved, although the X-Ray Report was unaltered. Any improvement seen could have been anticipated, I feel, without the use of sanocrysin, and, again, the good general condition seemed to be responsible for an absence of ill-effects from the drug.

Case 16. (George Critchlow - Age 11)

Physical Examination :- Pale of countenance, and becoming quickly flushed on least exertion or excitement.

Right lung dull to percussion, and bronchial breath-sounds over the apex. Whispered pectoriloquy. Diminished air entry in Left Lower Lobe.

X-Ray Report :- Definite disease Right and Left. Dense shadow right upper lobe, either pleural thickening or fibrosis.

B.S.R. :- 10 - 22 = 10.50.

P.C. :- 20 - 38 - 34 - 8 - 0. W.M. = 2.30.

Tuberculin Test :- (a) Quantitative Pirquet = Positive all dilutions.

Sanocrysin Treatment.

24.10.29 = 0.05 gm.
1.11.29 = 0.10 gm.
8.11.29 = 0.15 gm.
15.11.29 = 0.20 gm.
22.11.29 = 0.25 gm.

Total ● 0.75 gm.

Notes.

29.11.29 - Metallic rash, well developed, on upper arms and legs, and tending to show itself also on the trunk.
7.12.29 - Rash persists - dry. Advisable to stop treatment.

Course not completed. Probably a longer interval between injections, as already noted in certain cases, would have obviated the skin complication, the elimination of the drug being evidently much slower than the intake of it, with the result that here was a case of cumulative sanocrysin poisoning of a mild degree.

As it was, the physical signs began to improve after stopping the injections, and three months afterwards the child was discharged with a fairly hopeful prognosis.

Case 17. (Violet Richmond - Age 9)

Physical Examination :- General condition fair.
 Right upper lobe dull to
 percussion, and respiratory murmur harsh
 in both right and left lungs.

X-Ray Report :- Definite disease right and left.
 Right root very dense.

B.S.R. :- 9 - 23 = 10.25.

P.C. :- 18 - 28 - 46 - 8 - 0. W.M. = 2.44.

Tuberculin Test :- (a) Quantitative Pirquet = Positive
 all dilutions.

Sanocrysin Treatment.Notes.

2.12.29 = 0.05 gm.

9.12.29 = 0.10 gm.

Total = 0.15 gm.

4.12.29 - Tendency to be feverish.

11.12.29 - Temperature rising to
 102° every evening.

18.12.29 - Temperature persists.

25.12.29 - Still febrile.

1.1.30 - Temperature only now
 tending to settle.

A pyrexia, occurring after only 0.15 gm. of Sanocrysin had been taken, and persisting for over a fortnight, appealed to me as sufficient reason to stop the treatment. Note, again rather poor general condition in this case (compare with sister, - next case).

Case 18. (Winifred Richmond - Age 13)

See Thesis - page 46.

Sanocrysin Treatment.

2.12.29 = 0.05 gm.
 9.12.29 = 0.10 gm.
 15.12.29 = 0.15 gm.
 22.12.29 = 0.20 gm.
 27.12.29 = 0.25 gm.
 4.1.30 = 0.30 gm.

Total = 1.05 gm.

Notes.

4.12.29 - Tendency to be feverish
 19.12.29 - Angular conjunctivitis,
 right and left.
 9.1.30 - Definite metallic rash on
 arms and legs. Stop.
 16.1.30 - Rash persisting.
 Eczematous condition has
 developed, with wet
 surface.
 7.2.30 - Eczema has now spread to
 the face.
 14.2.30 - Gradual improvement on
 body. Face still affected.

Course incomplete.

The effect of the drug on the skin was most unpleasant in this case, and, because of the prolongation of the condition, one might conclude that the excretion of the drug was very slow. Like her sister (previous case), this child quickly became feverish after the injections were given, and, gradually, instead of the temperature quickly returning to normal, it remained high for a more or less indefinite period.

The general condition did not improve, and the signs in the chest were, if anything, worse, three months after the Sanocrysin was stopped.

Case 19. (Ethel Sharman - Age 13)

Physical Examination :- General condition good.
Percussion was dull over right lung, compared to that over the left, but both lungs affected. Post-tussive râles in right upper lobe, and fine crepitations in left upper lobe, which, however, were not constant.

X-Ray Report :- Definite disease right and left.
? Mediastinal pleurisy.

B.S.R. :- 12 - 27 = 12.75.

P.C. :- Not done in this case.

Tuberculin Test :- Intradermal Test = Negative all dilutions.

Sanocrysin Treatment.

2.12.29 = 0.05 gm.

and by regularly increasing doses to

7.2.30 = 0.50 gm.

Total = 2.85 gm.

Notes.

14.1.30 - Is taking Sanocrysin well.

This child took the drug well, and steadily improved, both generally and in her chest signs.

Perhaps one could have anticipated this improvement even if the Sanocrysin had not been given, but, though I am inclined to minimise the reward in favour of the drug, I feel that the improvement was possibly more rapid than it would otherwise have been.

SUMMARY :-

Number of cases treated	=	19
Number who, because of complications, did not finish the course	=	7
Number who, in spite of complications almost sufficient to stop the treatment, finished the course	=	2
Number who finished the course with no complication of importance	=	10

Types of Complications :-

- (1) Skin reactions - varying from erythema to definite dermatitis - occurred in 10 children.
 - (2) Albuminuria - variable in degree, and not persistent in any case - occurred in 7 children.
 - (3) Nausea and Vomiting - occurred in 4 children.
 - (4) Diarrhoea - occurred in 0 children.
 - (5) Increased pyrexia - persisting, and as a reaction primarily to the drug, occurred in 3 children.
 - (6) Angular conjunctivitis - occurred in 1 child.
-

Headache was complained of by most of the children, especially on the day of the injection. This was usually gone on the following day, except in two children who felt heavy and listless.

Of the 12 who completed the course - 10 children were improved:-

- (a) 6 showed general improvement.
 - (b) 4 showed both general improvement, and satisfactory improvement in chest signs.
-

Of the 7 who did not complete the course - 4 children improved but only satisfactorily in general condition. Local chest signs were still unsatisfactory.

CONCLUSIONS :-

- (1) Of 19 cases treated, 7 were unable to tolerate the drug. This is 37%. I am therefore disinclined to agree with Heaf who states that children take Sanocrysin well. Sanocrysin, if to be given at all to children, must be administered with extreme care, and under constant supervision. A Sanocrysin Clinic is out of the question.
- (2) I declare that, only where the condition of the child is generally good, can Sanocrysin be given without much fear of harmful reactions.
- (3) I feel sure that any improvement in the 12 cases who completed the course cannot be ascribed to Sanocrysin alone - the continued rest, which my method of treatment entailed, is, in my opinion, a much truer cause for the general improvement which was observed in these cases. I admit, however, that there are a few cases which, about to improve in any case under Sanatorium regime, may improve more quickly if they receive Sanocrysin.
- (4) Unfortunately, it is in these cases where one would like most to have the added service of some special treatment that the special treatment (if in the form of a drug) is not often tolerated.
- (5) If Sanocrysin is to be given to children, an interval of ten days between injections should be taken as a minimum. The longer this interval, the less likely are complications to arise.
- (6) In fine, however, I consider it unwise to administer Sanocrysin to children for the sake of the very small number who really take it well and appear to benefit from it, because
 - (a) These very children will surely improve without it.
 and (b) The others - the large majority - would be spared much discomfort and possible harm.

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