Tuberculin treatment / by Clive Riviere and Egbert Morland.

TUBERCULIN TREATMENT

CLIVE RIVIERE
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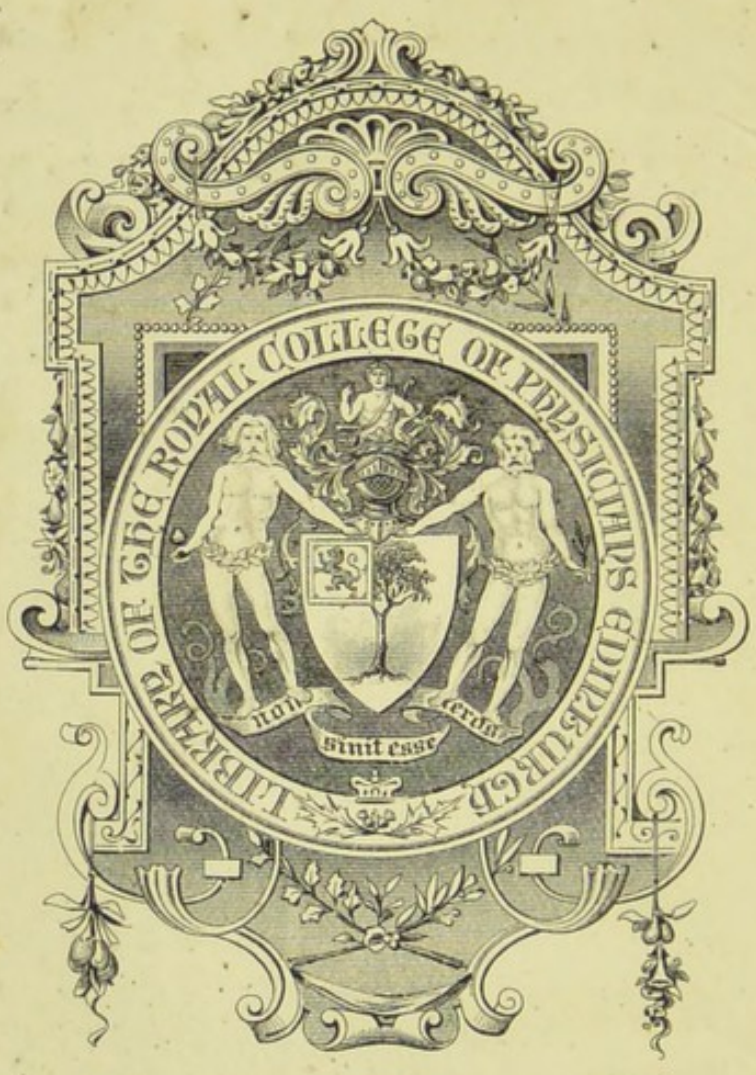
OXFORD MEDICAL MANUALS



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TUBERCULIN TREATMENT

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PREFACE

It so happened that each of the two writers of this book became aware that the other was on the point of publishing a manual of tuberculin treatment. Both had been convinced by personal experience of the value of the remedy, and desired to remove a certain atmosphere of misapprehension and controversy which was interfering with its more general recognition. Without predilection for dual authorship, the remembrance of a common *alma mater* and the affinity of aim and view determined the merging of the two books into one. This was done without sacrifice of guiding principle, and with a widening of scope, since the personal experience of the writers had been largely in different fields. In the book as it stands each writer claims equal share and responsibility.

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INTRODUCTION

TUBERCULIN has had a strange and eventful history, but nowhere so strange as in England. Entrusted by Robert Koch in 1890 to a small band of clinical workers, who returned from Berlin with the precious remedy, it was tested by them in the large increasing doses then in vogue—tested and found, not indeed altogether wanting, but not fulfilling the expectations which had been based upon it, and after a trial of but a few months, discarded again as a remedy [1] whose action was "to promote the formation of cavities, to lead to extension of the disease," "to exhaust the patient and to cause loss of weight and strength."

Nor was it discarded entirely or without prophetic voices being raised. One of the original workers never saw [2] in his "own practice harm done by the use of this remedy" and continued to use it in private. Another wrote [3] "If small doses gradually increased are

[1] Report of Tuberculin Treatment Sub-committee of the Brompton Hospital, quoted by H. Batty Shaw. *Clin. Journ.*, 1905, xxvi. 38.

[2] G. A. Heron, "A Lecture on the Treatment of Consumption and of Lupus by Tuberculin." *Brit. Med. Journ.*, 1898, ii. 77.

[3] J. E. Squire. A paper read before the Harveian Society on January 8, 1901, reprinted in *Essays on Consumption.* Sanitary Publishing Co., 1900.

equally efficacious, it may ultimately become possible by carefully regulating the dose to treat patients without interfering with their employment." And a third summarized the results thus :[1] "The injections of small quantities of the tuberculin, carried out with care, and spread over considerable periods, were free from danger of producing untoward complications, and if persisted in . . . were followed by improvement in a large proportion of the early cases of pulmonary tuberculosis." At the British Medical Association Meeting in 1891 also "several practical physicians appeared to disagree with the more general view that the remedy was of no value."

But in the aggregate these voices were few and faint, and fell on deaf ears for the profession as a whole, and although in 1897 and 1901 the newer forms of tuberculin were tested in the great consumption hospitals, the researches remained of an academic nature, and in 1905 it could truly be said of tuberculin[2] "its short-lived glory was succeeded by a period of absolute rejection, and then one of indifference, so that to-day it may be regarded as having dropped out of the pharmacopœia of even the serious medical practitioner."

The revival in England of tuberculin as a therapeutic agent was brought about in a very remarkable way as a result of the researches of A. E. Wright and his pupils into the mechanism of immunisation by bacterial products in general. The new principle was (1903) thus

[1] V. D. Harris and E. C. Beale, *The Treatment of Pulmonary Consumption.* Lewis, 1895.

[2] W. Bulloch. "The Treatment of Tuberculosis by Tuberculin." *Med.-chirurg. Trans.*, 1906, lxxxix. 69.

stated by Wright:[1] "The tuberculin inoculations have been . . . definitely invested with the character of therapeutic inoculations of a tubercle vaccine designed to call forth an antibacterial reaction in the organism": and "we ought cautiously to exploit in the treatment of localised tuberculous affections the tubercle vaccine which we owe to the ever fertile labours of Koch." Under the stimulus of this teaching there gradually developed the successful treatment of surgical forms of tuberculosis by means of small infrequent doses of the newer tuberculins, doses a thousand or more times smaller than those employed thirteen years earlier. As experience increased it was found that success was very great in the local forms of tuberculosis and attempts were made to obtain similar results in phthisis, but, except here and there in isolated cases, without success. And at this point, as far as England alone was concerned, the matter ended—successful treatment of localised tuberculosis after the method of Wright, with small infrequent doses of tuberculin.

In Germany the revival of tuberculin took quite another form. It came from the clinical side and dates from the publication[2] in 1901 of the experience that phthisis could be safely treated with large frequent doses of tuberculin, if, instead of starting with a large dose, small ones were used to lead up to it. This experience was confirmed, first by one and another in widely scattered centres, then more and more generally, especially

[1] A. E. Wright, "A Lecture on Therapeutic Inoculations of Bacterial Vaccines." *Brit. Med. Journ.*, 1903, i. 1069.

[2] Goetsch, "Ueber die Behandlung der Lungentuberkulose mit Tuberkulin." *Deutsch. med. Wochenschr.* 1901, xxvii. 405.

in sanatoriums, but always on the same lines—successful treatment of phthisis, after the method of Koch, with large frequent doses of tuberculin.

Such a discrepancy could hardly fail to excite comment, but this comment unfortunately took the form of scepticism and contempt. On the one hand the small-infrequent-dose school queried the safety of the large doses and the reality of the favourable results in phthisis which it failed itself to obtain. The large-frequent-dose school, on the other hand, was frankly contemptuous of the exhibition of the remedy in doses which it assumed to be inert, but failed with its own method to obtain comparable results in surgical tuberculosis. In each country there did not lack a few workers who adopted the other method, but it was in America that the necessary perspective was obtained and both methods seen and appreciated at the same time.[1] "The use of tuberculin may produce two opposite effects . . . according to the method of administration. When used in small doses not increased, tuberculin maintains the sensitiveness . . . it appears to be a rational method for localised forms of tuberculosis. On the other hand, a gradual increase in the dosage leads in favourable conditions of nutrition to a complete loss of sensitiveness and coincident improvement in health. In pulmonary tuberculosis at least, I feel inclined to select tuberculin immunisation as the goal for treatment." Here is a clear appreciation of the fact which must have been evident for long to an unprejudiced observer, that the two

[1] E. R. Baldwin, "Hypersusceptibility to Tuberculin in Tuberculosis: its Physiological and Clinical Importance." *Yale Med. Journ.*, 1909, xv. 257.

methods were not antagonistic but complementary; that each was successful in its own sphere.

Recognising this fact the writers have attempted in the following pages to give an account of the whole field of tuberculin treatment in correct perspective. They propose to show that the two methods are indeed based on the same essential principles, modified to suit certain definite requirements. The study of tuberculin treatment has hitherto been rendered difficult by the lack of a textbook bringing both methods thus objectively before the reader. This has been the chief hindrance to the appreciation of tuberculin at its proper value, not indeed as a panacea for all the baleful effects of Koch's bacillus, but as a specific remedy capable, if properly used, of doing good in most manifestations of tubercular disease.

Other hindering factors there have doubtless been. Some faint survival of the qualms and anxieties of the first tuberculin era; the confusion arising from the number and variety of preparations of tuberculin on the market; the mental difficulty of grasping the dosage in its various guises: these fears the writers hope to allay and the difficulties to simplify. But the chief and central aim of their book is to take tuberculin treatment out of the field of doubt and controversy, and to place its principles and practice alike on a firm basis.

PART I

THE GENERAL LINES OF TUBERCULIN ADMINISTRATION.

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PART I

THE GENERAL LINES OF TUBERCULIN ADMINISTRATION

THE ACTION OF TUBERCLE PRODUCTS IN GENERAL

Tubercle products are not toxic to the healthy ; enormous doses of tuberculin even up to 1,000 c.mm. have been injected without the production of any general disturbance ; but a different result occurs in those who have already made acquaintance with the tubercle bacillus, to them tuberculin is a powerful poison, and a comparatively minute dose leads to violent and characteristic symptoms. Previous contact with the bacillus has given their tissues a power not possessed by the tissues of the healthy, the power of rendering toxic the previously innocuous tubercle products. They have become " sensitive " to tuberculin : how is this brought about ?

The Tuberculin Reaction.—Before attempting to answer this question let us consider briefly the effects produced by the injection of tuberculin. In the healthy we find no symptoms appear, and the tuberculin meets the fate of a foreign albumin. But in the tubercular subject a sufficient dose gives rise to the phenomenon

known as the tuberculin reaction, which thus becomes the test of tubercular sensitiveness. This phenomenon shows itself typically in a threefold manner : as a **local** reaction at the place of injection, as a **focal** reaction at the site of tubercular disease, and as a **general** disturbance mainly of the nervous system leading to fever, malaise, pains, and other symptoms (page 29). Any one or more of these factors may be absent in a particular case. Where tuberculin is applied to the tissues locally, as by the cutaneous and conjunctival test and only the local manifestations appear, these are as much a test of tubercular sensitiveness, that is the power of the tissues to activate tuberculin, as is the appearance of the threefold phenomenon under subcutaneous injection.

The Immunising Response.—The tuberculin reaction is so striking a phenomenon that it is apt to distract attention from the less noticeable rebound which in most cases immediately follows it, and constitutes a phase of at least equal importance in the whole immunising response. This rebound is characterised by a feeling of increased well being, with diminution of symptoms previously present and improvement in areas of local disease. It corresponds, as we shall see later on, to an increase of antibody content in the blood, and to a lessened response to injected tuberculin.

TUBERCULAR SENSITIVENESS

What peculiar properties do the tissues of the tubercular acquire which make them susceptible to products of the tubercle bacillus which are innocuous to the healthy ?

Any wide discussion of the numerous theories ad-

vanced is outside the scope of this book, but the writers feel that a working hypothesis, and that as simple as possible, is essential to the rational therapeutic application of tuberculin. The theory which explains the facts most simply, and perhaps most satisfactorily, is that introduced in recent years by Wolff-Eisner. He supposes the production by the tissues of the tubercular of a specific antibody capable of breaking down the tuberculin molecule with the formation of toxic products much in the same way as a digestive enzyme breaks down an albumen molecule into a simpler and a highly toxic albumose. This antibody he calls a lysin (tuberculolysin), and it is immaterial to the theory on its broad basis whether it is a property of tissue cells or of the blood fluids. Let us see how this hypothesis explains the salient facts of the action of tuberculin.

A. In the non-infected organism no lysin is present : the injected tuberculin is not broken down and remains circulating as a harmless foreign albumen until eliminated. (Chart I.)

B. In the infected organism the tuberculin meets lysin at the site of injection and is broken down with formation of a toxin which produces the local reaction ; if in sufficient quantity this toxin reaches the general circulation and causes a " general reaction," and finally a " focal " reaction by irritation of the tubercular focus (Chart I). Finally the injection leads to a fluctuation of definite size in the tide of antibody content in the blood leading to an increase, probably, of bacterio-lysin, of bodies leading to tolerance the " antituberculin " of Wassermann, and of Opsonic power.

Its Value.—Having introduced tubercular sensi-

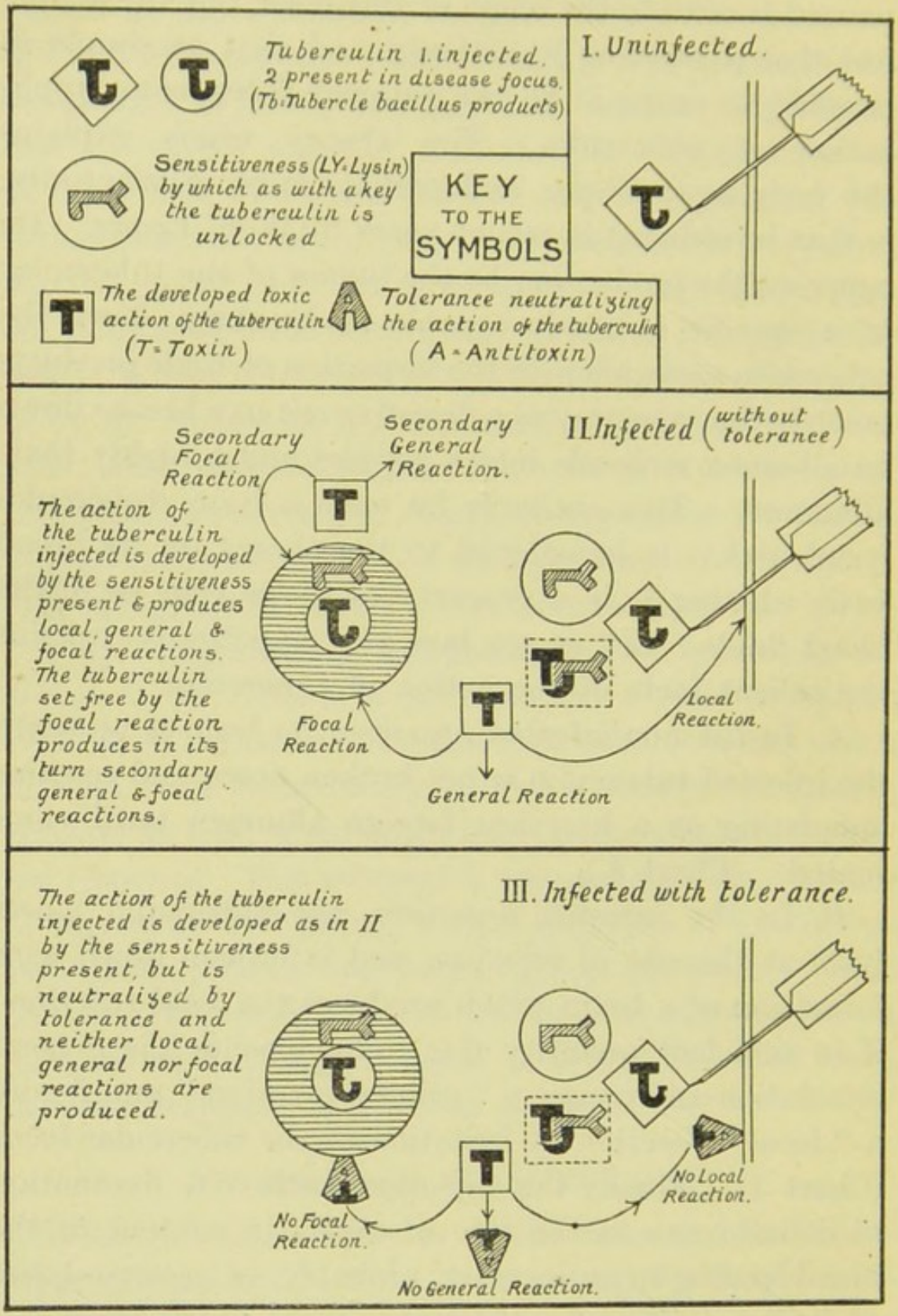


CHART I.—Diagrams illustrating the various effects of a tuberculin injection on the non-tubercular, and the tubercular without and with tolerance.

tiveness and advanced a simple theory as to its action we may ask whether it is of advantage or otherwise to the organism. From the results of **animal experiment** we can say at once that such sensitiveness or the conditions accompanying it afford real protection against infection. By numerous experiments in cattle and guinea-pigs, and also in apes, it has been proved that the presence of tuberculosis, whether naturally or artificially acquired, is an effective protection against infection by large quantities of virulent bacilli. Such bacilli are acted upon by the tubercular tissues and lead to an immediate reaction, but no further results, while in control animals the reaction is absent but rapid tuberculosis quickly follows. Sensitiveness thus goes hand in hand with immunity!

Clinical experience also affords similar evidence, both positive and negative. The freedom of the subject of phthisis from disease of neck glands, of intestinal mucous-membrane, of larynx to which he is constantly exposed, can only be attributed to a protection against the bacillus similar to that shown to exist in tubercular animals. On the side of negative evidence may be cited the fact, not disputed, that resistance to tuberculosis is notably low in those coming from countries or neighbourhoods where the disease is not yet rife: they supply similar conditions to those of the 'control' animals mentioned above which were not sensitive to tubercle and quickly succumbed to the injection of virulent bacilli.

On the side of **theory** the value of tubercular sensitiveness is not difficult to accept. We can find protection in the bacteriolysin which underlies perhaps the

static condition of sensitiveness itself: we can see help in the focal element of the tuberculin reaction when it is set free, and also in the increase in antibody content which follows it. The lysins would be of utility in "policing" the body, in destroying there and then any bacilli wandering out of a tubercular focus. In this way they would serve to protect the tissues most effectively from the deposit of fresh foci of infection. They might also assist the body-cells in taking up and removing the bacilli by phagocytic action, for it is commonly held that opsonic power is possessed by many or all antibodies as a sort of by-product of their action.

We find then that sensitiveness to tubercle products is an important factor in immunity. It gives the body the power of dealing with tubercle bacilli introduced from without or already present within reach of the body fluids. But their destruction also leads to the liberation of toxins, causing, in the case of a tuberculin injection, the tuberculin reaction, or, in the case of auto-inoculation, the symptoms we associate with tubercular disease.

Can anything but harm arise from the liberation of these toxic effects? We have considered shortly the tuberculin reaction and the divisibility of its symptoms into local, general and focal. Now it is obvious that the **general** symptoms, whether the result of tuberculin administration or of auto-inoculation, can have no other than a deleterious action. Under their influence, as we know well, the body is soon reduced to conditions of marked illness and finally death. If this were the only action of the tuber-

cle poison our sole aim would be the entire avoidance of such a result. But the toxin possesses another action which, owing to certain peculiarities of the disease, may be exploited to marked advantage. For not only is the tubercle bacillus resistant to the action of antibodies on account of its fatty capsule, but it is also protected from these by the peculiarities of tubercular tissues. These tissues are so strikingly non-vascular as to be in many instances almost outside the blood supply, and this difficulty can only be overcome by the production of an active hyperaemia of the part. This weapon of hyperaemia exists for us in the **focal** reaction whose main characteristic is the flooding of all tubercular areas in the body with blood. In this way nutriment is supplied, and antibodies brought to bear on the focus of disease, but at the same time bacterial products, and perhaps bacilli, are washed out into the surrounding parts, and so we must remember that this powerful asset in the treatment of localised tuberculosis may also lead to harm under certain conditions. We have then in the liberation of toxic action certain harmful symptoms to suppress and a certain useful action to encourage under fitting circumstances. Unfortunately for us the two are intimately bound together and we have no means of separating them. If focal action is to be used in a particular case, a certain amount of undesirable general disturbance must accompany it, and a convenient mean result has to be aimed at. In practice it must be admitted that where the focal reaction is out of reach the general symptoms will often serve as a convenient guide to the amount of effect produced by a dose of tuberculin.

Relation to Anaphylaxis.—Strikingly analogous to tubercular sensitiveness and requiring mention at this point is the phenomenon so closely studied of late years under the title anaphylaxis. When a foreign albumin formed (as bacterial protoplasm), or unformed (as egg albumin), is injected into an animal no obvious effect is produced; where however a second injection is given after a suitable interval, severe illness, spoken of as anaphylactic shock and often ending in death, rapidly ensues. The injection of albumin has caused the animal after a definite refractive period to become sensitive or anaphylactic to that particular substance. If the serum of such an anaphylactic animal is injected into a healthy animal a condition of passive anaphylaxis is set up, and, furthermore, the toxin causing symptoms of anaphylactic shock can be manufactured in vitro and will produce these symptoms on injection.

The striking resemblance of this phenomenon to tubercular sensitiveness has naturally led to many attempts to establish their identity. Tubercular sensitiveness as we find it under natural conditions requires the presence of living tubercle bacilli for its production. Attempts to set up the condition in a manner similar to that which calls forth anaphylaxis, by injection of tuberculin, or by the passive transfer of serum from a tubercular animal have led hitherto to very doubtful results. Claimants for success following the **injection of tubercle products** appear to have overlooked in nearly all cases the important differences between the symptoms of anaphylactic shock and the tuberculin reaction, and to have classed as tubercular-sensitive animals which are only anaphylactic. For it seems certain that the injection of large doses of tubercle endoplasm will produce anaphylaxis just as will other albumins, but the symptoms caused by reinjection differ widely from those produced by the same dose in a tubercular animal. The symptoms of anaphylactic shock are immediate—those of the tuberculin reaction follow an incubation period of many hours; the former is characterised by a marked fall of temperature, choking, dyspnoea, convulsions—the latter by fever and the absence of these other symptoms. Moreover, anaphylaxis can be carried over as passive anaphylaxis to another animal. When anaphylaxis is by these means excluded there appears little evidence that tubercular sensitiveness can be set up by the injections of dead tubercle products.

There remains the question of **passive transference** of tubercular sensitiveness analogous to passive anaphylaxis. Here the

transference is from animals with tubercular disease, and the fallacy of anaphylaxis no longer comes into play. The claims of Yamanouchi to success in this line were quickly discredited by Roepke and Busch, Bail, and others who showed that his results were attributable to the toxicity of the test tuberculin he employed. Friedemann failed to produce passive sensitiveness: Bauer obtained a fever reaction which was shown by Roepke and Starkloff to be caused by the enormous dose of test tuberculin used. They obtained similar reaction however with a smaller dose, but this also was shown by Joseph to be capable of causing fever in guinea-pigs. The latter relied on the intracutaneous as the most certain of tuberculin tests, and by means of this obtained only negative results after all attempts at transference of sensitiveness, both by injection of tubercular serum and by intraperitoneal injection of extracts of tubercular organs. Helmholz on the other hand appears to have set up some sensitiveness to the cutaneous test by the injection of tubercular serum into healthy guinea-pigs. On the whole the result of all these experiments tends to show that tubercular sensitiveness is a different phenomenon to anaphylaxis. The failure to obtain passive transference moreover demonstrates the interesting fact that, after all attempts to find it, no antibody in the serum, such as exists in the case of anaphylaxis, can be shown to occur in tubercular sensitiveness.

AMOUNT OF TUBERCULAR SENSITIVENESS

Having attempted to explain shortly the non-sensitiveness of uninfected and the sensitiveness of infected organisms to tuberculin, it remains to consider varying degrees of sensitiveness met with among the latter. It has been found as a result of the quantitive cutaneous test (page 64) that the sensitiveness of subjects repeatedly tested with the same dose (cutaneous) remained for a long period at the same level, if at least two weeks was left between the tests. Under these circumstances it was found that hundredfold difference in dose produced similar response in different individuals.

Such differences of original sensitiveness depend, in all probability, on differences in antibody content, and vary according to conditions of activity and distribution of disease.

Tolerance.—In addition to this variation in original

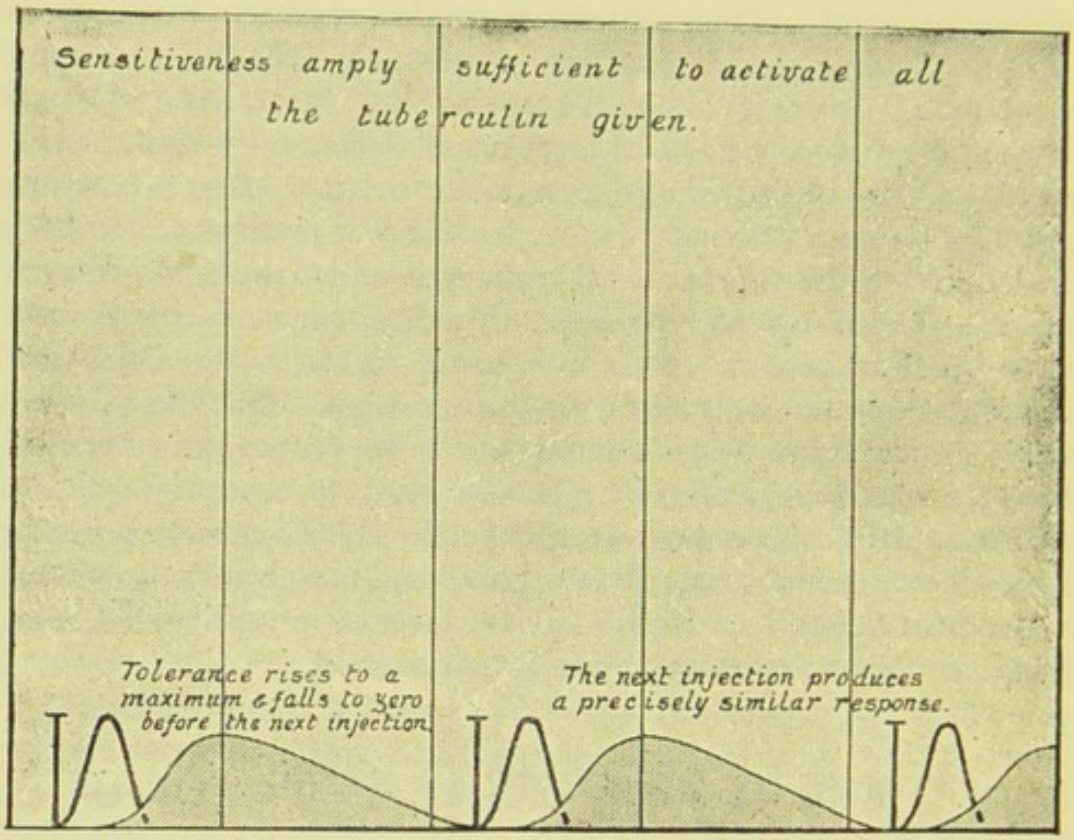


CHART II.—Method of immunisation without tolerance; a second equal small dose is given when the response to the first is over. The perpendicular line represents the dose, and the wave following it the activated tuberculin.

sensitiveness there exists, however, another factor about which we have more accurate knowledge and with the help of which we are able to tune our sensitiveness to any convenient pitch. This factor is what we call tolerance; it is this compensatory mechanism which enables a tubercular patient to go about his work in comfort though his disease is not cured, and which we attempt to establish where sensitiveness is leading

to excessive reactions under the influence of auto-tuberculin.

In tubercular cattle one, or at most two, large doses of tuberculin will so far remove reactively that they no longer respond to the diagnostic tuberculin test, and

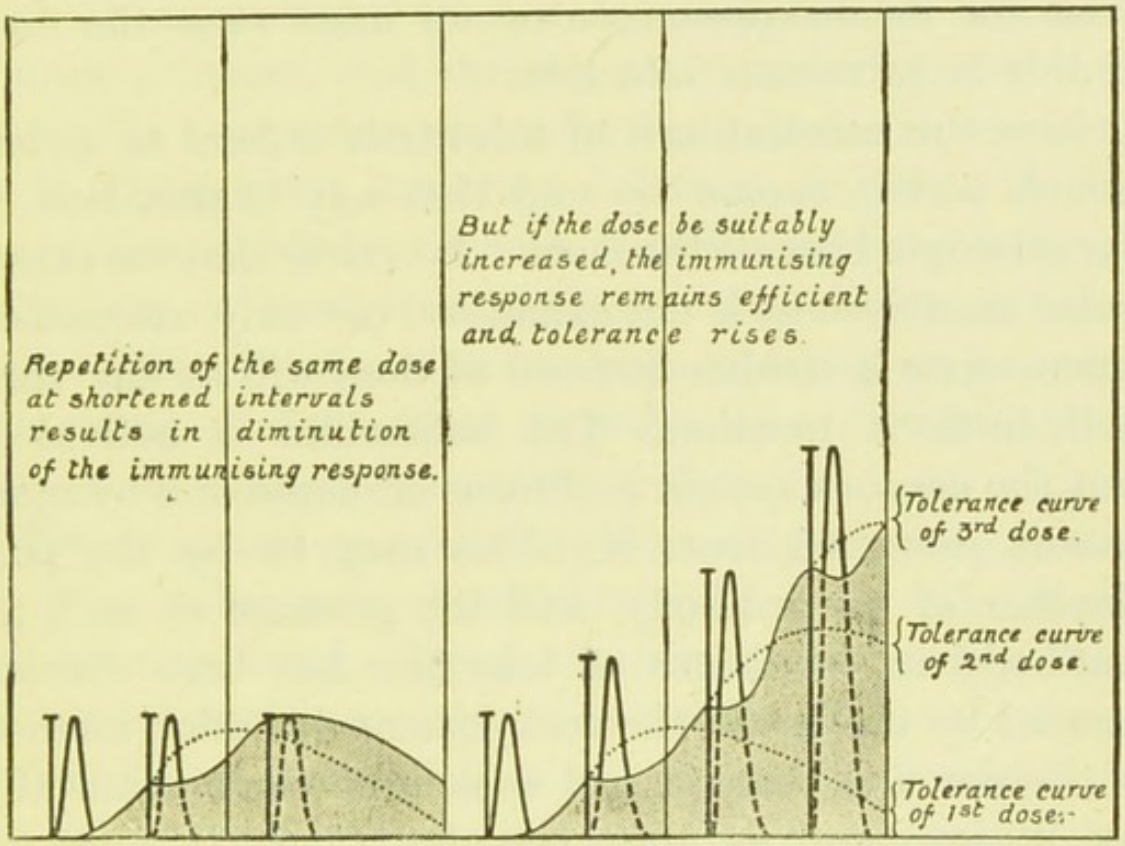


CHART III.—Method of immunisation with tolerance: showing that the essential factor is the diminished interval.

this fact is utilised by dealers to escape detection in the sale of diseased animals. In the human subject a similar but less striking development of tolerance follows the injection of an effective dose, and this after rising to a maximum again falls after a few weeks. If the same dose is repeated after tolerance has waned a precisely similar effect to that of the first dose is produced (Chart II). But if the dose is given while tolerance is present its efficiency will be diminished or

entirely annulled (Chart III). To obtain the same efficiency a larger dose must be given, and this is followed by a further rise of tolerance (Chart III), which again needs an increased dosage to overcome it. Thus we find that, whether we desire it or no, tolerance must always be taken into consideration; we must either wait for its disappearance or we must raise the dose if this is to remain effective.

Now the **mechanism of tolerance** is hard to understand, and it cannot be said that any explanation so far attempted covers the facts. It is clear that the tubercular sensitiveness is not exhausted but only encroached upon, since a sudden increase of dose will at any time call forth a reaction. The tuberculin is activated, but the nervous system and focus of disease are by some means protected from it. This may be by the production of an antibody, and the presence of such an antibody in conditions of tolerance has been demonstrated by the use of the complement-deviation method of Bordet and Gengou and spoken of non-committally by Wassermann as antituberculin (Chart I). Its increase and decrease has been shown by Pickert and Löwenstein to take the form of a curve like that of the tuberculo-opsonic index and we may accordingly associate immune opsonin, and antituberculin together as parallel if not identical phenomena.

SUMMARY.

We may sum up shortly the physiological action of tubercle products (tuberculin) as follows:—

1. In the healthy no action at all.

2. In the tubercular-sensitive a reaction, followed by a period of tolerance to tuberculin.

(*a*) **Sensitiveness.**—This is a loaded state ready to lead to discharge on the introduction of the tubercle bacillus or its products. It apparently serves for destruction (bacteriolysis) of any bacilli introduced from without or extruded from a focus of disease into surrounding tissues, and thereby toxins are liberated and cause the symptoms known as the tuberculin reaction.

(*b*) **Tuberculin Reaction.**—This is the effect of the toxin liberated from tubercle bacilli within the body or tuberculin injected from without. It consists of **local** hyperaemia (if tuberculin has been injected), of **general** symptoms, and of **focal** hyperaemia at the focus of disease, or of any one or more of these.

The local and general symptoms may be passed over as of no value save as indications of dose. The **focal** hyperaemia brings blood containing antibodies and nutriment to the poorly vascularised tubercular focus and is thus a potent factor in treatment. Corresponding to the reaction there is a lowering of the tuberculo-opsonic power of the blood—reaction corresponds to negative phase.

(*c*) **Immunising Response.**—This term refers to the whole effect of a therapeutic dose of tuberculin. The tuberculin reaction is the starting point and is followed in most cases by a rebound characterised by an increase in well-being, and a tendency to local healing in tubercular areas. A period of comparative tolerance to tuberculin accompanies it, and running parallel with it is an increase in the antibody content of the blood fluids.

(*d*) **Tolerance.**—By suitable interval and dosage the tolerance following injection may be made to encroach so far on sensitiveness that large doses of tuberculin and autotuberculin can be borne with impunity, and during such increase there is demonstrable an increase in the blood of complement-fixing bodies, the antituberculin of Wassermann.

CLINICAL APPLICATION OF THE ACTION OF TUBERCLE PRODUCTS

Hitherto we have considered tubercle products and their action on the tubercular only on general lines. It remains to consider how we can apply the manifold effects already touched upon so as to exert a beneficial influence on the course of tubercular disease. A condition of sensitiveness is already present, and with tuberculin we can supply the food for its action in any quantity and at any interval. We can increase antibody content with a suitable dose of antigen ; we can direct these antibodies to the focus of disease by setting up a focal reaction ; we can abolish any inconvenient sensitiveness of the tissues to toxic action by establishing tolerance.

Let us consider the common effects of a full therapeutic dose of tuberculin : an immunising response.

Reaction and Negative Phase.—Some hours after the injection a slight reaction occurs. On the clinical side some general symptoms, perhaps slight fever, nausea, malaise, are experienced ; locally if a visible focus is present some congestion and increased ex-

udation are observed corresponding to a slight focal reaction. On the side of experimental investigation these symptoms correspond to a negative phase, a diminution of opsonin, and probably other antibody power in the blood.

Tolerance and Positive Phase.—After an interval which varies according to the dose there is a marked rebound from the condition above described. On the clinical side the malaise gives place to a feeling of well-being, the local disease shows marked improvement, and there is a diminution of response to tuberculin. On investigation the antibodies are found to increase in the plasma, the whole immunising response lasting some two or three weeks, after which conditions return to their former, or, clinically, a higher level. After this interval a similar dose of tuberculin will be followed by a similar immunising response, the main points in which are the slight reaction, followed by a period of increased immunity, characterised by a rise in the antibody content of the blood. If doses are given at shorter intervals, before the response, including tolerance, returns to its former level, larger and larger doses are needed to ensure the same result, since by this means tolerance is gradually raised (Chart III). We thus have two possibilities before us in regard to dosage: we can obtain our immunising response on small constant doses, or we can obtain the same response on increasing doses.

THE TWO METHODS OF ADMINISTRATION

This fact is responsible for the existence of two methods of tuberculin administration. By the method

first introduced by Koch and mainly followed on the Continent and in America immunisation is accomplished by rising dosage given at short intervals so that a rising tolerance is achieved. The second method, introduced by Wright and mainly practised in this country, aims at the production of a mild immunising response by small doses given at long intervals and thus with no production of tolerance.

If we glance at the disease Tuberculosis for which these methods find employment we shall see a rational explanation of the success which both methods have achieved in a different class of case. Tuberculosis is naturally divisible into two well-recognized groups: on the one side stand cases where it is still a local disease; on the other side those cases where the disease has spread so far into vascular organs that large unequal doses of autotuberculin enter the blood stream. It is obvious that such different conditions call for somewhat different treatment: in all cases an immunising response can be obtained with advantage by the employment of tuberculin. But where auto-inoculation occurs this will interfere materially with treatment by small doses of tuberculin at long intervals, and no certainty in the response can be expected. For this reason, if for no other, it is convenient in such cases to obtain the necessary response from doses so large that the production of autotuberculin does not greatly interfere. But another reason also exists for the establishment of tolerance in these cases, for it is owing to a want of this compensatory mechanism that such patients go down hill under the influence of doses of unequal size and spacing issuing from their areas of disease. In producing

tolerance to injected tuberculin there arises at the same time tolerance to autotuberculin ; auto-inoculations cease to produce the train of symptoms attributable to the tuberculo-toxin and the patient loses his fever, night sweats, malaise. This amelioration of symptoms has been noted by all who have worked with the larger doses of tuberculin. In cases where no auto-inoculation occurs, as in local disease, there is no reason for giving tuberculin after this method. Thus the two methods of tuberculin administration find their proper field in the treatment of the two varieties of tuberculosis : the method of small equal doses at long intervals is suitable for all cases of localised disease, but where auto-inoculation adds tuberculo-toxin from other sources tolerance must accompany immunisation and the treatment by rising doses at short intervals is indicated. Thus the realm of the method of Wright is the localised and surface tuberculosis so commonly found in childhood : the realm of the method of Koch is *par excellence* the common tuberculosis of adult life, phthisis Pulmonalis.

SENSITIVENESS AND TOLERANCE.—SOME PROBLEMS EXPLAINED

The effect of tuberculin is bound up, as we have seen, in the sensitiveness acquired by the organism as the result of infection with the tubercle bacillus. Such sensitiveness is needed to " activate " the tuberculin and, when tolerance is absent, the full effect of the drug is apparent but when tolerance encroaches on sensi-

tiveness only that part of the dose which oversteps tolerance finds its effect. This relationship of tolerance and sensitiveness is of such vital importance to the understanding of tuberculin action that the writers make no apology for introducing the reader at as early a stage as possible to some of its simpler problems. The accompanying diagrams will be found to elucidate the matter in hand.

Chart II illustrates the method of immunisation without tolerance (see also Chart XXIV p. 193). It shows a tuberculin dosage given at such intervals that the tolerance due to the preceding dose has completely waned before the next. It will be seen that each dose falls wholly in the field of sensitiveness and hence is fully activated. Corresponding to the wave of tolerance to tuberculin there is represented on the chart also the immunising response in antibody content which presents a similar curve. An efficient dose causes a prolonged tolerance wave and immunising response, a subefficient dose leads to a shortening of both, and thus the indication for a shorter interval.

In Chart III it is apparent how when an efficient dose is repeated at too short intervals its effects are partially or totally swallowed up by the tolerance wave, and how at such intervals a rising dosage is necessary to maintain an effective dose above the tolerance level.

By the same system of diagrammatic representation also, certain apparent anomalies of tuberculin administration are readily explained.

Tolerance cannot be raised by dosage at long intervals.—A glance at Chart II makes this at once quite obvious. An interval of two or three weeks gives

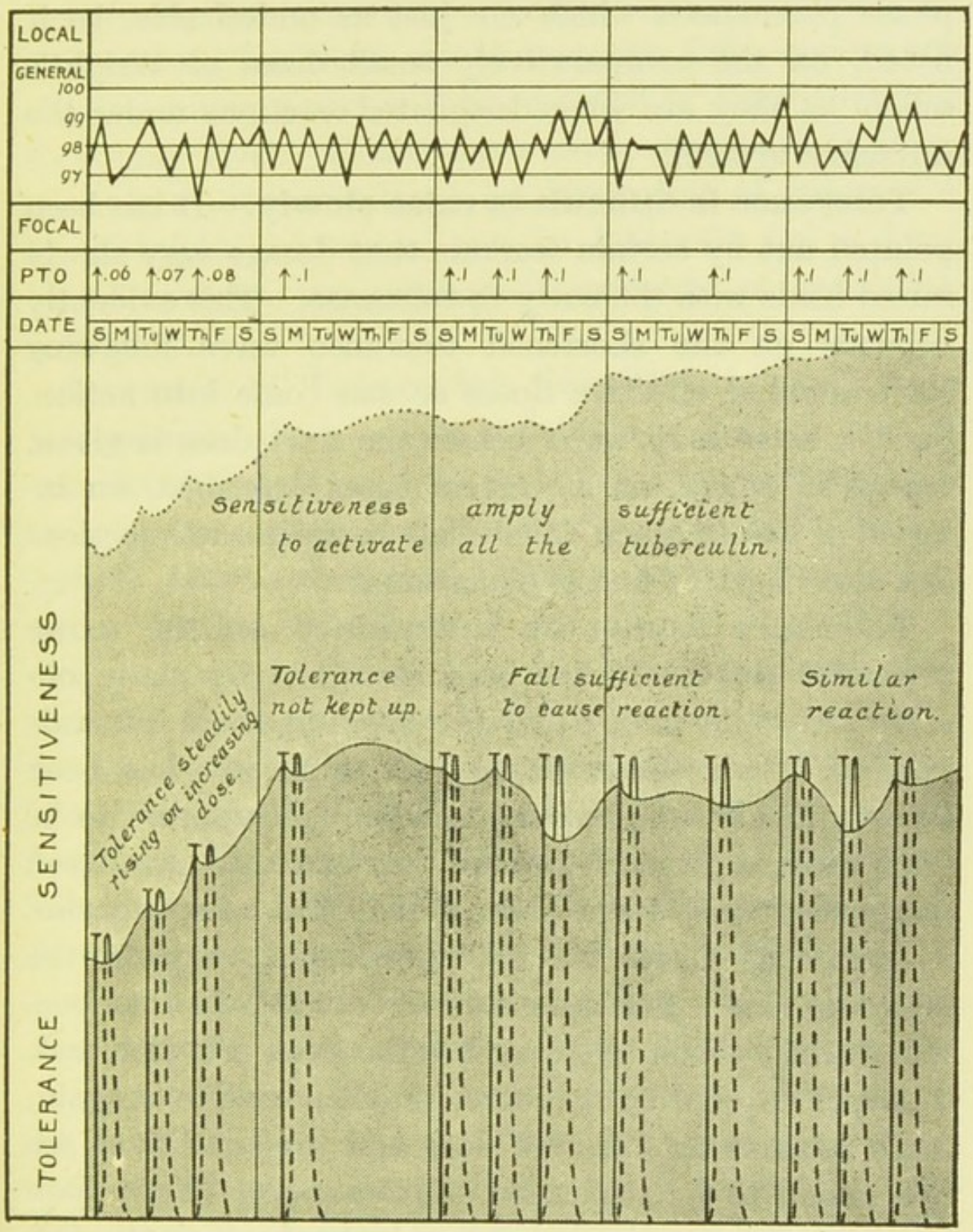


CHART IV.—Repetition of dose leading to fall of tolerance and unexpected reactions.

time for tolerance due to the preceding dose to wane, each dose is fully effective and any attempt to raise it only gives rise to overdosage with prolonged negative

phase phenomena which are just as undesirable, be it noted, on the comparatively small doses of Wright's school as they are when designated reactions under the intensive system.

Tolerance is difficult to raise slowly.—It has been pointed out by certain workers that dosage very slowly raised leads with difficulty to tolerance. This evidently depends on the shortened tolerance wave following such minimal effective doses as can come into action. Such a wave may wane before the next dose is given, especially where, as in certain cases described, an interval of five to seven days is left between the injections (see also Chart IV and explanation).

Tolerance cannot be maintained on the same repeated dose.—It has been remarked by many observers that doses of equal size given at short intervals lead to "hypersensitiveness." This matter has been investigated by the authors and the fact appears to be that when a certain amount of tolerance has been established this is soon lost if the dose ceases to rise. A glance at Chart IV will immediately explain the reason of this. For the effective dose is only that portion against which tolerance has not been provided and, if the same quantity of tuberculin is repeated over again, there remains no effective dose and the conditions are equivalent to a suspension of treatment. Thereupon tolerance wanes and, when it has dropped sufficiently far, the dose now left efficient by its fall calls forth a tuberculin reaction. Tolerance again rises in response to this but later falls again, and the temperature chart of such a case shows a series of ineffectual doses interspersed at intervals with marked reactions. It must

be remarked, however, that when a considerable amount of tolerance has been established this falls again very slowly, taking perhaps three months or more to reach its former level. Under these circumstances it is often possible to continue the same large dose of tuberculin at fortnightly or even greater intervals for a long period without any unpleasant evidence of returning reactivity.

Increase of Tubercular Sensitiveness.—This is a condition about which but little is known, but its occasional occurrence must be taken into consideration. It appears certain that tuberculin, though it cannot initiate sensitiveness in a healthy animal, yet causes under certain conditions a rise in the sensitiveness already present. When tolerance is also produced such increase of sensitiveness is lost to view; but tolerance for its production needs a regular series of rising effective doses and for that reason is apt to fail at the beginning of a course of treatment, or under the sudden introduction of full doses for diagnostic purposes. It is under these circumstances that the phenomenon of increased sensitiveness is apt to show itself, and that especially, in all probability, where sensitiveness was originally low. In Chart V and Temperature Chart VI will be seen the effect on sensitiveness of equal doses given (after Möeller and Löwenstein's method) for the diagnosis of a tubercular focus. Sensitiveness being low (probably due to inactivity of disease) the dose is not completely activated but there follows a rise in tubercular sensitiveness. Under its influence the next dose is further activated and the third fully so, with the result that a tuberculin reaction, which failed at the first

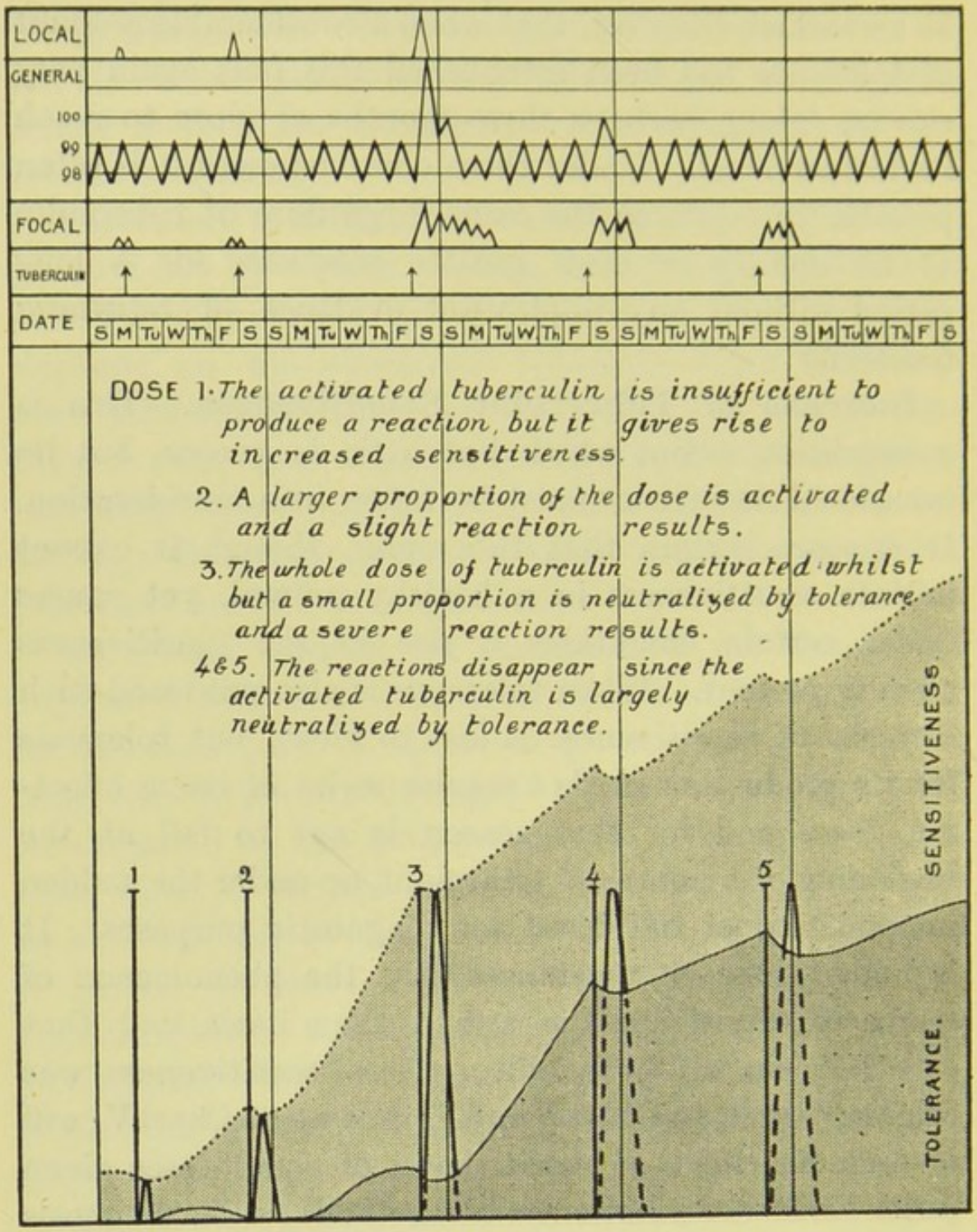


CHART V.—Illustrating increasing reaction on repetition of the same dose, due to an initial low sensitiveness failing to activate the whole dose of tuberculin given.

injection and is slight at the second, appears in marked form at the third dose. Such conditions of increased sensitiveness serve also to explain the ready

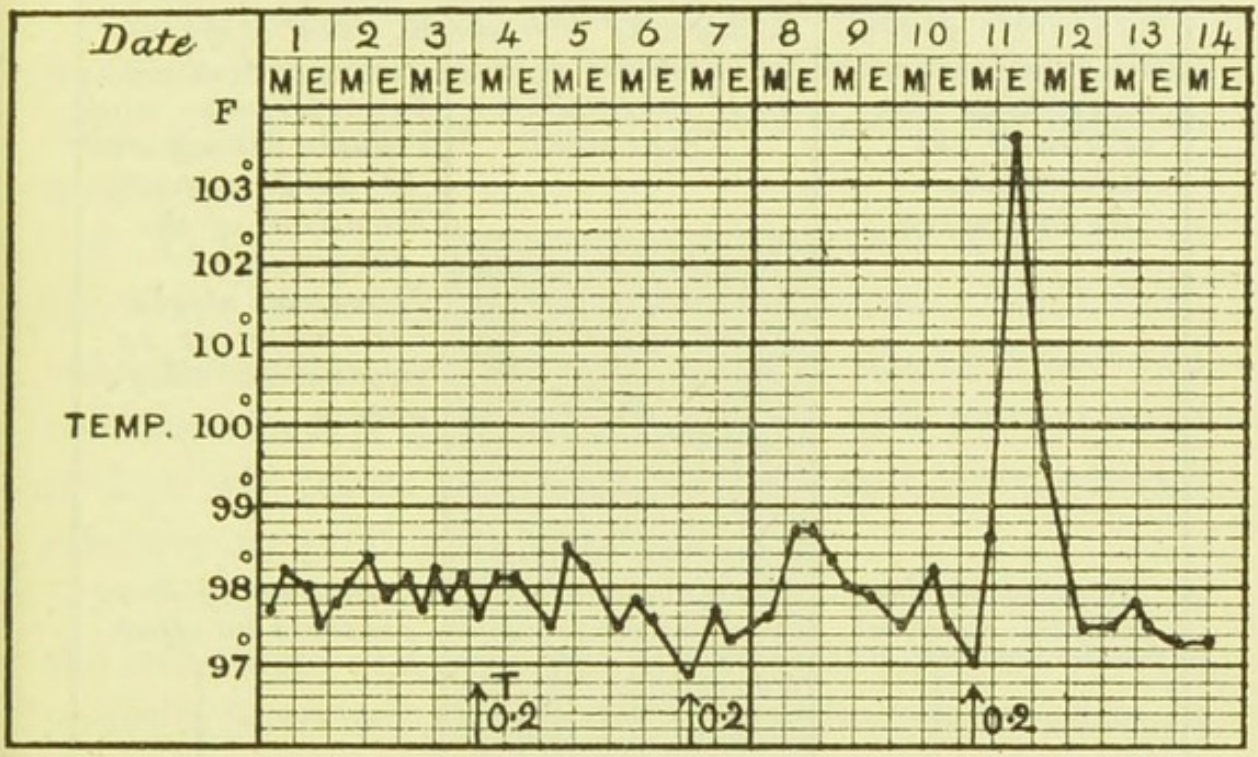


CHART VI.—Chart showing increasing reaction on repetition of the same dose. (From Löwenstein and Kauffmann, *Zeitschr. f. Tub.* X, 29.)

occurrence of reactions at the beginning of a course of tuberculin treatment in certain cases of early or

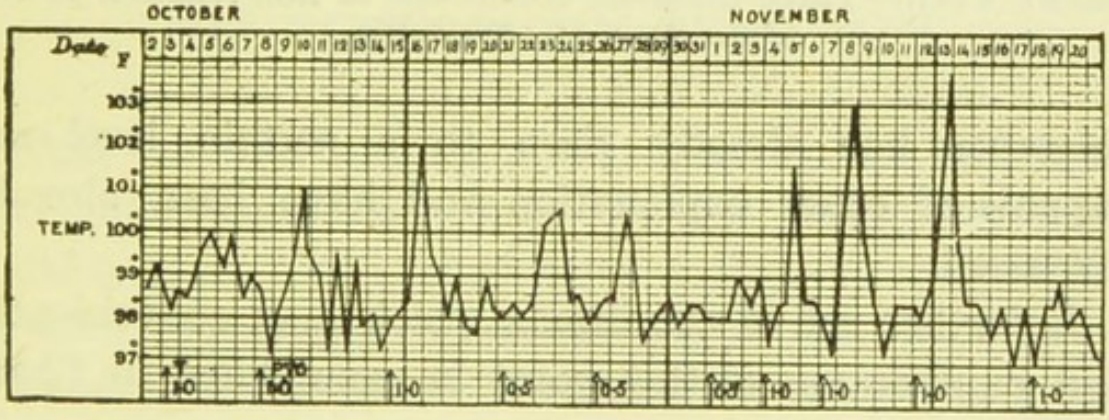


CHART VII.—Chart showing increasing reaction on repetition of the same dose. (Kindly lent by Dr. Hilda Clark.)

slight disease (see Temperature Chart VII). Reactions occurring under equal or ineffectual doses where

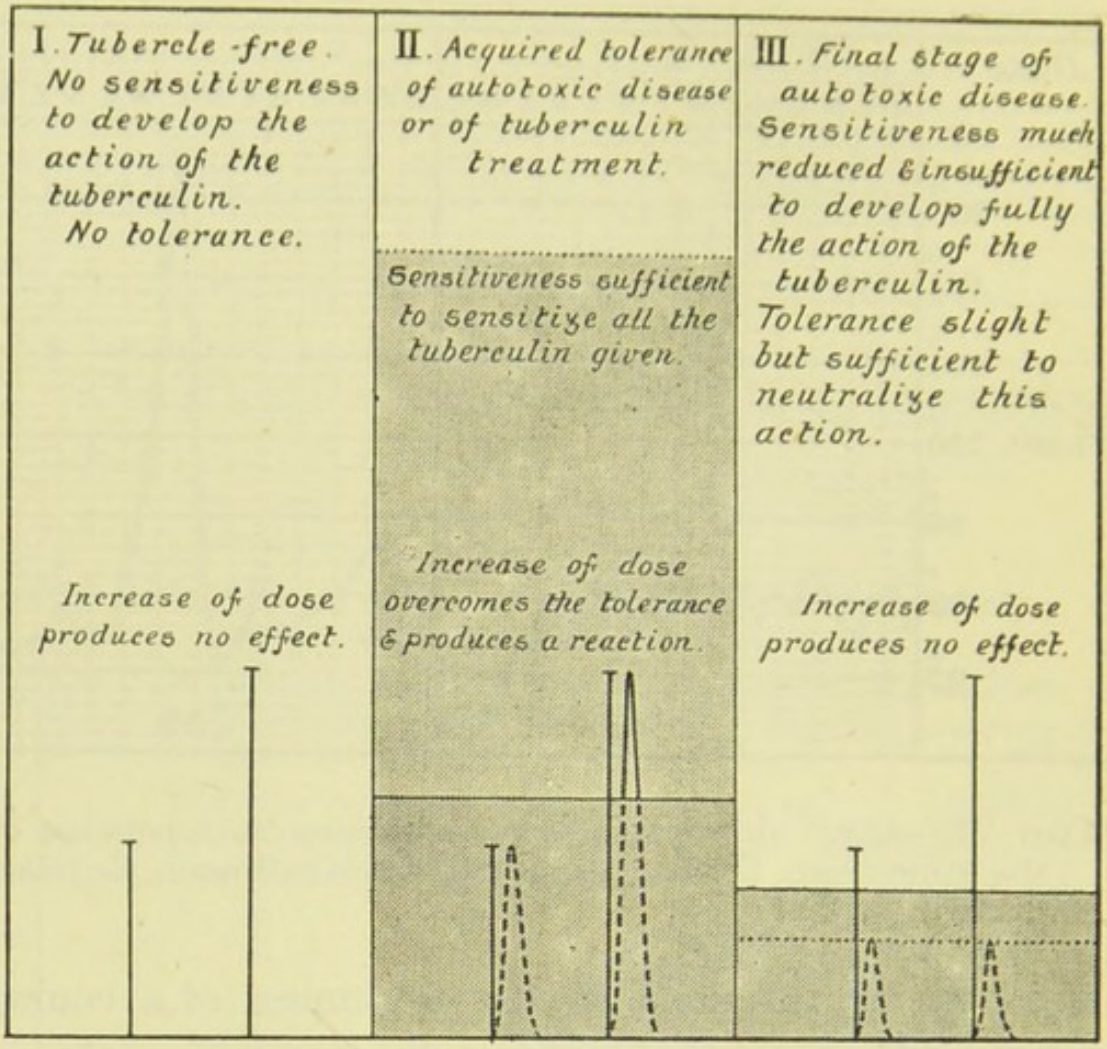


FIG. 1. FIG. 2. FIG. 3.

CHART VIII.—Three different conditions of non-reaction to the same dose of tuberculin.

tolerance has already risen to a certain level are capable of other explanation and have been already discussed.

A further set of conditions which may conveniently find explanation at this point is exemplified in Chart VIII.

Non-reaction to Tuberculin.—If a dose of tuberculin of size generally sufficient to call forth a reaction in the tubercular is given and no response obtained three different explanations are possible.

1. The patient may not be tubercular, in which case his tissues have not the power to activate the tuberculin which remains inert however much the dose is increased (Fig. 1).

2. The patient has acquired tolerance whether as the result of chronic auto-toxic tuberculosis, or of tuberculin treatment and the dose remains wholly below the tolerance level (Fig. 2). In this case a sufficient increase of dose will pierce the tolerance level and leave enough effective to produce a reaction.

3. In the third possible condition come patients in the last stages of auto-toxic disease ; the tissues of such patients have lost their power of antibody formation in response to antigen. Their tolerance is low but their sensitiveness is still lower. As will be seen in the diagram there remains no sensitiveness above the tolerance layer to activate tuberculin and a large dose produces no more effect than a small one.

THE TUBERCULIN REACTION

This, the most striking phenomenon in the action of tuberculin, demands a more careful description than could be given to it in the section dealing with the action of tubercle products in general. It is the main guide to, and to a less extent the aim of, tuberculin treatment, and it remains the test of tubercular sensitiveness through one or more of its manifestations. These are of threefold character and consist of—

1. Local reaction : at the site of injection or application.

2. General reaction : affecting the body as a whole.

3. Focal reaction : at the site of the tubercular lesions.

Each of these must now be considered in detail.

1 **The Local Reaction.**—An injection may produce no local phenomenon whatever ; after the bleb of fluid has subsided nothing further is noticeable at the site of puncture. On the other hand a red and painful swelling may occur, gradually developing to its maximum by the second or third day and then passing off. Two varieties of reaction have been distinguished—

(*A*) What is known as the **depôt reaction** where the tuberculin is deposited in the subcutaneous tissues ; this is appreciable in its slightest forms only by picking up a fold of skin, but if well marked it produces visible redness and œdema.

(*B*) The **needle-track reaction** due to a minute dose of tuberculin escaping from the needle as it is being entered or withdrawn and characterised by vivid redness round the puncture and, it may be, a painful nodule in the skin itself. The needle-track—which corresponds to the diagnostic intracutaneous—reaction is the most sensitive of all the tuberculin reactions and may occur with the merest trace of fluid.

The local reaction is of no other therapeutic importance than as a valuable indication of the approach of other reactions. Denys called attention to its constancy in preceding the general reaction, and Hamman & Wolman with many others regard it as a test of approaching intolerance, that is the approach of a dose which will produce a general reaction. In its production the different tuberculins play a various rôle.

Pure extract such as **BF** [1] or **TO** is least likely to produce a local reaction, **BE** or **TR** most likely, and that for the reason that the former is immediately carried away in the blood stream, while the latter remains for long as an insoluble deposit at the site of injection. It seems likely also that mechanical disturbance of the tissues at the point of injection, such as that caused by a coarse or blunt needle, may precipitate this local infiltration.

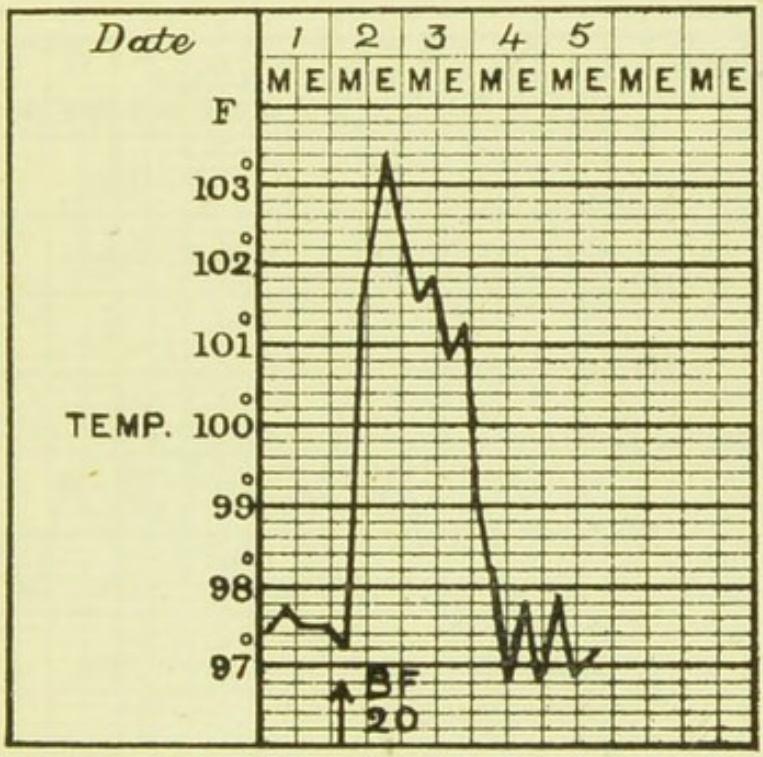


CHART IX.—A sudden sharp febrile reaction. (From Denys' *Le bouillon filtré*, p. 33.)

The use of the local reaction for the diagnosis of tubercular sensitiveness has led to the introduction of a variety of methods of application. Of these the cutaneous, intracutaneous, and conjunctival may be mentioned as convenient additions to the subcutaneous local reactions,

[1] Throughout the book preparations of Tuberculin are denoted by block letters. For identification, see Index. The explanation of the symbols will be found on pages 43–47.

but these need no further comment in a book devoted to treatment.

2. **The General Reaction.**—An injection may produce no general disturbance whatsoever or it may give rise to a group of characteristic symptoms in a varying degree, of which rise of temperature is the most constant and the most easily measured; it is this rise of temperature which forms the main criterion in the

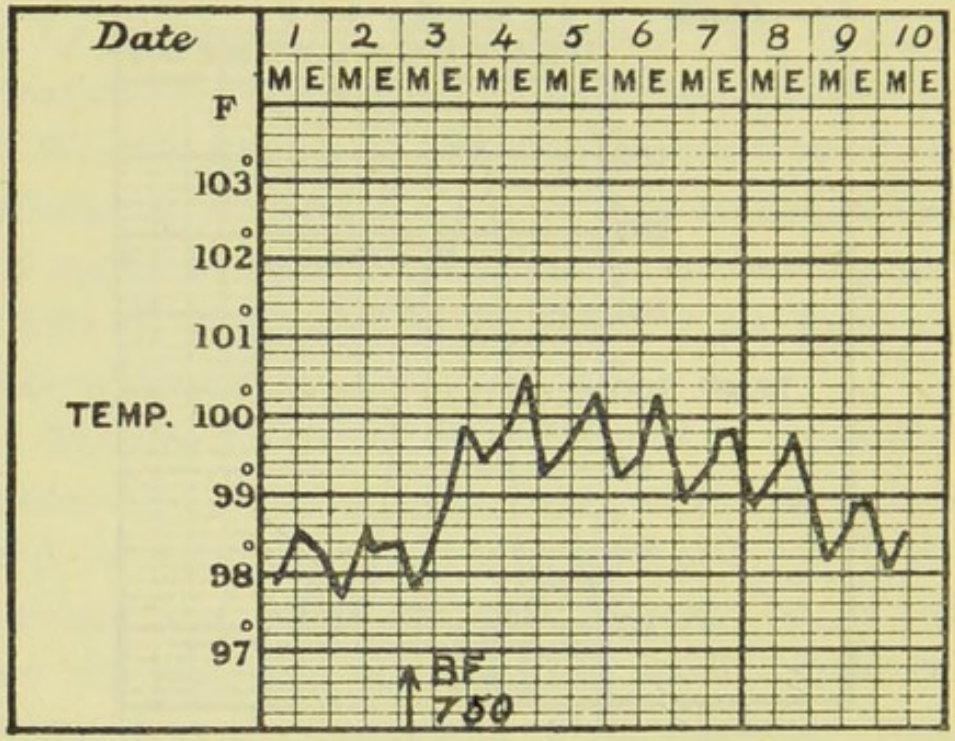


CHART X.—A prolonged mild reaction. (From Denys' *Le bouillon filtré*, p. 36.)

diagnostic use of the injection. In its slighter grades no other subjective symptoms may be present, but there is generally headache, which may be severe, and malaise, with loss of appetite and sometimes persistent nausea and vomiting. For rarer manifestations of the general reaction the reader is referred to page 127 and to the table on page 165.

Very characteristic is the sharp rise of temperature,

and Denys accepts as due to the injection no rise beginning more than twenty-four hours afterwards; this may be true for **BF** but it is certainly not true for **BE**, and any rise up to seventy-two hours after the injection must be critically examined. Confusion with rise of temperature due to natural incidents of the disease is difficult to avoid, but a step-like rise higher from day

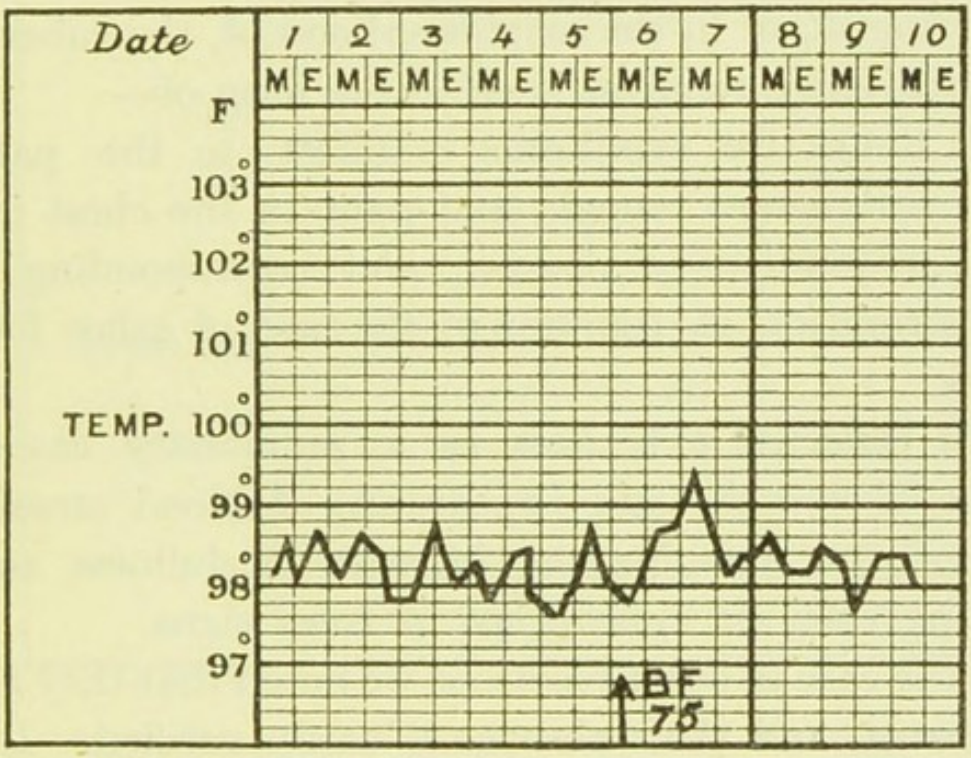


CHART XI.—A short mild reaction. (From Denys' *Le bouillon filtré*, p. 128.)

to day is very unlikely to be due to the tuberculin. A further difficulty exists in the fact that there may be secondary rises following on the focal reaction and to this we shall return shortly. For various types of temperature reaction see Charts IX–XIII. The relation of the general to the other reactions is, commonly, that it requires for its production a larger dose than the local,

and a smaller than the focal. The local reaction is accordingly a guide to it, and it to the focal.

The general reaction occurs most easily with the more soluble tuberculin, i.e. **T** or **TO**, much less with **BE**: owing doubtless to a larger dose entering the circulation at one moment. It is especially liable to appear in very early cases and in them under treatment with quite small doses.

3. **The Focal Reaction.**—This is due to change occurring in, or in the neighbourhood of, the tubercular foci, and may manifest itself in the form of—

(*A*) **Subjective** symptoms manifest to the patient, such as dyspnœa, cough, and pain in the chest in the case of pulmonary disease, and corresponding pain and alteration of function in the case of other localisations.

(*B*) **Objective** evidences, as in pulmonary cases increase of sputum and appearance of blood streaks in it; and, on examination, increase of dullness and of existing râles or appearance of fresh signs.

In the case of other reactions we noted that they might be absent, and their absence is easily verified. In the case of the focal reaction it would never be possible to dogmatise about its absence, as the slight grades must always escape detection save in visible lesions.

Most observers find no perceptible focal reaction (visible lesions apart) without a preceding local one. Opinions are largely divided about its relation to the general reaction. Turban considers that it may occur without a general reaction and give the clue to a correct dosage. C. Spengler also and Philippi find it preceding the general reaction, but Hamman and Wolman have

never heard an increase in râles without some evidence of a general reaction. It is doubtless partly a matter of care and frequency in examining for altered signs, and the method for so doing, but the matter is also complicated by the occurrence of :—

Secondary Reactions.—The injection may be in-

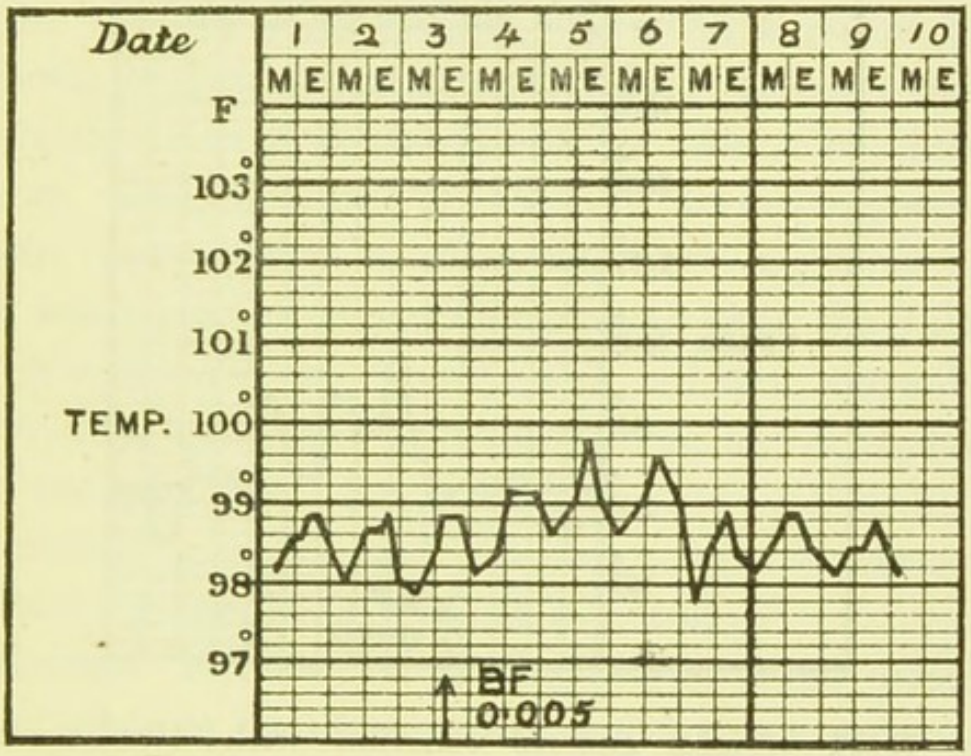


CHART XII.—Secondary general reaction : on day following injection more cough and expectoration and then rise of temperature. (From Denys' *Le bouillon filtré*, p. 38.)

sufficient to cause a general reaction in itself, but by giving rise to hyperæmia of the local lesion a secondary absorption of auto-tuberculin may take place giving rise to general symptoms (Temperature Chart XII). In cases, also, where general and focal reaction are both present and marked, a secondary disturbance may agitate the temperature level over many days, suggesting a series of slight focal reactions, echoes of the first reaction

and like echoes becoming less and less (Temperature Charts X and XIII). It is this secondary general reaction which is by no means restricted in time to the twenty-four hours after the injection.

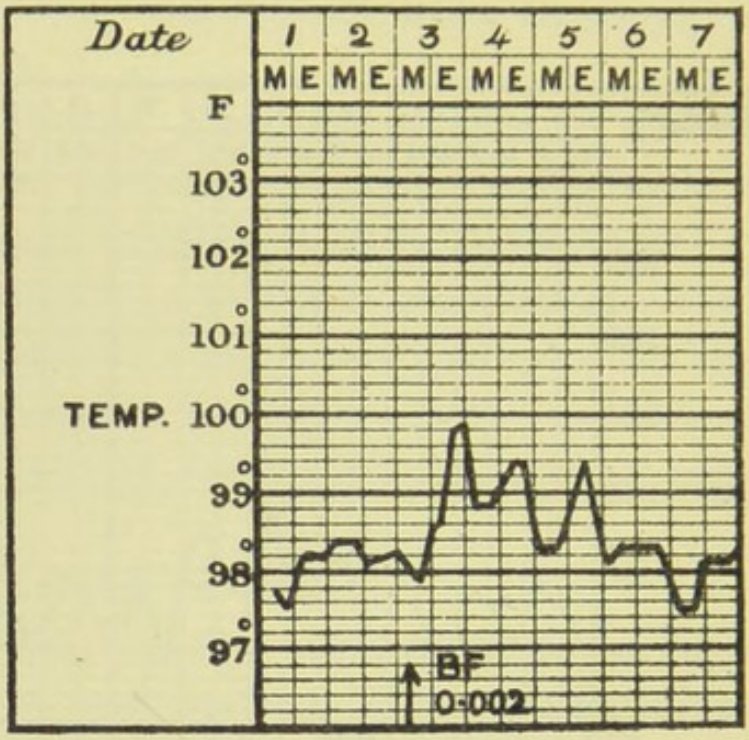


CHART XIII.—Slight general reaction with two secondary oscillations due to focal reaction. (From Denys', *Le bouillon filtré*, p. 38.)

For the reasons already noted tuberculin extract is more likely to produce the focal reaction than endoplasm. The danger or value of these reactions will more conveniently be considered in connexion with the various methods of administration of tuberculin to which they form a valuable guide.

THE CHOICE OF A TUBERCULIN.

Name and Definition.—Tuberculin is the general term applied to any product of the tubercle bacillus capable of producing a " specific reaction " in the animal organism infected by the bacillus. The name was first used in 1884 by Pohl Pincus who read a paper before the Berlin Medical Society in which he proposed a method of immunisation and treatment by means of bacterial extracts, and the use of various terms—tuberculin, variolin, scarlatinin—to describe these extracts. The paper was so much ahead of the time that the *Deutsch. med. Wochenschr.* in reporting it adds a special disclaimer that the views expressed were not accepted by other pathologists. Koch himself first called his old tuberculin " lymph " and it was known for some time in general parlance as " Koch's lymph."

Different Forms of Tuberculin.—The products of the tubercle bacillus, called collectively tuberculin, may be classified into three groups according to the method of their preparation :—

1. Those containing only the soluble products of the tubercle bacilli in the medium in which they are grown.
2. Those consisting essentially of the insoluble fragments of the tubercle bacilli, i.e. endoplasm.
3. Those containing both 1 and 2.

The type of the first of these is Koch's old tuberculin **T** ; of the second Koch's new tuberculin **TR** ; of the third Koch's bacillus emulsion **BE**. For convenience we may call the first extract, the second endoplasm, and the third extract + endoplasm. It was at one time

thought that the action of these was different in essential respects, that, for instance, the tuberculin endoplasm conferred a bacillary immunity which the tuberculin extract did not; we shall now give some of the reasons for believing that this is not so and that the essential action of all tuberculin is the same.

Essential Unity of the Tuberculins.—It is of the utmost importance that the clinician should accept at the outset the essential "oneness" of the tuberculins so that he may not lose himself among the countless preparations of this substance now on the market. The reasons for believing that all forms and preparations of tuberculin have essentially the same action can be put very briefly under four headings.

1. The **Tuberculin Reaction.** — Whatever form of tuberculin is used, and however it is applied the reaction is precisely the same in quality, though varying markedly in degree.

2. Similar **blood changes** in respect to opsonic content and the production of Wassermann's antituberculin are observed under treatment with all forms of tuberculin. It must however be stated that the production of agglutinins was in the hands of Koch and others more active on the new endoplasm tuberculins than on the extract preparations.

3. **Histologically** extract tuberculin will produce, just as will endoplasm, the characteristic aggregation of epithelioid and giant cells generally called tubercles.

4. **Clinical** experience. Clinicians in all parts of the world, using all manner of different kinds of tuberculin, have put on record similar results, and there appears again and again under various distinguished signatures

the same old formula variously expressed :—in the administration of tuberculin more depends on the method of administration than on the kind of tuberculin employed. All the better known tuberculins have led to good results in various hands, and this is the true significance of the number of preparations on the market and not the deduction of Sobotta that "the actual specific preparation has not yet been discovered."

Differences in the Action of Tuberculin Preparations.—The essential unity of the tuberculins being laid down it remains to refer to certain differences in their action which require explanation. These appear to depend on three factors.

1. **Strength.**—With the same essential ingredient the quantity of this per unit of volume varies greatly in the different preparations. Since the nature of the active principle is not known, and it cannot be isolated in pure form, tuberculin cannot be standardised ; but attempts have been made to test its efficiency on animals infected with tubercle, and clinical comparisons have been made between different kinds of tuberculin. By the former means Neumann, though coming to no very definite conclusions, was enabled to arrange preparations in a series with strength diminishing from left to right—**T, PT, BE, Tp** ; **T** and **PT** were however regarded as identical. Von Behring found **T** = 42 times **TR.** Clinical experience can fill in certain gaps : **TR** and **BE** are generally held to be weaker than **T.** Cevey found **BF** = 100 times **TR. PTO** is always regarded as milder than **PT,** and Wilkinson, Wynn and others find **PT** about 40 times **PTO.**

A serious discrepancy exists in the comparison of **T** with **TO** and **PT** with **PTO**, for there appears to be evidence that **TO** is stronger than **T**; Philippi thinks 1,000 times stronger, and Turban supports this belief.

Denys records reactions with inconceivably small doses of **BF** which is the equivalent of **TO**. These discrepancies can be partially explained as follows. The Farbwerke, who are responsible for the manufacture of all four preparations, state that the mere concentration of a tuberculin extract *in vacuo* to one-tenth of its volume does not increase its strength but only its stability. In addition **PT** has, in the process of manufacture, been brought up to the strength of **T**, whereas **PTO** is behind **TO** on account of the lesser luxuriance of growth of the Perlsucht bacillus.

2. **Toxicity.**—Old tuberculin contains about 10 per cent. of albumoses which are in themselves toxic when injected subcutaneously. Extract tuberculins probably contain in addition products toxic to the healthy derived from the culture medium in which the bacillus is grown, and varying according to the nature of this medium. This toxic element is not present, or present to a much smaller extent, in endoplasm tuberculin. Little success seems to have attended any attempt to make **T** less toxic, and its toxicity must be small indeed when 1000 c.mm. can be given with only slight local manifestations in the healthy. Gabrilowitsch prepared a "*tuberculinum purum*" for which it is claimed that all poisonous proteid ingredients of **T** have been removed, and only the specific immunising properties left. Its action does not appear to differ appreciably from that of untreated **T**. Beraneck follows the more promising line of cultivating the bacillus on a medium free from peptones, obtaining thus a preparation free from these bodies without the need of submitting the tuberculin to a purification which may well result

in the alteration or destruction of the immunising substance. The Farbwerke Höchst also supply an albumose-free old tuberculin **ATh.** Summarising what is known of the relative toxicity of the various preparations, they may be placed in a series somewhat as follows, the toxicity diminishing from left to right—**T**, **BF** or **TO**, **TBk** or **Tp.**

3. **Rate of Absorption.**—**T** is rapidly absorbed and has a rapid and sure action, which soon passes off, leaving behind the results of the general and the focal reactions to which it has given rise. The same applies to other extract tuberculins and is especially marked with **TO** and consequently **BF.** The extract tuberculins are on this account of special use for purposes of diagnosis. **BE**, like other bacterial vaccines, is only slowly absorbed from the site of injection and exerts a relatively mild and prolonged action; the same applies to other forms of tuberculin endoplasm. **BE** and **TR** are therefore by common consent held to be better borne in febrile and severe cases, but they have the drawback according to American authors (Baldwin, J. A. Miller) of irregular absorption which may lead by accumulation to unexpected reactions. Weicker holds that **BE** produces lysins in larger quantities, and this might account for the fairly general view that it protects more against relapse than does **T.** Summarising the indications briefly we may say—

(*A*) The action of (soluble) extract tuberculin is more rapid and certain; more likely to produce immediate reaction; easier to dose.

(*B*) The action of (relatively insoluble) tuberculin endoplasm is milder and more prolonged; less likely

to produce immediate reaction ; more difficult to dose when large quantities are reached.

Tuberculin from Bacilli of Different Origin. Bovine or Human.—The fact, of which there remains no doubt, that a proportion of cases of tuberculosis in man are caused by the bovine bacillus has opened the door to much speculation as to the suitability of tuberculins of bovine or human origin in treatment. On the one hand are those who assert the doctrine (well established both in practice and principle for vaccine-therapy in general) of the autonomous vaccine, on the other hand are those who follow C. Spengler in the use of bovine vaccine for tuberculosis due to the human bacillus and *vice versa*. That any qualitative difference between the two varieties of tuberculin exists has never yet been shown. It seems undoubted that both organisms are strains from the same stock, and the immediate effect of their administration in tuberculosis is precisely similar. Denys states that patients immunised against his **BF** of human origin did not react to **BF** of bovine origin, and that he could detect no difference between immunisation with **BFH** and **BFB.** Koch made no claim for a difference in their specific action. The majority of clinicians, also, who used the bovine preparations of C. Spengler came to a similar conclusion. In addition animal experiment, notably in the hands of Römer, and Weber and Dieterlen, shows a similar identity in the qualitative action of tuberculins of various origin. The only difference appreciable to modern tests between the bovine and human tuberculins appears to be one of strength, due when present to a difference in luxuriance of growth. On this account

the bovine preparation **PTO** has been found convenient as an initial course to precede **T** in the treatment of phthisis, and very good results have followed its use. Though we hold the use of "unlike vaccines" to be irrational in theory (the conditions being wholly different to those of a vaccination with living bacilli) we think that at present all such theoretical considerations should be put on one side in the use of tuberculin, and the bovine preparations, when tried, should be used solely on such merits as they have disclosed as the result of practice. Nevertheless, it seems to us sensible to change a bovine for a human vaccine (or *vice versa*) where, in the treatment of some form of tuberculosis which may be due to either strain, the tuberculin first used fails, after adequate trial, to produce the satisfactory result expected from it.

Autogenous Tuberculin.—Some writers have laid stress on the probability of peculiar value attaching to autogenous tuberculin, that is to say tuberculin prepared from the host's own bacillus. Krause has treated patients on these lines and thought that better results were obtained than with stock products. Löwenstein showed that the leucocytes from a tubercular focus may ingest other tubercle bacilli presented to them while refusing to take up those with which they have been in contact, and Rothschild has made this a further reason for the use of autogenous tuberculin. The argument has also been freely used to support the practice of "autoinoculation," that is the measured supply of toxins from the patient's own focus of disease. Thereby is avoided the enormous labour and delay from preparing pure cultures of the bacillus from each case

of tuberculosis. Such labour and difficulty places autogenous tuberculin at present outside the scope of practical measures, and the common success of the stock product makes it unlikely that this will ever be replaced by the autogenous vaccine except on rare occasions.

A further and very pertinent consideration has been raised by E. C. Hort. He holds that any tuberculin acts by producing hyperæmia around the tubercular lesion, leading secondarily to an absorption of the toxins there present, in other words to an auto-tuberculinisation. On this view any tuberculin which is specific enough to produce a focal reaction results in the utilisation of the patient's own tuberculin, and the particular brand of tuberculin employed is therefore a matter of quite secondary importance. (*See also* Polygenous Tubercle Bacilli Emulsion, page 46.)

Change of Preparation.—C. Spengler was the first to point out that a change of preparation may be of assistance when the one first employed is not well tolerated or is not producing the full benefit that was to be expected. It is difficult to explain how such a change can act, except it be that the dosage is necessarily altered at the same time, and quite empirically the more suitable dose may be struck with the second preparation. Different observers set store on different combinations, but apart from the special indications of the special tuberculins the sequence appears to have been a matter of individual taste.

THE TUBERCULINS AND THEIR PREPARATION.

1. **Extract Tuberculin—Koch's Old Tuberculin.** This is the preparation introduced to the world by Koch in the year 1890, the first of all the tuberculins. It is conveniently designated by the letter **T** which is distinctive and has not been used for any other body. **AT** (Ger. Alt-Tuberkulin) has also been used, but it is unnecessary and to be deprecated in England where the letter **A** does not suggest "old." It is incorrect to use the letters OT or TO which were employed by Koch in another way, namely for TO (Ger. Tuberkulin-Oberer), a by-product in the preparation of new tuberculin and of no further interest, and also for the preparation **ATO** (Ger. Alt-Tuberkulin-Original), the original unconcentrated extract. It would be well to use the O exclusively in the sense of Original, which has an English equivalent.

T is manufactured under State control by the Farbwerke Höchst (Meister, Lucius and Brüning), and standardised by animal experiment. A pure culture of the tubercle bacillus of human origin on nutrient broth containing 5 per cent. of glycerin is sterilised by steam for half an hour, evaporated at a temperature not above 70°C. to one-tenth of its volume, and then filtered. Finally 0·5 per cent. of phenol is added and the preparation allowed to stand for some weeks and again filtered. It contains 40 to 50 per cent. of glycerin (some has evaporated, glycerin being volatile with steam), about 10 per cent. of peptones

or albumoses, the toxic secretions of the tubercle bacillus into the culture fluid or such of them as are soluble in 50 per cent. glycerin, and substances extracted by the alkaline broth from the bacterial bodies during the process of sterilising and evaporating.

T is a clear dark-brown fluid of syrupy consistence, miscible with water in all proportions without producing any turbidity. It apparently keeps an indefinite period, but as there is the possibility of changes in potency occurring without alteration of appearance it is not advisable to use brands more than twelve months old. As it is cheap, $6\frac{1}{2}d.$ per c.c. in London, this is not a matter of moment.

Of other preparations on the same lines **TO** is the filtered broth culture which has not been concentrated. It is variously called **ATO** and **TOA,** but **TO** is definite and distinctive. It contains proportionately less glycerin and less peptones; the effects of heat will also be absent both in dissolving out certain substances from the bacillary bodies and perhaps in rendering others less active. **TO** was used by Koch in animal experiments, was given by him to C. Spengler for therapeutic purposes, and a similar preparation has been extensively used by Denys under the name of **B**ouillon **F**iltré **BF.** These have all proved useful under the same conditions as **T.** (Of the relative strength of them something has already been said.) **PT** and **PTO** (Perlsucht Tuberkulin) correspond to **T** and **TO** but are made from cultures of bovine origin. Raw and C. Spengler have made their own preparations on these lines, but they can now be obtained from the Farbwerke Höchst. As we have seen above the Farbwerke also supplies an albumose-free old tuberculin **ATh.**

2. **Endoplasm Tuberculin—Koch's New Tuberculin** (**TR.**)—This was introduced by Koch in 1897 with a view to the avoidance of marked reactions and the production of a bacterial as opposed to a toxic immunity. It is prepared by grinding dried cultures of

virulent bacilli till no intact organisms remain. On treatment with distilled water and centrifuging there results a clear, light yellow liquid containing the soluble parts of the bacillus, and below it a white deposit. The liquid is decanted off, and from the deposit **TR** (**T**uberkulin-**R**ückstand) is made by further grindings and treatment with water till the slightly opalescent fluid known by this name is obtained. It contains the insoluble parts of the bacillary bodies, and to it glycerin up to a strength of 20 per cent. is subsequently added for purposes of preservation. Each c.c. of **TR** contains 2 milligrams of solid substance but is prepared from 10 milligrams of powdered tubercle bacilli. This, representing the endoplasm tuberculins, is a very stable preparation, and can be kept for long periods even in considerable dilution without any notable loss of efficiency. Its cost, 8*s.* 6*d.* per c.c., is its most serious drawback, but this becomes of little moment when the preparation is used, as is generally the case, in the minute doses suitable under the method of immunisation without tolerance (p. 199).

3. **Combined Extract and Endoplasm Tuberculin. Koch's Bacillus Emulsion (BE).**—This is the second of the New tuberculins introduced by Koch (1901) after the results obtained by the earlier New tuberculin (**TR**) had not entirely fulfilled his expectations, especially in the direction of producing agglutinins in the blood. It is designated **BE** and manutured by the Farbwerke in the following manner. Half a gram of finely powdered tubercle bacilli is suspended in 100 c.c. of a mixture of equal parts of glycerin and water, and by prolonged shaking a fine emulsion is

produced. This contains, therefore, 5 mg. of solid substance in every c.c. About half of the substance goes into solution in the 50 per cent. glycerin, but the rest remains as an insoluble precipitate which must be well shaken each time before use and before dilutions are made. It will be seen from its preparation that **BE** is but **TR** with the supernatant fluid containing the more soluble products of the tubercle bacillus unremoved. It is a mixture of extract and endoplasm tuberculins. It thus contains the somewhat less stable soluble products as well as the very permanent endoplasm and, as it is inexpensive, $10\frac{3}{4}d.$ per c.c. in London, the same remark applies to keeping it more than twelve months as was made under **T**.

The Farbwerke Höchst also supply a " Polygenous Tubercle Bacilli Emulsion " prepared from 8 strains of bacilli differing as widely as possible in their morphological and cultural properties. This preparation, analogous to the polyvalent serums, was prepared at the suggestion of Rothschild of Soden as the nearest approach to the autogenous tuberculin theoretically so desirable, but in practice so difficult to supply. In addition a further variety of the bacillus emulsion has recently been prepared at the suggestion of Fritz Meyer. Before comminution the bacilli are left some time in contact with immune serum, from which they take up a specific substance and become sensitised. The claim is made that this sensitised bacillus emulsion **SBE** is better borne and is little likely to produce local infiltration. Experience appears to bear this out, but it is not yet known whether the immunising action has been reduced or not. Bovine preparations **PTR** and **PBE** corresponding to **TR** and **BE** are also obtainable at the prices respectively of 25*s.* 6*d.* and 2*s.* 8*d.* per c.c.

Beraneck's Tuberculin (TBk).—Of the milder acting tuberculins that of Beraneck is taken as the best example. It is manufactured at Neuchâtel under the

supervision of Professor Beraneck, director of veterinary medicine in the university. The tuberculin is a mixture of equal parts of two components ; one a filtered culture of human tubercle bacilli in a medium free from albumose and not altered by heating, the other an extract of the bacillary bodies in 1 per cent. phosphoric acid in which therefore endoplasm is present in the form of acid albumen. Thus the tuberculin contains endoplasm in real solution and the dilutions are easily made with perfect uniformity. It was submitted to searching animal tests by the inventor, and for a series of years was used by Sahli and others in the clinic at Berne before it was put on the market. At Neuchâtel 10 c.c. of the concentrated tuberculin or of any dilution of it costs Fr. 3. In the British Isles it can only be obtained through A. K. Stewart of Edinburgh who charges 6*s*. to 3*s*. for the same quantity according to strength, on a decimal scale devised by R. W. Philip.

Of other tuberculins alleged to be only slightly toxic we have already mentioned that of Gabrilowitsch which has the great drawback of expense. In this category come also the watery extract of v. Ruck and various preparations by Baldwin, Calmette and others.

THE STANDARD OF DOSAGE.—THE CUBIC MILLIMETRE (C.MM.)

Koch always spoke of T in terms of milligrammes, meaning thereby the thousandth part of a gramme, or strictly speaking of a cubic centimetre, of the original fluid tuberculin itself. Afterwards with **TR** and **BE** he used the same term milligramme to denote, not a volume, but the weight of solid substance—tubercle

bacilli—from which the new tuberculins were prepared. The milligramme was hence already used in two different senses, and when later on Wright called attention to the fact that **TR** would more properly be measured in milligrammes of the actual weight of the solid substance contained in it (and not of the substance from which it was made, a large proportion of this disappearing in the manufacture) confusion could hardly be carried any further.

Hence in the last edition (1911) of Bandelier and Röpke's textbook these authors, in consultation with the Farbwerke Höchst, adopted the uniform plan of speaking of all tuberculins in terms of the original fluid, using the cubic centimetre as the standard. Thus **TR** ·0001 denotes a one ten-thousandth part of a cubic centimetre of the original fluid of **TR.** Whilst possessing the merit of uniformity, the form of this measurement is cumbersome in the extreme, as the doses in most frequent use begin with 3 or 4 decimals and the usual initial dose with 5 decimals. And the clumsiness of the form is accompanied by a corresponding difficulty in mentally grasping the doses. It is as though an apothecary should weigh his morphia and strychnine in hundredweights or tons instead of grains.

We therefore propose the use, not of the cubic centimetre, but of the cubic millimetre as the unit of volume: a standard one thousand times smaller and the equivalent in volume of the milligramme in weight. With this standard the largest dose in ordinary use is 1,000 and the smallest one-thousandth or ·001 which are quantities easily conceived and remembered. Kössler, Neumann and we believe others, as well as ourselves,

have already employed this standard for a number of years, and it is remarkable that it has not yet been widely adopted.

A table is appended giving the equivalent of the cubic millimetre (c.mm.), its multiples and fractions, in terms of the cubic centimetre (c.c.), and of the other

THE CUBIC MILLIMETRE AS UNIT OF VOLUME.

CUBIC MILLIMETRE c.mm.	CUBIC CENTIMETRE c.c.	Contained in 1 c.c. of dilution	Equivalent on older systems of measurement to:				
			T. PT. TOA PTO. BF.	TR. PTR		BE. PBE. SBE	TBk
				Old basis (Koch)	New basis (Ruppel)		
1000	1	Original	1000 mgr.	10 mgr.	2 mgr.	5 mgr.	
100	0·1	(1)	100 mgr.	1 mgr.	⅕ mgr.	½ mgr.	TBk_1 1·0
10	0·01	(2)	10 mgr.	1/10 mgr.	1/50 mgr.	1/20 mgr.	TBk_2 1·0
1	0·001	(3)	1 mgr.	1/100 mgr.	1/500 mgr.	1/200 mgr.	TBk_3 1·0
0·1	0·0001	(4)	1/10 mgr.	1/1000 mgr.	1/5000 mgr.	1/2000 mgr.	TBk_4 1·0
0·01	0·00001	(5)	1/100 mgr.	1/10,000 mgr.	1/50,000 mgr.	1/20,000 mgr.	TBk_5 1·0
0·001	0·000001	(6)	1/1000 mgr.	1/100,000 mgr.	1/500,000 mgr.	1/200,000 mgr.	TBk_6 1·0

quantities in which it has been customary to speak of the various tuberculins. Thus 1/2000 mgr. of **TR** (old basis) is equivalent to ·05 c.mm. and 1 mgr. of **BE** to 200 c.mm. and so on. In the third column is given the designation of the dilution, in one cubic centimetre (or syringeful) of which a given dose in cubic millimetres is contained (*see* p. 56.)

Throughout this book the cubic millimetre (c.mm.) alone is used as the standard of measurement for tuberculin and the symbol c.mm. is to be understood wherever figures stand alone. The table is repeated for con-

venience on p. 103. Those who still prefer to think in cubic centimetres have only to move the decimal point three places to the left to obtain their familiar equivalents.

ROUTE OF ADMINISTRATION

Tuberculin has been administered for diagnosis or treatment by a number of different routes which divide themselves naturally into :—

1. Application to the intact skin or mucous membrane.
2. Injection beneath the skin.
3. Administration by mouth or rectum.

Of these the first group is eminently suitable for diagnostic tests where absorption of a certain quantum of tuberculin is not the only aim ; but for therapeutic application it has not much importance, although C. Spengler has used inunctions of tuberculin with some success in hypersensitive cases as a preparation to subcutaneous injection ; and Woodcock has published some interesting results from the absorption of tuberculin from the surface of a blister produced in the first instance for diagnosis, whilst Inman has demonstrated the absorption from the conjunctiva. The inhalation of sprayed tuberculin (Kapralik) is only a clinical curiosity.

This leaves injection beneath the skin, and administration by mouth or rectum ; and we may at once restrict the field of inquiry still further by excluding intravenous medication, which if swift and accurate is not for everyday practice ; and rectal medication, partly

for the same reason, and because Pfeiffer and Leyacker have shown that it requires 300 fold the subcutaneous dose to produce the same result, and it would demand a certain hardihood to introduce this quantity of tuberculin into the body with the risk of irregular absorption.

As between subcutaneous and oral administration various considerations present themselves :—

1. **The Fact of Absorption.**—Doubt has been raised as to whether tuberculin is absorbed at all by the oral route, but for **TR** given thus Latham, with the help of Inman and Spitta, has proved the affirmative by the production of characteristic temperature and opsonic response. And a case under the care of one of us gave a well-marked general reaction from a dose of **TR** 0·2 c.mm.

Latham considers that the dosage of **TR** given by the mouth should be about double the subcutaneous dose. But the matter does not end here and the important question arises as to whether any

2. **Alteration of Properties** occurs by the oral route. Neumann states that in animals tuberculin is so altered in the stomach as to preserve its "irritative" whilst losing its immunising action. Barr considers that vaccines administered in this way are deprived of some toxic quality, and Latham finds a characteristic shortening of both negative and positive phases. In the case of **T** it is doubtful whether this alteration does not result in complete inertness. Hell has recently given to tubercular patients under observation in a sanatorium doses of **T** by the mouth up to 80 c.mm. without producing any perceptible reaction; Löwenstein up to 100 c.mm. in a smaller number of cases; and Pfeiffer

and Trunk showed that T is much weakened by pepsin, less so by pancreatin, and not affected by acid alone. It can be easily understood that this should be the case with T and not so with the relatively very insoluble TR which is perhaps absorbed in a particulate form in the same way as tubercle bacilli reach the abdominal lymphatics. Inclusion in keratinised pills or capsules (Freymuth, Möller) removes this difficulty to some extent.

3. **Accuracy of Dosage.**—Alteration by the digestive juices and irregular absorption result in the dosage by the oral route being less exact than by the subcutaneous, and with a remedy of the potency of tuberculin it is necessary, other things being equal, to give the preference to the more exact method. It is only fair, however, to add that certain careful clinicians who have worked with pepsin-proof capsules (Möller, Krause) have obtained concordant results.

4. **Convenience.**—The taking of a draught is more convenient for the patient than the prick of a needle, but with careful technique the latter can be made a negligible discomfort. More serious is the repugnance to an " inoculation " ; but this is rarely great when it is understood that no animal product is being introduced, but the same substance as is already circulating in the patient's own blood.

Put categorically the advantages of the subcutaneous route are :—

(*a*) Certain absorption

(*b*) in unaltered form

(*c*) and accurate dosage.

In addition to these, two other considerations—one

practical and one theoretical—suggest the preferment of the subcutaneous to intravenous or oral administration. The local reaction is a helpful guide to dosage, and the subcutaneous tissue is very probably (Wright) the special seat of antibody formation.

Summing up we may say: **T** and probably **TBk** should not be given by the mouth. **TR** and probably **BE** may be so given, but certain advantages are sacrificed thereby.

TECHNIQUE OF SUBCUTANEOUS INJECTION.

The principles involved in the technique of subcutaneous injection are the combining of sufficient accuracy and asepsis with a minimum of apparatus and labour. There are doubtless many ways of attaining these ends, but the following have proved economical and efficient in the experience of the writers.

1. **The Syringe.**—The syringe should be all-glass, its capacity 1 cubic centimetre (c.c.) divided into tenths, i.e. divisions of 0·1 c.c. or 100 cubic millimetres (c.mm.). These divisions of the syringe are henceforth spoken of in this book as simply "divisions." The barrel of the syringe should be of small diameter so that the divisions are widely spaced and can be read off with accuracy.

All-glass syringes of simple form are now obtainable for 1s. 6d. to 2s. apiece wholesale. They are entirely adequate for giving an already measured dose as from an ampoule, or the same repeated equal dose from a stock solution. For giving doses which increase on a geometric scale (*see* p. 106) it is a great convenience to use a syringe in which the divisions are marked at the halves, and in which the tenths can be approximately estimated with the eye. Lieberg's syringe possesses a scale of which

the divisions are nearly half a centimetre apart (the actual size is shown on Chart No. XX p. 107); consequently the second place of decimals can be read off with fair accuracy. It costs however 3 or 4 times as much as the shorter and stouter-barrelled syringe, but its life is indefinitely long if not dropped. It fits the needles in common use.

The needle should be of platinum-iridium, which can be repeatedly flamed without becoming blunt or rusty. The bore must be small and the point sharp (a small hone being kept for this purpose) and with a little attention to these details the puncture can be made quite painless.

Two methods of **sterilisation** are used, a normal and an emergency.

(*A*) **The Normal Method.**—Syringes and needles are, in the first instance only, thoroughly boiled and then kept immersed in separate sections in absolute alcohol in the flat metal box in which the larger syringes are supplied. When required the syringe is taken out of the alcohol, put together, and washed out with tap water several times. Freshly drawn tap-water in a glass is all that is required for this purpose, as the water from a good town supply is practically sterile. Where this is not the case boiled water should be used. Ordinary distilled water should not be used for this purpose unless sterilised, as it is apt to contain hay-spores, etc., from the carboy. The needle should then be heated red-hot in the flame of the spirit-lamp. After use the syringe should be washed out with two relays of fresh water, and placed in sections in the alcohol. In this way it is always sterile and always ready for use at a moment's notice.

(*B*) **The Emergency Method.**—To be used if for any reason the sterile syringe of Method *A* is not available.

Olive oil is heated to a temperature of 140°C. and drawn up twice into the barrel of the syringe which with the needle is rapidly and completely sterilised thereby. In an emergency, e.g. on a visit, the oil may be heated in an iron spoon (not a white-metal one, which melts) over a spirit lamp or candle, and the right temperature judged by a bread crumb just charring. This ingenious method is due to Wright, but it is not recommended for routine use in the consulting room, as the hot oil has a disagreeable smell and the syringe occasionally breaks with the heat.

2. **The Preparation of Dilutions.**—In the interests of economy and exactness it is strongly advised to prepare the dilutions oneself and this can be done with scarcely any trouble. The first requirement is the diluent, a half per cent. solution of phenol in normal saline, according to the formula :—

Acidi carbolici liquefacti	5
Sodii chloridi	8
Aquæ distillatæ	1000

Ten c.c. of this are measured into a number of small stoppered bottles of about twice this capacity and the whole series sterilised in a saucepan of boiling water for half an hour, and then kept until required. This is the only troublesome part of the procedure and sterilised bottles containing ten c.c. of this diluent or the sterilised diluent in bulk could be obtained from any dealer.

The measure used is the syringe itself, which will accurately deliver one c.c. (the whole syringeful) or one-tenth c.c. (a single division). Starting then with the stock, i.e. the original undiluted tuberculin, proceed as follows :—

To make	Or a dilution of	Remove of the diluent	And replace it with the same quantity of	This contains in one c.c. so many c.mm. of original fluid.
(1)	1/10	One syringeful	Stock	100
(2)	1/100	One division	Stock	10
(3)	1/1,000	One syringeful	(2)	1
(4)	1/10,000	One division	(2)	·1
(5)	1/100,000	One syringeful	(4)	·01
(6)	1/1,000,000	One division	(4)	·001

In this way any required dilution can be made without waste and in at most three stages. The dilutions should be labelled **T, BE,** etc., as the case may be, (1),(2),(3),(4), etc., signifying so many powers of ten. For instance **TR** (4) signifies the fourth power of ten, or one followed by four noughts, i.e. a 10,000 dilution of **TR,** containing in the syringeful ·1 c.mm. of original fluid ; a reference to the chart on p. 49 will show the equivalent on the older basis. On this uniform system there is no risk of the confusion of a stronger with a weaker dilution.

The method of preparing dilutions described above is the standard one applicable to all kinds of tuberculin for all purposes, and requiring nothing but ordinary care and cleanliness. Two modifications are now mentioned : the first to effect a still further economy of time and material for those constantly requiring weak dilutions ; the second to meet the need of small equal doses of **TR** over a long period.

The Drop Method.—If an exact syringeful of any tuberculin be taken, the syringe held vertically, and the tuberculin allowed to fall from the needle at a speed at which the drops can be counted, it will be found that for a given tuberculin, and a given needle, the number of drops will always be the same, and will vary between 80 and 180 according to the bore of the needle and the

glycerin content of the tuberculin, the size of the drop itself varying accordingly between 12 and 5 c.mm. We therefore suggest to any one who is making the weaker dilutions of a certain tuberculin to ascertain for himself the number of drops delivered by a certain needle, and to obtain dilution (3) in one stage by letting this measured drop fall into the quantity of diluent shown in the subjoined table. From (3) thus obtained (4) and (5) can be directly prepared in the ordinary way and (6) by a repetition of the drop method, the drop in this case being determined previously for the diluent. The weakest dilution is thus obtained in two stages with no waste and a minimum of time.

THE DROP METHOD.

Number of drops in syringeful.	The size of the drop in c.mm. and the amount of diluent in c.c. is therefore	Number of drops in syringeful.	The size of the drop in c.mm. and the amount of diluent in c.c. is therefore
75	13·3	99	10·1
76	·1	100	·0
77	·0	101	9·9
78	12·8	102	·8
79	·7	103	·7
80	·5	104	·6
81	·3	105	·5
82	·2	106	·4
83	·0	107	·3
84	11·9	108	·3
85	·8	109	·2
86	·6	110	·1
87	·5	111	·0
88	·4	112	8·9
89	·2	113	·8
90	·1	114	·8
91	·0	115	·7
92	10·9	116	·6
93	·8	117	·5
94	·6	118	·5
95	·5	119	·4
96	·4	120	·3
97	·3	121	·3
98	·2	122	·2

Number of drops in syringeful.	The size of the drop in c.mm. and the amount of diluent in c.c. is therefore
123	8·1
124	·1
125	·0
126	7·9
127	·9
128	·8
129	·8
130	·7
131	·6
132	·6
133	·5
134	·5
135	·4
136	·4
137	·3
138	·2
139	·2
140	·1
141	·1
142	·0
143	·0
144	6·9
145	·9
146	·8
147	·8
148	·7
149	·7
150	·7
151	·6
152	·6
153	·5
154	·5
155	·4
156	·4
157	·4
158	·3
159	·3
160	·2
161	·2

Number of drops in syringeful.	The size of the drop in c.mm. and the amount of diluent in c.c. is therefore
162	6·2
163	·1
164	·1
165	·1
166	·0
167	·0
168	5·9
169	·9
170	·9
171	·8
172	·8
173	·8
174	·7
175	·7
176	·7
177	·6
178	·6
179	·6
180	·6
181	·5
182	·5
183	·5
184	·4
185	·4
186	·4
187	·3
188	·3
189	·3
190	·3
191	·2
192	·2
193	·2
194	·2
195	·1
196	·1
197	·1
198	·1
199	·0
200	5·0

Method for TR.—**TR** is as we have seen the most stable of all the tuberculins, and it is therefore permissible to keep the dilutions a considerable time, which has the advantage in practice of insuring the absolute identity of the small equal doses given to children (*see* p. 199) over a period of months. For this purpose **TR** (3) may be made in larger quantity in a single stage by taking half a division of stock and dropping it into 50 c.c. of sterile diluent in a bottle. From this **TR** (4) and (5) can be directly prepared in the ordinary way.

3. **The Conservation of Dilutions.**—Prepared in this way dilutions of tuberculin will be perfectly sterile, and there is no objection to keeping them for a fortnight in a cool place, not exposed to light. Longer than this no dilution of extract tuberculin should be kept, as even without visible change it may decrease perceptibly in activity.

4. **Ready-made Dilutions on the Market.**—All the large wholesale druggists supply ready-made dilutions of tuberculin sealed up in glass phials sterilised and ready for injection. These can be used by any one who is not prepared to take the minimal trouble involved in making them himself. But when so obtained a statement of the date of the making up of the dilutions should accompany the phials.

The size of the next dose on the tolerance method is never exactly known until the effect of the previous one has been seen, hence doses of definite size cannot be dispensed in advance.

5. **The Preparation of the Patient, and the Site and Manner of Injection.**—(*A*) The **skin** should be cleaned by rubbing with alcohol or ether ; or even more conveniently (Wright) by puncturing through a small

dab of pure lysol which is rubbed off again immediately the needle is withdrawn, as it will otherwise blister. By the latter method a trace of lysol is carried into the puncture by the needle and will prevent the development of any cocci which may be carried in from the skin ; although this must in any case be an exceedingly rare occurrence.

(*B*) The **site** of injection should be (1) where it can be easily observed afterwards ; (2) situated in loose cellular tissue where any inflammatory swelling will not be needlessly painful ; and (3) where it is not likely to be soiled. For the bedridden patient it should not be at any site which he will lie on. The best situations are the extensor surface of arm or forearm (easily controlled) ; in the loin below the last rib ; in the abdominal wall a little internal to the anterior superior spine. Between the shoulder blades is not a good place as the local discomfort may obscure any internal sensations due to focal reaction which may arise. C. Spengler recommends with some justice the flexor surface of the forearm where the local reaction is easily seen and rather acutely felt, regarding this as the best control to the focal reaction.

(*C*) The **depth** of the injection. It should be subcutaneous, not intramuscular ; a fold of skin should be picked up and the needle introduced obliquely through it ; only so will the local reaction be properly seen and appreciated. On the other hand the injection should not be made into the skin, as the intracutaneous reaction is a painful one.

(*D*) No **dressing** of any sort is required if the needle be a very fine one, when the minute opening will at once

close up by the natural elasticity of the skin. Any covering will obscure the local reaction.

DIAGNOSIS

The first essential for treatment with tuberculin is the certainty of the presence of a tubercular disease. If disease were synonymous with infection this would be a simple matter. The Vienna school has proved beyond doubt that tuberculin is a trustworthy reagent in the detection of tubercular infection. In the poorer section of the Vienna population the cutaneous reaction of v. Pirquet, rare in infants up to six months of age, becomes increasingly frequent among older children and at puberty occurs almost without exception. The post-mortem table has shown that this reaction actually coincides with and is an indication of tubercular infection.

Now in infants a tubercular infection implies a disease which is nearly always fatal; the infant if infected dies of tuberculosis as surely as it dies of smallpox, and treatment is likely to be unavailing. But older children rarely die of tuberculosis, and from the seventh year upwards healed or inactive tubercular glands, combined in most cases with a small healed focus in the lung, are a very frequent condition. And it is this condition which gives rise to the cutaneous as well as to the other tuberculin reactions, which are all due to the sensitiveness produced by the tubercular infection, and persisting after the disease to which the infection gave rise has become quiescent or been cured.

Tuberculin is, as we have seen, quite non-poisonous to the human body which has not been infected with tubercle. Ten cubic millimetres of Koch's old tuberculin has generally been put as the arbitrary limit above which even the healthy human body may react. Koch gave himself 250 c.mm. and had a severe and painful reaction which he attributed to the poisonous action of the old tuberculin in a healthy body. Koch was probably wrong; Hamburger has injected 1000 c.mm. into a boy of twelve with nothing more than the local irritation caused by the strong glycerin and peptones, and Koch must have been dealing in himself with the sensitiveness of an old childhood's infection. As time goes on this sensitiveness becomes diminished, but it may take half a lifetime to disappear. (Cf. Chart No. XXI, p. 119.)

It will be seen how this fact vitiates the qualitative value of tuberculin in the diagnosis of tubercular disease. A reaction obtained by whatever method indicates that tubercular infection has occurred, but not that there is tubercular disease present requiring active treatment. There remains however the possibility of the reaction being quantitative in the sense that a small dose suffices to produce a reaction in the presence of active disease. And in the main this is true. If a patient gives a really well-marked reaction with

subcutaneously T ·1
or cutaneously a drop of T 1 per cent.
or conjunctivally a drop of T ½ per cent.

sensitiveness is present in a marked degree and probably recent tubercular disease. But clinical experience does not bear out the contention that a reaction with

subcutaneously T 5 or 10

or cutaneously a drop of T 50 or 100 per cent.

indicates recent or active disease. And on the other hand the reaction may fail to appear with the smaller quantities when disease is both present and active when

1. antibody formation is defective, or
2. tolerance has been developed.

The Quantitative Tuberculin Test.—The writers have made no attempt to deal with diagnosis in this book except in so far as it bears immediately on the indication for treatment. Regarding as untenable the standpoint that reaction to a particular large subcutaneous dose of T can decide the presence of active tubercular disease, they consider only the quantitative application of the tuberculin tests as likely to be of help in this direction. The difficulty is twofold. On the one hand, sensitiveness may be profoundly altered by a subcutaneous dose of T, so that the second or third dose of a series may only indicate sensitiveness which has been artificially raised to a level of clinical importance. On the other hand, where sensitiveness of an important degree is present, it may be obscured by tolerance of spontaneous origin.

The artificial increase of sensitiveness is a strong argument against basing any indication for treatment on the result of successive tests whether subcutaneous, conjunctival or even cutaneous. The obscuring of reactivity by tolerance is a reason for being sceptical when a negative test is found in the presence of autotoxic symptoms. What is required as an indication for treatment is information as to the degree of sensitiveness at the time of examination, allowing for any reduction of reactivity by tolerance. Let us see how the various tuberculin tests are likely to help in this quest.

1. **Subcutaneous.**—Most clinicians hesitate to give a larger initial dose of T than ·1. A marked reaction to this indicates a high degree of sensitiveness and is strong presumptive evidence of the presence of active tuberculosis. But if the test is negative, as in the great majority of cases, it can only be repeated after a prolonged interval (weeks at least) without running the risk of merely discovering a sensitiveness artificially raised by the first dose.

2. **Conjunctival.**—This test cannot be safely applied with a stronger reagent than 1 per cent. T, and as no one would care to test both eyes at once, it can only be used at one time with a single concentration. A marked reaction to 1 per cent. T indicates as before a high degree of sensitiveness with the same presumption. But for the same reason again the test cannot be repeated.

3. **Cutaneous.**—Here the test can be simultaneously carried out with any number of different concentrations of tuberculin, and a note made fo the lowest concentration that just gives a perceptible reaction. White and Graham, Ellermann and Erlandsen, and Radcliffe have done work on these lines without yet coming to conclusions that can be clinically applied. It appears to the writers that the work of Ellermann and Erlandsen is particularly deserving of attention. By means of a simple series of measurements and an ingenious formula, the lowest percentage concentration of T that still just gives a reaction is determined. The reciprocal of this is regarded as the measure of sensitiveness, and the numerical values so obtained can be easily compared and utilised. The intensity of the reaction is certainly affected by tolerance, but it is in the writers' opinion possible, that the sensitiveness value obtained by the method is independent. If so, its clinical importance can hardly be exaggerated. Ellermann and Erlandsen provisionally put a 1 per cent. concentration or a sensitiveness figure of 100 as the limit beyond which active disease may be assumed.

4. **Intracutaneous.**—Mantoux and Römer have shown that reactivity can be estimated by an intracutaneous dose so minute that it could hardly lead to any alteration in sensitiveness. But the test is said to be too painful for general use.

More research is urgently required in this hopeful direction, and it is much to be desired that an extended use of one or other of these methods should clear up their clinical value. Help may be gained not only in diagnosis of active disease, but in the choice of an initial dose of tuberculin with which to begin treatment. For the rest, the diagnosis must be based on a careful weighing of all the information afforded by history, symptoms and physical signs ; the finding of tubercle bacilli in the

secretion from an open lesion being much facilitated by the antiformin method of Uhlenhuth, with Löffler's chloroform modification.

SELECTION OF CASES: INDICATIONS.

Of the considerations governing the selection of patients for tuberculin treatment two are paramount; to treat only cases of tubercular disease: and to include all those to whom tuberculin can be of benefit. Tuberculosis has a strong tendency towards spontaneous arrest, and it is often stated that all early cases of phthisis can be restored to health by hygienic treatment. But any one who has had to deal largely with cases drawn from the well-to-do classes, to whom efficient hygienic treatment is open, knows that some come under observation with very slight physical signs which steadily increase in extent during treatment and do not ultimately get well. And those who use tuberculin in sanatoriums are unanimous in stating that certain cases which are stationary or going down-hill under the best hygienic treatment receive their first stimulus to recovery from a course of tuberculin. About one in eight of those infected with tubercle die directly from it; but we can only guess at the amount of recurring indisposition over and above this due to the undetected disease noted by Nägeli and others in those who have died from other causes. And furthermore with our present knowledge we cannot tell which of the infected will have a serious illness. Of localised tuberculosis many forms tend to persist from year to year; untreated adenitis may give

trouble at intervals from infancy to adult life, and lupus be almost conterminous with the span of life itself.

The question of indication is then primarily the question of accurate diagnosis and prognosis in tubercular infection ; and since prognosis is so uncertain there is a wide indication for a method which can do no serious harm and may oftentimes spell a saved life or restored working efficiency. Analogy can be drawn with no other disease, for there is no other widespread infection so often missed in its early stage, which takes such heavy toll of this omission in later years. It is literally the old Roman decimation : one out of every ten lives must be sacrificed ; there is no certain indication on whom the lot will fall ; but in our case amnesty can be claimed by any who have undergone a course of specific treatment.

In the light of these general considerations the indications may be stated thus :

1. **Before symptoms occur ;** where we must at once distinguish between

(*A*) Non-infected,

(*B*) Where infection has occurred but disease has not manifested itself.

(*A*) Before infection has occurred would seem to be an ideal time for immunisation against tuberculosis. Meissen, in fact, in classifying tubercular patients allotted a special division to "prophylactics," those who were disposed to the disease by nature or inheritance without having actually been infected, e.g. the children of tubercular parents. Sahli draws an analogy with inoculation against smallpox. But unfortunately such

immunisation is impossible, and for the simple reason that tuberculin is inert in an uninfected person and produces no response.

(*B*) To insure against breakdown those who are already infected with tubercle, but have not as yet shown any signs of ill-health ; to prevent disease following on infection : this in certain cases is the opportunity of the family doctor, who knows where infection is likely to occur, and who may often suspect occult disease, whether glandular or pulmonary. We should advise him to consider thus treating prophylactically : the children of phthisical parents whom it is impossible to remove entirely from their surroundings ; the other members of families in whom tubercle has become manifest repeatedly at a particular age ; any other person in intimate relation with a phthisical patient, especially under the conditions favourable to the development of tubercular disease, such as dusty trades or unhealthy indoor occupations.

2. In tubercular **disease which has become manifest,** it must first be decided which of the two methods is in place. The decision turns, as we have seen (*see* p. 18), on the presence or absence of auto-toxæmia, which determines whether tolerance is desirable or not. Auto-inoculation is the rule in pulmonary disease of any but the slightest grade, and may occur in extensive peritoneal tuberculosis and in affection of the larger joints, as well as exceptionally in other localisations. But it is only in phthisis that it is the most important clinical feature of the disease, the origin of all the more troublesome symptoms. Hence phthisis, and phthisis alone, is the special object of the method of immunisa-

tion with tolerance, and only accidentally do laryngeal or intestinal tuberculosis become the subject of this treatment when they are associated with phthisis. To the occasional instances in which tolerance is found to be desirable in surgical cases, allusion is made under the usual treatment in Part II (p. 156.). The further consideration of indications is taken separately for the two methods : Part II (p. 74), Part III (p. 183).

PART II

THE METHOD OF IMMUNISATION WITH TOLERANCE (KOCH)

THE TREATMENT OF AUTO-TOXIC TUBERCULOSIS

CONTENTS

PART II

THE METHOD OF IMMUNISATION WITH TOLERANCE (KOCH)

THE TREATMENT OF AUTO-TOXIC TUBERCULOSIS

This section of the book deals with the method of immunisation by means of tuberculin in increasing doses producing tuberculin tolerance, which is, as we have seen, the method applicable to the treatment of cases of auto-toxic tuberculosis, i.e. those in which tubercle products are poured into the general circulation and produce an effect on the body as a whole. The arge majority of such cases occur in the pulmonary disease of adults, and hence it will be convenient to regard this section from the point of view of the treatment of adult phthisis, reserving for separate discussion at the end considerations applicable only to children or to other forms of tuberculosis.

OUTLINE OF THE COURSE OF TREATMENT

In a previous section we reached the point at which the case was diagnosed as one of tubercular infection

developing into disease requiring treatment, and one associated with auto-toxæmia so that the production of tolerance is a desideratum. We have seen further what preparations of tuberculin are at our disposal, how they are prepared and how they differ among themselves, as well as the best means of applying them. In what follows all this is assumed as ground already covered, and we have now to consider a little more closely whether the particular case presented is suitable for tuberculin treatment, what may be expected from it, and what are the limitations imposed. The conditions of administration will then be inquired into, the necessity of simultaneo s or preceding hygienic treatment, and the class of cases that the practitioner will be called upon to treat at home and at work. Certain contra-indications are considered although there are none of an absolute character, and exclusion from specific treatment must be a matter of individual judgment in each case. A period of observation is necessary during which the symptoms are carefully noted and the natural tendency of the disease studied. A record of temperature and pulse will be made on some convenient chart. The patient must be trained in accurate observation and possess a certain minimum of intelligence in order to provide reliable information on which to base the treatment, as also some steadfastness in order to go through with a course of treatment which is to extend over a period of months. The treatment must be approached by doctor and patient with a measure of confidence and the fixed intention of surmounting initial difficulties.

The two sides of the picture will both be viewed: the nature and extent of the disease, and the nature and

extent of the resistance which the body is offering to it. An estimate will be obtained if possible of the degrees of sensitiveness and of tolerance present. The principles of dosage will then be discussed when it will be seen how closely they depend on the view taken of reactions ; there is the choice between ignoring, avoiding or utilising these, and grounds will be given for a method based on the utilisation of reactions. The choice of tuberculin for the tolerance method demands some further consideration, and then in succession the size of the initial dose, the increase of the dose, the interval between them and the final dose attained. The duration of treatment depends on the ease with which the dose can be increased, and on the effect of the dosage employed ; it cannot be forecast, although a minimum of three months will be required. Under certain circumstances the course may have to be repeated one or more times after an interval ; the indication for this repetition can hardly take the form of a simple biological test but all the circumstances will come into review. A consideration follows of the precise way in which reactions are to be utilised for the immunising course ; the various forms in which the reaction may present itself ; the possible dangers of the reaction and how they are to be avoided. Various evidences of success or the reverse occurring in the course of treatment will then be considered, and attention specially directed to the clinical controls which can be made without great expenditure of time and labour, or the help of complicated apparatus.

After this general survey of the methods applicable to the average case, the special points will be considered in connexion with the treatment of febrile cases, of

mixed infection; with the relief of symptoms in cases too advanced for arrest or cure; with the treatment of phthisis complicated by pregnancy. Then a section is devoted to the treatment of auto-toxic disease in children. Finally the ambulant treatment of phthisis comes up for consideration in various aspects, when it will be found that this form of treatment is not a novelty but its advantages and drawbacks are already known to some extent in the light of clinical experience.

SELECTION OF CASES: INDICATIONS

In an earlier section of this book (page 65) we introduced the subject of the selection of cases and the indication for tuberculin treatment before symptoms of disease appeared. We also saw that infection was not synonymous with disease and that evidence of infection alone does not necessarily call for treatment. Here it remains to deal with cases already showing tubercular toxæmia or its results; cases in which treatment of some kind is demanded. It is convenient to consider them under the headings of early, moderately advanced, and advanced; understanding thereby cases in which complete recovery is to be expected, some measure of active life can be restored, or only relief of symptoms is possible.

1. **Early Cases.**—It may be taken that tuberculin should be given in all early cases of phthisis, where the external conditions are suitable and no contra-indication is present. Few, if any, even of the most experienced clinicians are at present in a position to say: this

patient will certainly get well without tuberculin, tuberculin is therefore unnecessary. Improvement to a point may be certain, but to the patient himself the essential matter is: shall I return to my ordinary conditions of life without being liable to break down again? And even if hygienic treatment alone can be counted on to restore him to temporary working efficiency there is very strong ground for the belief that a course of tuberculin will ensure his remaining there.

Of early cases we must distinguish between those with urgent symptoms and those without. Where there is no febrile movement, no hæmoptysis, little if any cough, and no diminution of the nutritive powers, tuberculin as the first and only treatment can be considered, the patient remaining at work or in the usual conditions of life. Where fever or any serious depression of nutrition is present, or hæmoptysis occurring, the first indication is not so much specific treatment as that radical change in the environment which is generally called sanatorium treatment, although it is best designated by its German equivalent of hygienic-dietetic treatment. Of this more in the next section.

Very specially indicated for specific treatment is any case in which hygienic treatment alone has failed to produce improvement, where the physical signs remain unaffected or certain symptoms persist unchanged; and such cases are good material on which to demonstrate the efficacy of tuberculin.

2. **Moderately advanced Cases.**—Where complete recovery is in the nature of things no longer possible a great field is still open for specific treatment in bringing about what Sahli describes as a "compensation"

of the disease, in which an active life may be lived subject to certain disabilities. The immunity from toxæmic symptoms brought about by tolerance, and the increased fibrosis due to judicious focal hyperæmia, will in many cases accomplish this result. It must however be considered in each individual case whether there is anything in the patient's present condition susceptible of improvement, and how far the symptoms are due to a loss of function which cannot on anatomical grounds be restored.

3. **Advanced Cases.**—In advanced cases the chief aim of treatment is the production of tolerance for the relief of symptoms. This and the frequent supervision may make all the difference to a patient whose condition is indeed incapable of arrest or essential improvement, but who may nevertheless have long quiescent intervals free from annoyance and discomfort.

THE CONDITIONS OF ADMINISTRATION: HOME OR SANATORIUM

The administration of tuberculin can no more be confined to the specialist than can the treatment of tuberculosis in general. To do so would be to refuse to treat nine-tenths of the cases. The principles governing specific treatment are capable of exact statement, the necessary precautions are well recognised, and the ways of meeting them have been carefully studied. It is essential that tuberculin should be in the *materia medica* of the practitioner and that he should co-operate with the specialist, and as a matter of fact Koch's old tuberculin does actually appear in the *Pharmacopœia*

helvetica, 1907. The question therefore of whether the specific treatment of any particular case should take place at home or elsewhere is determined on other grounds than that tuberculin can only be administered by the specialist.

The question is rather whether the specific treatment is the chief and only need, or whether a complete change in the patient's environment is necessary for his recovery. In early cases the latter is essential—

1. Where an acute breakdown has taken place.
2. Where urgent symptoms, spoken of in the last paragraph, are present.
3. Where there is fever.
4. When the disease has become open and mixed infection must at all cost be avoided.

In all such cases an entire change in environment is necessary and experience has shown that this is best obtained under the conditions of a sanatorium. Even where the means are sufficient to admit of similar facilities at home, results are as a rule not so satisfactory. The stay in a sanatorium should suffice to reduce the initial fever, improve the general nutrition, bring up the weight to the normal, and to begin a course of specific treatment.

The practitioner will then have to treat—

1. The early cases after leaving the sanatorium until the specific course is complete.
2. The chronic cases of medium severity in which tuberculin treatment is leading to compensation.
3. The advanced cases in whom tolerance is being maintained. Unless indeed these latter can, as is most desirable, be isolated in special institutions.

It remains to be seen how far he should undertake the primary tuberculin treatment of patients remaining at home and at work. This is discussed in more detail under the subsequent heading "ambulant treatment" (p. 157). As early diagnosis becomes the rule, the number of such cases not requiring preliminary sanatorium treatment will increase. In any case the sanatorium is only an incident in the treatment of these cases, a period of instruction and training, in which nutrition is raised to a higher level and the best line of treatment worked out. The time available will never suffice for complete arrest of the disease while in the sanatorium, nor is this necessary if the practitioner will acquire the necessary technical knowledge to carry on the treatment at home.

CONTRA-INDICATIONS

After what has been said, it is impossible to exclude from tuberculint reatment a certain class of case because it will recover without ; or another because no improvement is possible. In practice such classes cannot be defined, and those whose experience of tuberculin is the greatest (e.g. Bandelier and Röpke, Sahli, Pottenger, Citron) do not draw up lists of contra-indications, but decide from case to case on grounds of expediency. Meissen has in fact reproached those who employ specific treatment for their attitude of insisting that tuberculin must succeed if given properly, and of attributing their failures to faulty method and not to the futility of the remedy itself. But it is natural

that as experience increases and difficulties are overcome, the range of application of a remedy should also increase, and cases be included which do not respond so easily and require some management.

There are however various considerations bearing on what we may call relative contra-indications.

1. **Extent of the Disease.**—Rapidly advancing progressive disease should be excluded. Some careful administrators (Petruschky, Römisch, Scherer) exclude cases with large areas of consolidation, liable to break down, although even here the method of avoiding reactions (p. 94) may be employed without risk, especially after a preliminary period of rest and hygienic treatment have removed the inflammatory element in the case. Turban excludes cases where several organs are affected, the practical difficulty being that the disease is at a different stage in each and reacts differently to tuberculin. Severe mixed infection is widely held to exclude from specific treatment, but the subject is an important and complicated one and we shall return to it under a separate heading (p. 142).

2. **Intensity of the Disease.**—(*a*) It is a *sine qua non* of all active immunisation that the tissues shall possess **some power of response.** In conditions of cachexia and grave debility this may be no longer the case. Here every effort must be made to begin by raising the general tone with hygienic measures, and the immense value of preceding sanatorium treatment is most apparent in such cases. Where on the other hand the debility is palpably the result of auto-tuberculinisation specific treatment for producing tolerance is specially indicated.

(*b*) **Fever** has often been held to exclude specific treatment, and it is quite true that febrile cases are less amenable to any measures. Other things should be first tried for the reduction of fever, and if these are unsuccessful, then tuberculin should be given on the lines laid down under the heading of febrile cases (p. 135).

(*c*) A **rapid pulse,** of 120 or more, generally implies auto-toxæmia and is not very amenable to any form of treatment. Both Turban and Neumann refuse to give tuberculin in these cases ; but it is quite justifiable to make the trial, and Amrein has found T of substantial help in the reduction of the pulse rate.

So far then as debility, fever or rapid pulse are the result of an intoxication with the patient's own tubercular products, they are an indication for the limitation of such auto-toxæmia by rest and all other available means. Only when such limitation has been reached or shown to be impossible should tuberculin be employed ; in the latter case, in order that artificial tolerance may; be induced in the absence of the natural production.

3. **Other Factors of the Disease itself.**—(*a*) **Hæmoptysis** is not a contra-indication. Quite the reverse ; there are some cases in which a dose or two of tuberculin arrest a constantly recurring bleeding. But specific treatment will not prevent the bursting of an aneurysm in a cavity, although it may lessen the erosion which leads to such cavitation. A focal reaction occasionally shows itself in some streaks of blood in the expectoration, amenable to rest, and not followed by a considerable hæmorrhage in a larger proportion of cases than in those not specifically treated

(*b*) Neumann points out with justice that tuberculin

cannot be expected to affect the **results of past disease ;** e.g. deformities, adhesions, strictures, amyloid or fatty changes ; and if these are marked the course of specific treatment can hardly be a success.

(*c*) Sahli states that certain cases are simply **intolerant** of tuberculin in any form and on any mode of administration, and that there is no good in pushing it under these circumstances. The writers have not yet met such a case, although they have had patients with a very low " individual optimum " dose as described by the same author.

4. **Accidental Concomitants.**—Association with diabetes of a severe form is fateful for the prognosis of phthisis, but tuberculin may still be tried in cases where the general condition is not hopeless. Organic heart disease, which *en passant* is rarely combined with phthisis, does not, when compensation is perfect, interfere with treatment on the usual lines.

Epilepsy merely demands increased care in administration. A high degree of " nervousness " may render specific treatment impracticable and that for various reasons. It may make the data by which the treatment is controlled so uncertain as to afford no safe basis. Weihrauch has shown what a large part suggestion plays in the temperature reaction after an injection ; in certain patients an *injectio vacua* produced an oscillation with regularity. In such cases it is wiser to desist. Tuberculin may on the other hand increase any existing hysterical or neurasthenic symptoms and make continuance impossible.

Pregnancy is not a contra-indication ; in fact, tuberculin is strongly indicated in the interest of both mother

and child ; a special section is allotted to this later (p. 149). It is generally advised to suspend injections during the menstrual period ; the rationale of this is quite obscure. The premenstrual rise of temperature is a physiological occurrence, and although it is probably more marked in phthisis is rarely of any significance ; it is during this rise that a negative phase is present and the general resistance, probably to any and every infection, diminished ; hence there might be some theoretical ground for not injecting during the seven to ten days preceding the period. But during the period itself, when the temperature and the opsonic curve have both returned to their average line there seems no practical reason for withholding tuberculin. An exception should be made for those rare cases in which there is a *post*menstrual rise of temperature denoting a relapse occurring regularly at this epoch and always of serious import.

5. **External Considerations.**—Tuberculin should never be given where there is no possibility of proper control. This applies to careless and unreliable patients in all ranks of life, and not necessarily only to the poverty-stricken. The treatment must be based on the possession of a certain number of reliable data.

OBSERVATION AND CONTROL

Accurate knowledge of the condition of the patient is necessary before the course of tuberculin can be commenced ; a complete routine examination should of course be made in which there remain certain points to emphasise. The family practitioner will have the

great advantage of knowing his patient and his peculiarities to start with. The institutional officer will take two to four weeks to make the observations. The longer time is in general none too long, but where the stay in the sanatorium is limited to three months and it is essential to get started with specific treatment, the shorter time may be all that can be spared.

Temperature.—An accurate record of temperature is the first requisite. This is synonymous with rectal measurement. It is useless and misleading to employ an exact instrument in an inexact manner ; and although for recording considerable deviations of temperature from the normal the mouth reading is sufficiently exact, it is not so for the small excursions with which we are here dealing. The advantage of rectal measurement does not end with its accuracy ; it is quicker—three minutes by the watch suffice, whereas in a cool external atmosphere five and often ten or twenty minutes are required even for an approximate mouth reading. Nor can the rectal temperature sin against the æsthetic sense, with which it has been charged, since it is taken in private. To illustrate how little serviceable the mouth reading is for small variations, it is only necessary to mention that with millions of records, the fact of the regular monthly rise and fall of the temperature in the female during the period of sexual activity was entirely overlooked ; although as a matter of fact it can always be observed even with mouth readings taken under special precautions. And again it is a frequent observation of sanatorium doctors that, with a mouth chart before admission, degrees of pyrexia urgently needing rest in bed have been overlooked.

As a preliminary measure the temperature must be taken four times in the twenty-four hours ; in bed on waking and retiring, and twice between after a period of rest of half an hour or longer. Unless intended deliberately as an " exercise temperature " the rectal measurement must be taken after rest. After the normal daily curve has been discovered it will in most cases be necessary only to measure twice : once before rising and again between 4 and 6 p.m.

In male patients going about their work the temperature may very conveniently be measured in the stream of urine, which gives a reading practically the same as in the rectum, but less affected by exercise.

As well as these rest temperatures it will be of service in many cases to know what the rise after exercise is ; the limit in health of the rectal temperature after a walk of three miles in an hour may be taken as 100·4°F. Any rise in considerable excess of this points either to auto-inoculation from a disease focus or to a condition of muscular weakness associated with want of training.

Pulse Rate.—The frequency of the pulse at rest on an average of several days must be known. If it is as much as 100, complete rest is urgently needed and the case should be regarded in the same category as one with febrile movement and treated accordingly.

Nutrition.—The body-weight should be measured every week, at the same time of day and under precisely the same conditions. The relation to the normal weight in health and to the highest known weight should be noted ; and where the weight is below normal, the effect of rest and feeding studied. An increase of body-weight where the conditions of life are profoundly

altered, as in entering a sanatorium, is a favourable indication, but too constant to form the basis for any prognostic conclusion. It is otherwise with a steady increase of weight occurring under specific treatment carried out at home and at work, which is then a favourable sign of great importance.

Examination of the Urine.—The examination should of course exclude diabetes and Bright's disease. With regard to the latter it must be borne in mind that albumen in small quantity as well as casts are very frequently to be found in the urine of tubercular patients after relatively slight exertion. During a single winter one of us found granular and hyaline casts in the urine of eighteen out of twenty-three patients examined immediately after a journey from England to Switzerland; thirteen times without albumen. In every case the condition passed off in a few days. Such temporary renal irritation may even be of value in diagnosis, and Lüdke and Sturm have recently found slight albuminuria in 102 out of 140 phthisical patients who were made to stand for an hour, and almost constantly in the early cases. The negative results all became positive on repetition after a small injection of tuberculin. These facts must be considered and conclusions drawn only from urine passed after a period of rest.

Examination of the Sputum.—This is not the place to deal with the information gained from examination of the sputum, but it may be said that the clinician should never be content with merely ascertaining the presence or absence of tubercle bacilli. Much further help is to be obtained from observing the

number, size and grouping of these ; and whether they are intraphagocytic or not ; the cellular content of the sputum, and the proportion of the various types of cells ; the presence of other organisms in the washed sputum.

Application of the Tuberculin Tests.—The period of observation is a suitable time for the application of the tuberculin tests where this has not already been done. When the diagnosis is assured a certain value still attaches to the degree of sensitiveness present, since this is, as we have seen (p. 63), an index of the activity of the disease and a possible clue to the size of the initial dose.

Control during Treatment.—As the treatment will last for at least three months and be largely controlled by slight variations of temperature during the whole of this time, it is very desirable that the whole chart should be seen at a glance. At the suggestion of one of the writers Messrs. Bale and Danielsson print a "Sanatorium Chart" extending over a period of three months or thirteen weeks, which is admirably adapted for the record of a course of tuberculin treatment. The two curves illustrated at the end of this book have been transferred to this long chart. Other suggestions for records in ambulant treatment are given under that heading (p. 157) and these, with the necessary modifications, will be found of use in sanatorium and private practice.

THE PRINCIPLES OF DOSAGE

We are dealing here with the treatment of cases of

auto-toxic disease and have seen in a previous section (p. 18) that the indication is to produce immunisation along with tolerance. The mechanism of this proceeding was illustrated by a diagram (Chart III) which we repeat here; it shows how in theory the repetition of increasing doses at a certain interval leads to the production of equal immunising stimuli; or in other

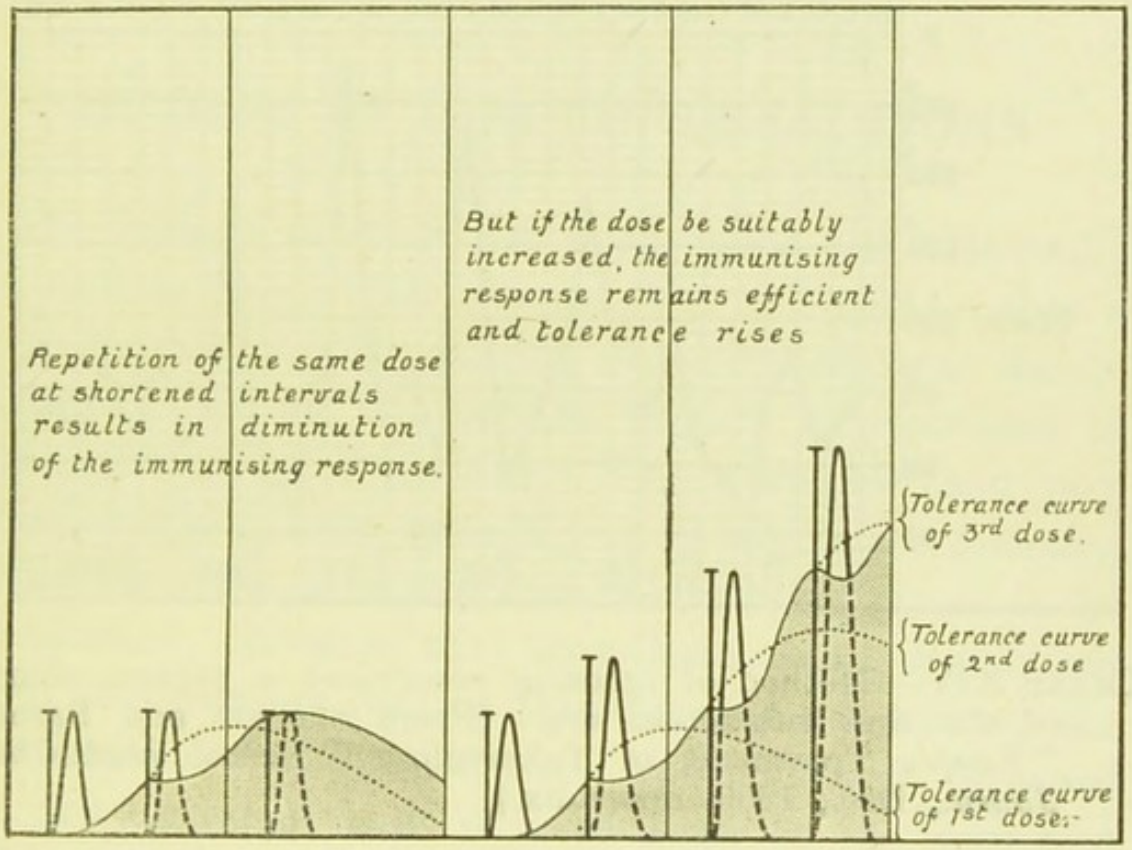


CHART III. repeated.—Method of immunisation with tolerance: showing that the essential factor is the diminished interval.

words that tolerance is developed in the process of immunisation And even with ultimately large doses the stimulus may never be large enough to produce symptoms which can be clinically appreciated as a reaction. The clinical course of these cases depends accordingly on the size of these stimuli. If small there will be nothing that can be called a reaction although

changes will take place imperceptible to the thermometer and to ordinary methods of physical examination. If large there will be reactions of the character described in a previous section (p. 29). Regarding the production of tolerance as the essential and only aim of tuberculin treatment, Koch and his contemporaries of the

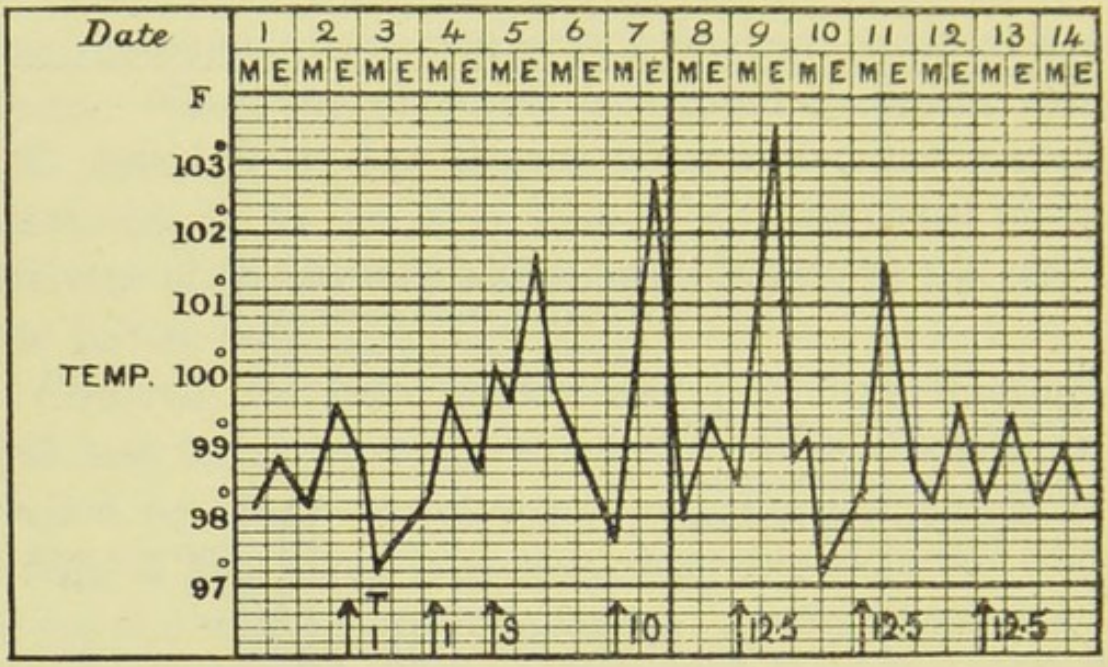


CHART XIV.—Method of ignoring reactions: a typical chart of the first tuberculin era. (From Skerritt and Baron "Koch's Treatment of Tuberculosis," *Bristol Med. Chi. Journ.*, Dec., 1890, appendix.)

first tuberculin era gave increasing doses resulting in severe and repeated reactions, and were satisfied if in so doing the largest doses were ultimately tolerated. Chart XIV shows a typical example of such a course in an adult case of phthisis previously apyretic. It was, however, soon discovered that reactions had drawbacks and efforts were made to secure the advantages of the immunisation with tolerance without the reactions. Three distinct methods developed in the attempt to

reconcile the two factors and can most conveniently be dealt with in historical order leading up to the third which is the method recommended by the writers. We call these methods :—

1. Method of ignoring reactions.
2. Method of avoiding reactions.
3. Method of utilising reactions.

METHOD OF IGNORING REACTIONS

The history of what has been called the tuberculin delirium is still a little obscure, but it is certain that a large share in the discrediting of the remedy was due to inappreciation of the serious import of reactions in advanced cases of phthisis. The reactions then produced could not be ignored ; it was often a question of kill or cure, in which the risk was too great to be overlooked. Even at that time there were voices raised both in Germany and in this country advocating the avoidance of severe reactions ; but they were drowned by the universal cries of execration at the apparent failure of the remedy on which so many hopes had been based, and it was not until the publication by Götsch in 1901 of ten years' experience of administering tuberculin in a country hospital without giving rise to severe reactions, that tuberculin treatment began to be practised again at all widely.

It must not be supposed that during this interval tuberculin was not used at all as a remedy. Koch, who induced Götsch to publish his results, wrote a short note to the paper in which he cited eight authorities,—five in Germany, two in Switzerland, and

one in England,—who were agreed that tuberculin was a remedy of value in a febrile cases of phthisis not too far advanced, and that it was advisable to avoid severe reactions. And the list is by no means an exhaustive one. But until the publication of Götsch's results the prejudice against tuberculin amongst the medical profession itself was such that very few cases were available for treatment with tuberculin even by the few who specialised in the remedy.

Götsch set himself to avoid all larger reactions, but seeing that in one of his illustrative cases the temperature passed 101° four times and once reached 103° whilst the dose was still pushed, he must rather be regarded as the founder of the modern method of ignoring reactions.

The method then takes for granted that a reaction is an inevitable part of a course of tuberculin ; but that it is unwelcome and to be regarded in the light of a hindrance ; a disturbing factor to be got rid of as soon as possible in order to make way for the even progression of dosage up to a certain final large amount of tuberculin. The method is the traditional one of Germany's largest popular sanatoriums at Belzig and Beelitz, practised in succession by Möller, Pickert and Löwenstein. Löwenstein adopted for some time the next method described, that of avoiding reactions, but discarded it again ; he does not even find it helpful to begin with a small dose but starts off in every case with 0·2 of **T** repeated until it fails to give a reaction. In England the method is recommended and practised by Wilkinson and others who have followed him.

Chart XV illustrates the immunisation curve in this method ; the relatively large initial dose producing a reaction and repeated until it is tolerated ; the rapid

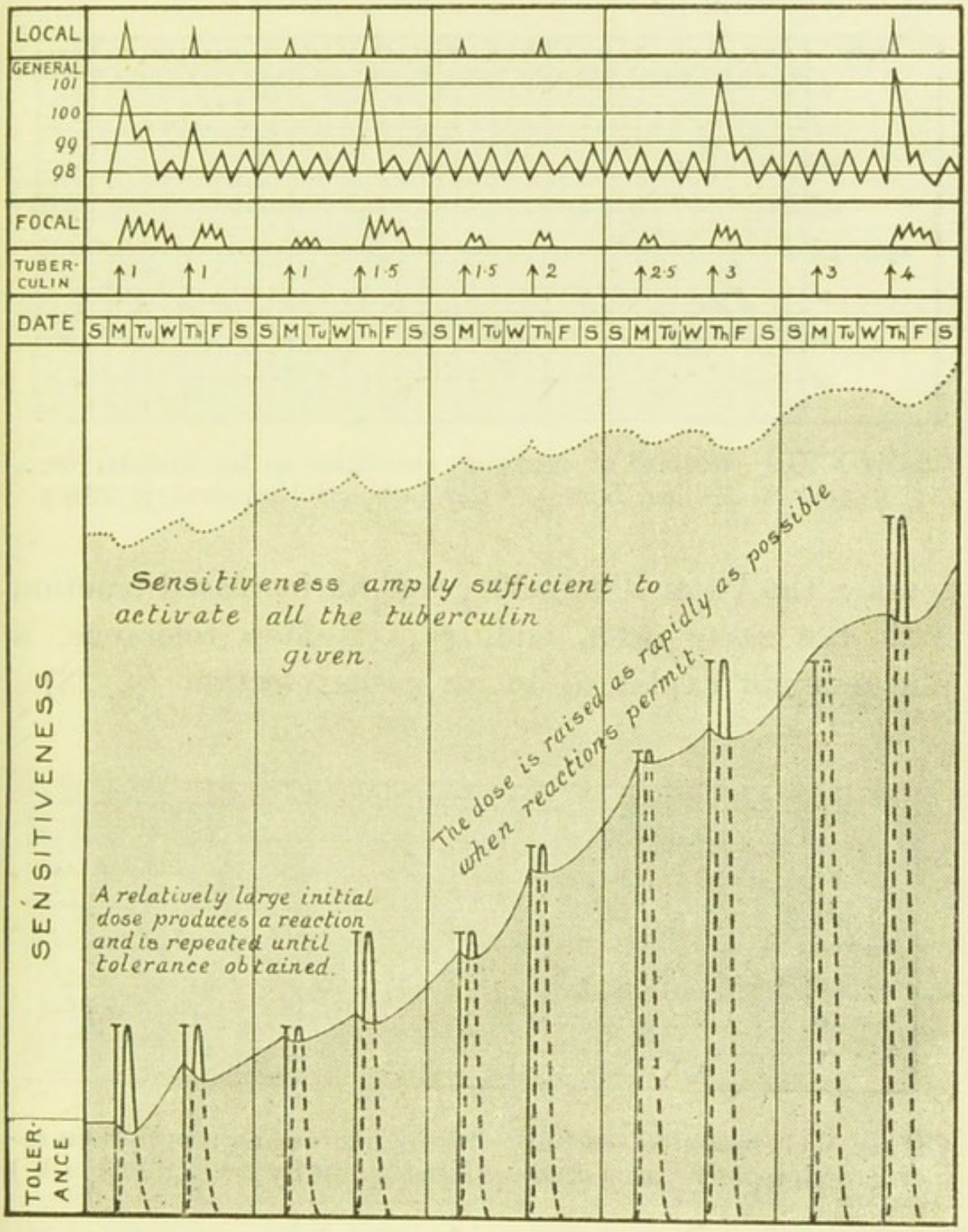


CHART XV.—Method of ignoring reactions. Straightforward case, commencing with a dose producing a general reaction, which is repeated until tolerance is obtained, and so on.

rise of dose with reactions reappearing at various points and tolerance now rising fast now slowly.

Temperature charts are shown from Möller and H.

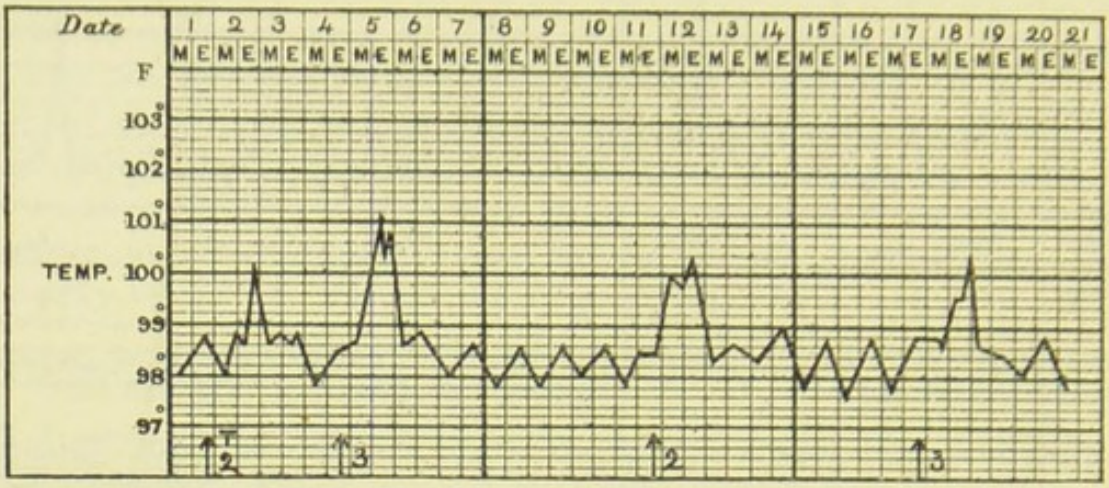


CHART XVI.—Method of ignoring reactions in its modern form. (From A. Möller, *Lehrbuch der Lungentuberkulose*, p. 238.)

Clark ; the latter illustrating well an increased reaction with the same dose, ending in sudden tolerance, a phenomenon explained in an earlier section (p. 23).

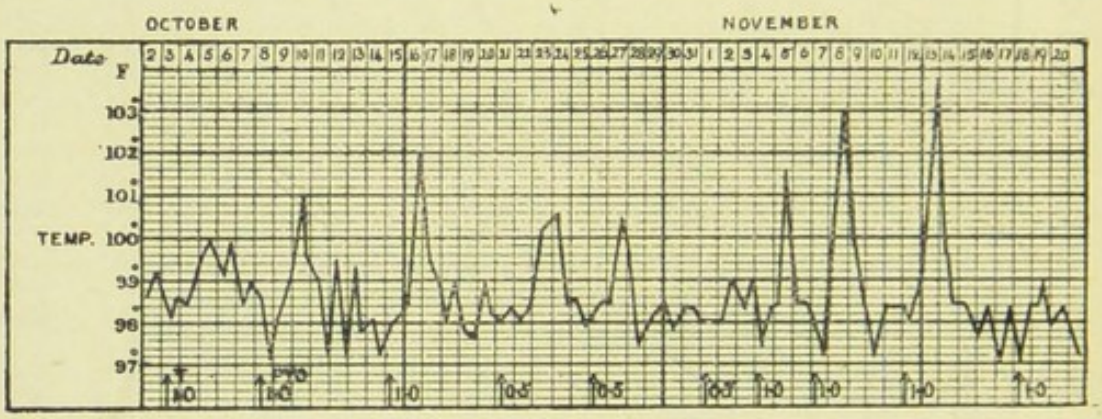


CHART VII. repeated.—Chart showing increasing reaction on repetition of the same dose. (Kindly lent by Dr. Hilda Clark.)

Other charts may be seen in Bandelier and Röpke's textbook ; although their method is approximating rather to that described under (3).

It seems probable that there is a weighty objection to the pushing of tuberculin through the reaction limit. Insufficient time is allowed for the further development of sensitiveness which accordingly fails to activate the whole dose of tuberculin injected.

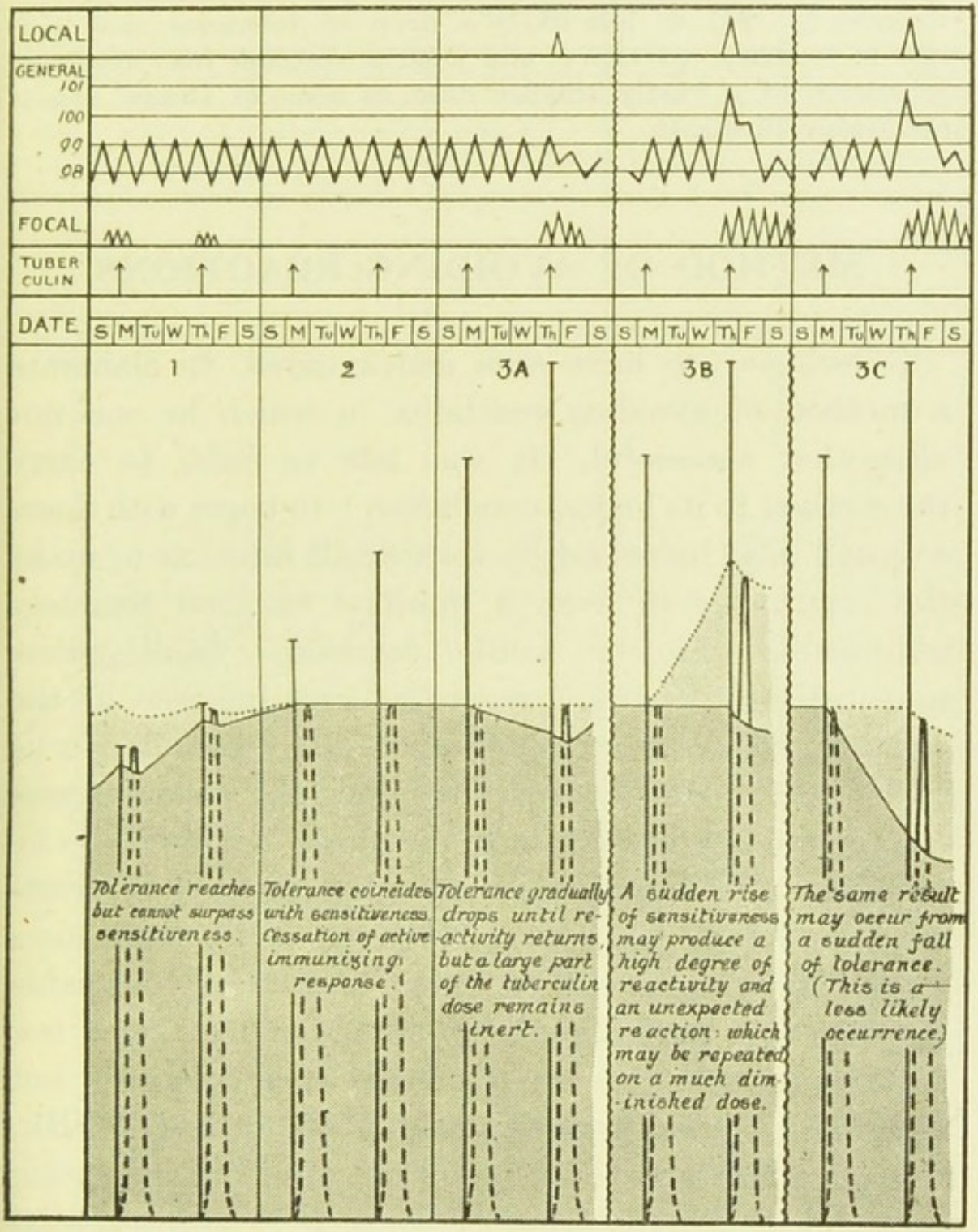


CHART XVII.—Illustrating the pushing of tuberculin beyond the limit of sensitiveness, when all immunisation ceases for the time. Normally (A) tolerance falls slowly and immunising responses return. (B) and (C) illustrate other possibilities.

Hence it comes about (*see* Chart XVII) that sensitiveness and tolerance remain stationary while the dosage increases. It is evident that under these circumstances a sudden rise of sensi-

tiveness (p. 24) or less likely a drop of tolerance, may give rise to a sharp reaction ; and such a reaction may recur on repetition of a vastly smaller dose, as some of Denys' charts admirably illustrate.

METHOD OF AVOIDING REACTIONS

Götsch as we have seen endeavoured to elaborate a method of avoiding reactions, in which he was not altogether successful. It was left to Sahli to carry the method to its logical conclusion ; to begin with doses so small, and increased by such small ratio, as to make the occurrence of even a minimal reaction remotely improbable. For the word " reaction " Sahli prefers to substitute " harm," regarding any increase in the existing inflammatory condition of the tubercular focus as harmful. He discards altogether the subcutaneous employment of tuberculin in diagnosis, holding it to be irrational to advocate a reactionless method of treatment, and then to produce reactions at its commencement. The treatment on these lines being incapable of doing any harm the disadvantage of treating a few patients in the absence of active tuberculosis is not material. He begins with a dose of ·003 or less of **TBk**, repeating the same dose more than once and increasing on about a " twenty basis " (*see* p. 107) with a special series of dilutions of **TBk** of which each is but twice as strong as the preceding, instead of the usual multiple of ten. At the slightest sign of a reaction the dose is reduced and increased again with greater care, and the same small dose may have to be repeated for months at a time. The whole period of treatment extends

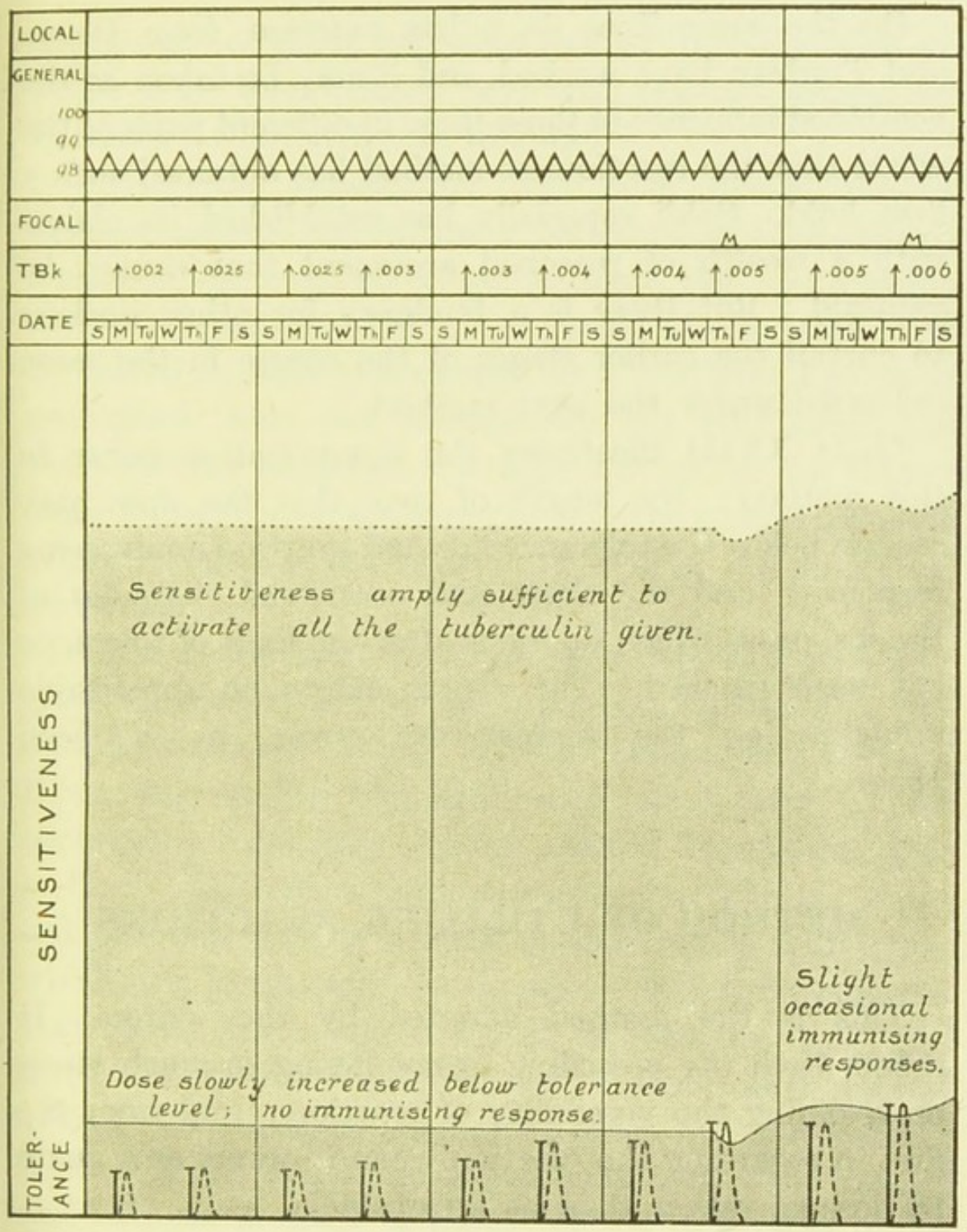


CHART XVIII.—Method of avoiding reactions. Straightforward case, the dose remaining for long below the reaction limit, and then giving rise to an occasional minimal response.

over a year or eighteen months at the shortest, perhaps much longer, and it is therefore a matter for the family doctor with maybe the assistance of the specialist.

On the same lines in a less extreme form Denys and Trudeau have worked, and it may be taken as the combined influence of these three in different parts of the world that the reactionless method has obtained such a firm hold. Sahli especially has established its claims with a wealth of reasoned argument that cannot be gainsaid. But there is a tendency for other workers to curtail the earlier stages of the course in the sense indicated under the next method.

Chart XVIII illustrates the immunisation curve in this method; the length of time that the dose may remain below the tolerance line and exert no immunising response; and the slight and occasional character of the responses which do occur after the limit of tolerance has been reached. The course exerts no appreciable influence on the temperature curve, as is seen above.

METHOD OF UTILISING REACTIONS

This is the method adopted by the writers. It differs from the preceding in not laying so much stress on avoiding the possibility of reaction; and from the first in regarding the reaction when it occurs as a guide to dosage, rather than as an obstacle.

With efficient treatment indeed the writers frankly recognize with Turban the impossibility of avoiding reactions altogether, at the same time insisting on absolute rest when they do occur; if this be done the reaction is often the starting point of more rapid progress. This view is entirely in accord with the

experience of slight reactions due to auto-inoculation, which have been utilised with such marked success by Paterson ; who writes as follows :—

"After the sanatorium had been opened about eighteen months and further experience had been gained, I came to the conclusion that patients who had a slight rise of temperature (99°) as a result of overwork, and for whom in consequence rest for a few days had been prescribed, were not infrequently not only none the worse for this sequence of events, but rather the better. Some patients even appeared to date the commencement of their improvement from the period of rest following overwork."

We shall see later that the local reaction generally gives the clue to an impending general reaction (p. 121) and the latter should not be lightly undertaken as there is an appreciable although very small risk in its occurrence, especially under certain conditions (*see* p. 128). This risk is unquestionably less than the other risk of losing time by continuing indefinitely with doses which are producing no response. Römisch suggests that doses far below the limit of reaction have the efficacy of distilled water (we should rather say of normal saline) ; in this there is no great harm if hygienic treatment is being simultaneously carried out with success and with no pressure of time. But if tuberculin is the principal treatment, or if time is pressing, it must be efficiently given.

This method consists then in pushing the dosage only until the occurrence of a reaction and then keeping it just below the reaction limit. In the words of Hamman and Wolman :

"When we have reached the height of the patient's tolerance we quietly wait rather than force them on to higher doses through repeated reactions. And the question may be put if we are not accomplishing all that tuberculin can do by thus remaining just below the reaction point? Certainly there is no clinical evidence to show that these patients do not progress as satisfactorily as those going uninterruptedly to the higher doses."

Quite a small dose is given to commence with; a dose that cannot give rise to reaction, or so increase the sensitiveness (*see* p. 24) as to activate subsequent larger doses unexpectedly. This dose is then rapidly increased to the point at which a reaction occurs; and by keeping a careful watch on the site of injection, this point may often be noted before the occurrence of a febrile reaction at all. After the limit of tolerance has been reached, the dose is increased on a much smaller ratio which must be determined by experience from case to case. If a careful chart be kept the limit of tolerance may often be observed in a depression of the temperature, a "flattening" of the chart. Latham and Inman state in this connexion:—

"If we take the opsonic curve as representing accurately the immunity curve, it is obvious that the best method of administering tuberculin is progressively to increase the dose until a prolonged positive phase is produced by a particular dose (as is shown by the 'opsonic' curve and by the 'flattening' of the temperature), and when this dose fails to produce its former effect to increase it."

Which is doubtless the same phenomenon from the

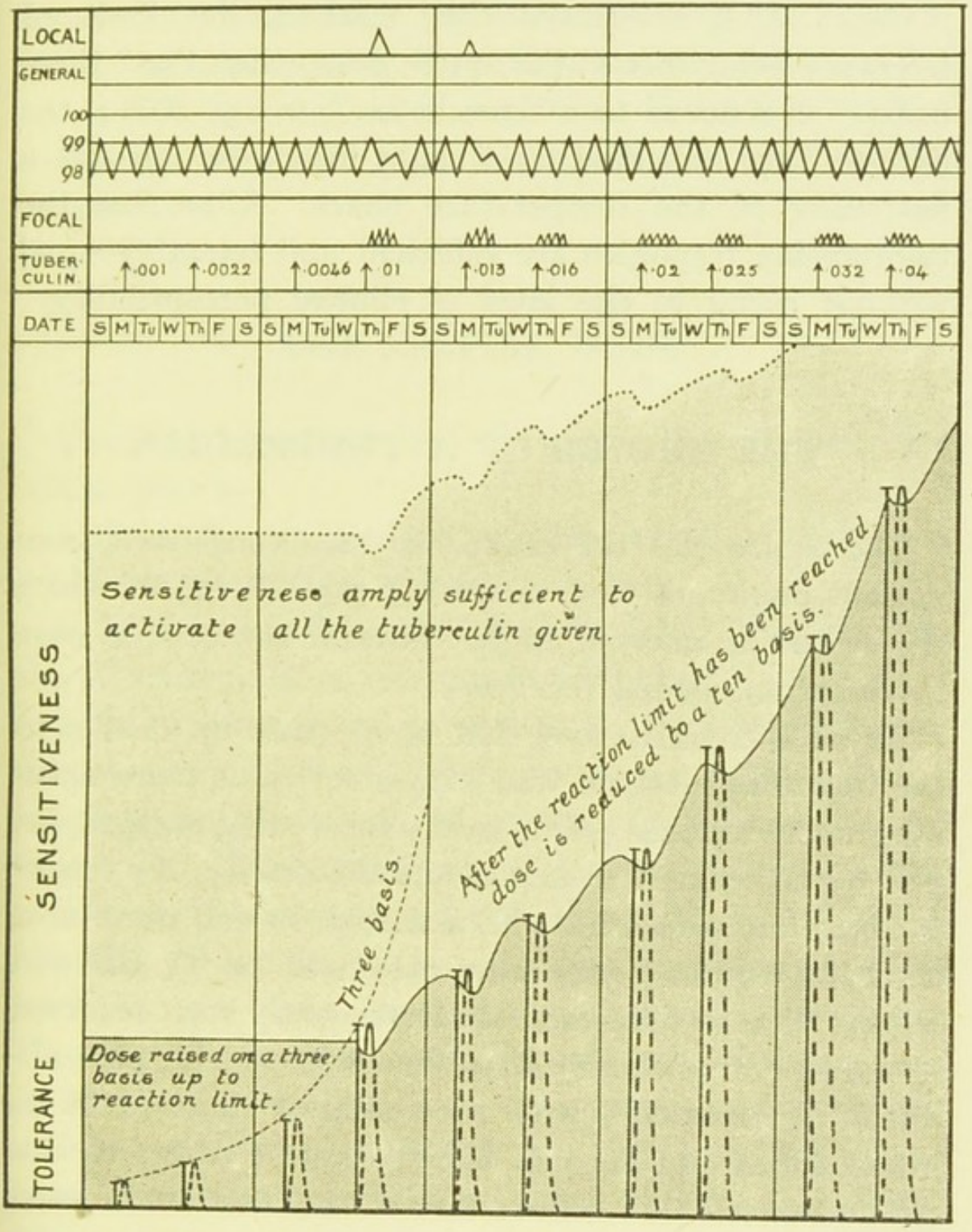


CHART XIX. — Method of utilising reactions: the method of election, the dose being rapidly raised up to the reaction limit, then slowly, keeping close to this limit.

laboratory side. In what follows we shall keep this principle in view for the majority of cases, pointing out where a certain amount of latitude may be allowed.

Chart XIX illustrates this method, the limit of tolerance being met at the fourth dose, when the " three basis " is reduced to a " ten basis " (*see* p. 107) ; the limit is here indicated by a slight local reaction and a flattening of the temperature chart. After this the immunising responses are sufficient and tolerably equal without rising to the level of clinical perceptibility.

THE CHOICE OF A TUBERCULIN

The choice of a tuberculin has been considered from various points of view in Part I (pp. 35–42) to which the reader is referred back. Several tuberculins were there recommended for use.

There is little to add that is specially applicable to the tolerance method, which does not come more naturally under various points in the succeeding paragraphs. But for the sake of clearness and uniformity, the reader is advised to concentrate his attention on two, or at most three, tuberculins, and these may well be **T, BE** and **TBk**. This recommendation has recently been endorsed by no less an authority than Penzoldt, who himself submitted to treatment with tuberculin at the time of its introduction and ascribes his subsequent career to this circumstance. We believe that **T** may and can be used on any and every occasion ; but it is certainly easier to surmount the initial difficulties of dosage with **TBk** and safer to use **BE** for febrile and highly sensitive cases. One of the writers has for years used **TBk** without encountering any of the difficulties in dosage described by other administrators. He has formed the

impression that **TBk** is the easiest tuberculin to administer whilst possessing very high specific content, but he would not suggest its exclusive adoption as the experience of others with **T** and **BE** has been equally satisfactory.

THE INITIAL DOSE

Two considerations are of weight in choosing the initial dose :—

1. It must not produce a severe reaction or indeed be likely to produce a reaction at all.

2. It must not be so small as to delay unnecessarily the attainment of an immunising response.

1. In recent cases of early phthisis, where sensitiveness may be very high and tolerance as yet undeveloped, a reaction may be provoked by even a minute dose of tuberculin. Most writers state that they have not seen a dose of ·001 produce a febrile reaction, and the few recorded instances where a smaller dose has done so were in cases where there was a tendency to febrility. These febrile cases demand separate consideration (*see* p. 138), and what is said here is intended to apply in the main to patients without fever. In more advanced cases, where it is essential to avoid an initial reaction, it is fortunately not a difficult matter as some spontaneous tolerance is already present reducing the reactivity. The reaction produced by a minute dose in an early case is almost always harmless, for in the first place the tissues are well able to withstand the small charge of toxin ; the focal reaction tends to be slight

in a closed lesion on account of the relatively small lymph flow where there is no outlet ; and this reaction in the focus brings no risk in the absence of any considerable area of consolidation. It is rather the secondary inflammatory area surrounding actual tubercular tissue in which focal reaction is apt to have a marked influence for good or for bad.

2. The dose must not be unnecessarily small since no satisfactory immunising response will occur until it approaches the reaction limit. But in the method adopted the initial dose is rapidly increased up to this limit and may reach a tenfold dose in four injections and a hundredfold in eight injections. The delay is therefore inconsiderable and the disadvantage overborne by considerations of safety.

We therefore recommend the adoption of a uniform initial dose of ·001, being the one-thousandth part of a cubic millimetre of the original fluid of any tuberculin on the market. It is contained in 1 c.c. or a whole syringeful of dilution (6), or in ·1 c.c. or a single division of the syringe of dilution (5). The preparation of these dilutions has been described on pp. 55–59. The chart repeated here gives at a glance the equivalent of this dose in milligrammes of solid substance or other measurements which have sometimes been used.

The reasons for adopting this uniform dose may be restated briefly :—

1. **Simplicity.**—The dose can be easily remembered and simply and accurately administered with no troublesome calculation.

2. **Safety.**—It is a dose that cannot give rise to a

THE CUBIC MILLIMETRE AS UNIT OF VOLUME.							
CUBIC MILLIMETRE c.mm.	CUBIC CENTIMETRE c.c.	Contained in 1 c.c. of dilution	*Equivalent on older systems of measurement to:*				
			T. PT. TOA PTO. BF	TR.	PTR	BE. PBE. SBE	TBk
				Old basis (Koch)	*New basis (Ruppel)*		
1000	1	*Original*	1000 mgr.	10 mgr.	2 mgr.	5 mgr.	
100	0·1	①	100 mgr.	1 mgr.	⅕ mgr.	½ mgr.	TBk_1 1·0
10	0·01	②	10 mgr.	⅒ mgr.	1/50 mgr.	1/20 mgr.	TBk_2 1·0
1	0·001	③	1 mgr.	1/100 mgr.	1/500 mgr.	1/200 mgr.	TBk_3 1·0
0·1	0·0001	④	⅒ mgr.	1/1000 mgr.	1/5000 mgr.	1/2000 mgr.	TBk_4 1·0
0·01	0·00001	⑤	1/100 mgr.	1/10,000 mgr.	1/50,000 mgr.	1/20,000 mgr.	TBk_5 1·0
0·001	0·000001	⑥	1/1000 mgr.	1/100,000 mgr.	1/500,000 mgr.	1/200,000 mgr.	TBk_6 1·0

dangerous reaction, and will probably give rise to no reaction at all.

(N.B.—Febrile cases are excluded for separate consideration.)

3. **Expediency.**—The patient is not alarmed by any unpleasant consequences from the first dose ; and since it can be rapidly increased, the delay in producing an immunising response is not material.

If this standard for the initial dose is held to be arbitrary the reader is referred to the following table of initial doses given by writers with large personal experience of the various preparations of tuberculin.

T (including **PT** as well as the unconcentrated extracts **TO, PTO** and **BF**).

(Where no letters are appended to the name, **T** is to be understood.)

·001 to ·00001, Denys (**BF**), Hamman and Wolman.

·001, Hammer, Wolff-Eisner, Savoire.

·01 to ·0001, Weddy-Poenicki.

·01 to ·001, Rolly, Philippi.

·025, Aufrecht, Neumann.

·1 to ·001, Bandelier and Röpke.
·1 to ·01, Götsch.
·1, Möller, Philip, Freymuth.
·2, Löwenstein.
·5, Wilkinson (**PTO**).

Where two figures are given the smaller refers to the dose for febrile cases. The list makes no pretension to completeness, but it is a fair sample of the practice of actual clinicians. The figures above ·1 are attached to the names of those who do not hesitate to produce initial reactions. ·1 and below are given with the intention of producing a response short of a clinical reaction. Freymuth has found ·1 to be about the limiting dose for the new albumose-free tuberculin extract of Koch known as **ATh** (**A**lt **T**uberculin **h**ell).

TR and **BE** (including the bovine and other preparations).
·0001, Rothschild.
·002, King (New York).
·005, A. E. Wright, Neumann.
·01 to ·002, Latham and Inman.
·01, Bosanquet.
·02, Krause (Görbersdorf).
·025 to ·017 Hyslop Thomson.
·1, Götsch, Möller.
·2 to ·02, Bandelier and Röpke, Philip.
·2, Heron, Römisch, Weicker.
·4 to ·04, Litzner.
·5, Krause (Hanover).

It will be noted that the general consensus is higher than the dose suggested in the text ; and it is in the use of these preparations that a dose exceeding ·001 may sometimes be given at the start. But this dose is still recommended for routine use.

TBk.
·000025, Rollier.
·001, Philip.
·002 to ·0002, Amrein.
·006 to ·001, Sahli.

Here ·001 is about the average dose. One of the writers has long used a dose a little larger than this and has never been obliged to reduce it, while at the same time it has always evoked a satisfactory immunising response when the blood has been tested for bacteriotropic substances.

Mention must be made here of attempts which have

been made to determine in advance the most suitable dose of tuberculin to inject. Saathoff has proposed to use the diagnostic tuberculin injection as a guide to the therapeutic dose ; but, as we have seen, any considerable sudden dose of tuberculin may so increase the sensitiveness, with or without affecting tolerance (*see* p. 24), as to afford no clue to the dose which can be administered afterwards short of producing a reaction. A much more fruitful line of inquiry is that of White and Graham developed further by White, Norman and Züblin. They perform simultaneously a series of cutaneous (v. Pirquet) tests with the same volume of various dilutions of T, noting the dose which produces a reaction of a certain intensity as determined by the size of the papule. They then inject subcutaneously after a suitable interval the dose which has given this standard cutaneous reaction. The method has been alluded to earlier under the heading of diagnosis (*see* p. 63) ; it has not yet been worked out sufficiently in actual practice ; but the writers believe it likely to afford valuable information as to the degree of reactivity existent at any particular moment.

INCREASE OF DOSE

In accordance with a practice which is nearly universal we have described the preparation of tuberculin dilutions on a decimal system, each successive dilution being ten times weaker than the preceding one. And in administering we proceed each time from the weaker to one ten times stronger, i.e. in a geometrical progres-

sion. The syringe, on the other hand, is divided into ten equal parts, and if we increase the dose a division at a time, we are proceeding only in arithmetical progression. The result is that in advancing to the next stronger solution and continuing with single divisions of the syringe we suddenly increase the dosage. To give a concrete example, the successive doses reckoned as divisions of the first dilution may be : 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, etc., when it will be noted at once that at 10, 20 there is a sudden increase, the dose being doubled instead of being increased by one-ninth. It is exactly at these cliffs in the dosage that reactions are likely to occur ; and they do as a matter of experience occur here in the practice of those who increase their doses on these lines. It may be advisable to double the dose sometimes at the risk of producing a reaction ; but this should be done deliberately and with open eyes, and not merely to satisfy the calibration of a syringe.

To avoid such cliffs the simplest method is to insert a dose, say 1·5 between 1 and 2, and to miss out some of the higher divisions, giving let us say the series 1, 1·5, 2, 3, 4, 5, 6, 8, 10, 15 and so on. Bandelier and Röpke give 1, 1·5, 2, 3, 5, 7, 10, 15, etc. Neumann uses the series 1, 1·3, 1·6, 2, 2·5, 3, 4, 5, 6·5, 8, 10, 13, 16, etc. But all these are merely makeshifts and there is no logical way of dealing with the increase of dosage except by making it the same multiple from dose to dose ; e.g. to double the dose each time, or to increase it by one-half or one-quarter or some other fraction. Pope at Lawrason Brown's suggestion worked out a scale on these lines, in which it is only necessary to decide how

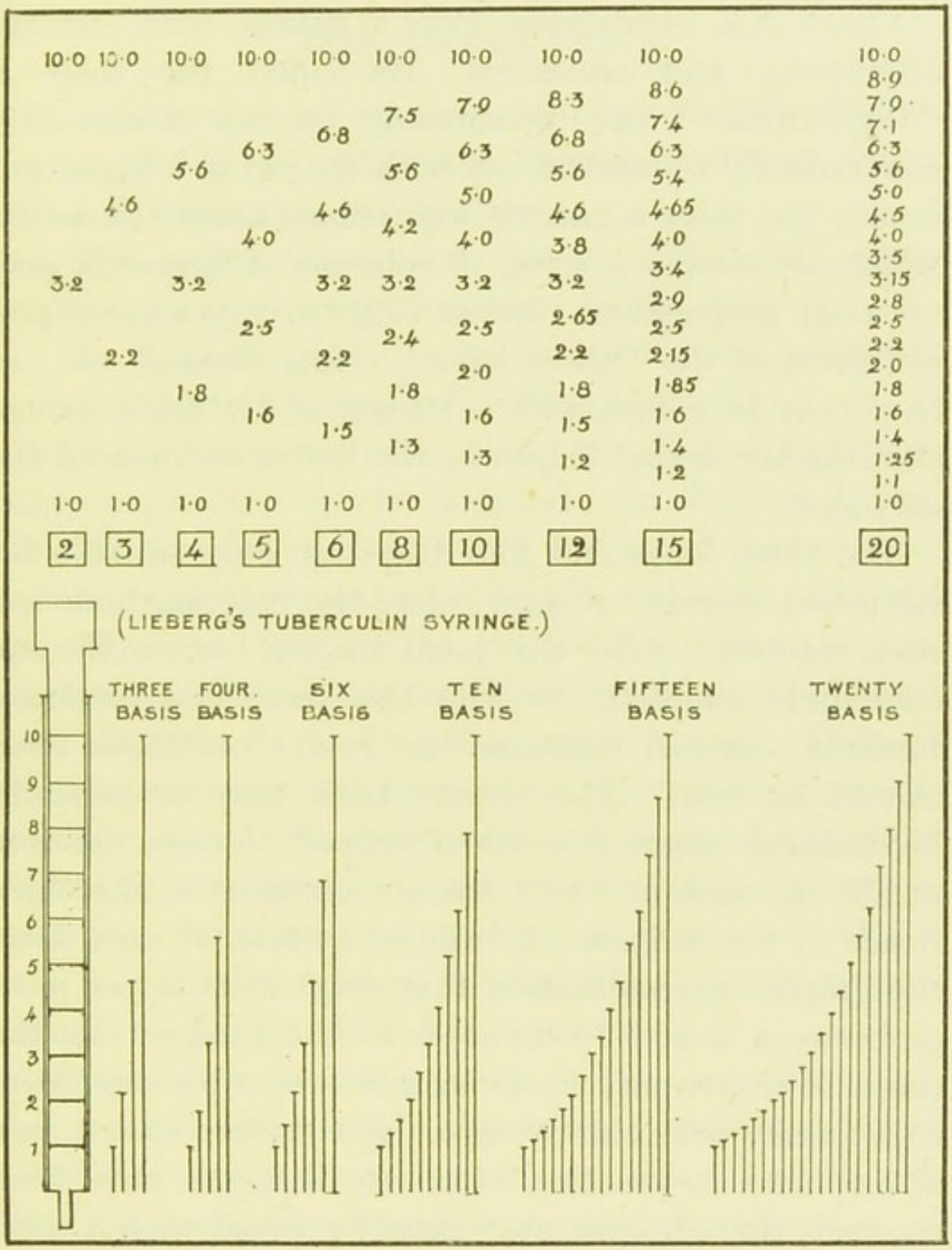


CHART XX.—Scheme of dosage in geometric progression. In any series each dose is the same multiple of the preceding one. Above: the numerical values in divisions of the syringe. Below: the same given graphically in length of the barrel.

many doses of a particular dilution will be used and refer to this number on the scale to find the exact doses.

Chart XX reproduces Pope's figures with certain alterations and omissions. He called the scale a "logarithmic" one, presumably because it can only conveniently be worked out with the aid of a logarithm book ; but there is nothing logarithmic about the results which are simply a series of columns of figures in geometrical progression. Below is given a graphic representation of the "three basis," "four basis," etc., as they may be called, with a tracing of Lieberg's syringe showing the actual length of the barrel and size of the divi-ions.

The three basis and four basis are only suitable for the rapid increase of dose before the reaction limit has been reached. After this point the ten basis is the one commonly adopted. If with this there is a tendency towards repeated reactions the twelve or fifteen basis should be tried. The twenty basis may occasionally be desirable where it is found difficult to raise the dose at all, but such an event has not occurred in the experience of the writers. It will be evident at once from the graphic representation that only in its upper part, or between 5 and 10 divisions of the syringe, can the doses of the twenty basis be measured with any claim to accuracy with this syringe. If therefore such a case is met with in practice, after ten divisions have been reached, the administrator should proceed with a solution only twice and not ten times as strong, giving first five divisions and then proceeding as before with 5·6, 6·3, etc. Sahli has elaborated a dosage with a multiple of two instead of ten, to which reference may be made.

THE INTERVAL

The interval is as we have seen the crucial point in the production of tuberculin tolerance and is determined by balancing two factors—

1. The second dose must not be given until there has been an immunising response to the first.

2. It must be given before the tolerance produced by the first has returned to its original level.

In determining the first point both clinical and laboratory experience can be adduced. In the first tuberculin era doses were given every day and it was evident in some cases there was no adequate response, although probably even then in the majority of cases the response was sufficient and the febrile reactions diminished from day to day. In other cases a summation of reactions occurred and resulted in fever of continued or remittent type. Nowadays the majority of clinicians work with an interval of from two to five days, with a preference for three to four days, or injections twice a week. And the interval is generally lengthened to a week after a dose of 10 has been reached.

Laboratory experience points in the same direction. The negative phase has in the writers' experience never lasted longer than three days in any instance where the dose was carefully chosen with due consideration of the clinical factors.

Opsonic estimations carried out by one of us have indicated that the negative phase tends to shorten during the production of tubercular tolerance, and that even with effective immunising doses it may be twenty-four hours or less. On the other hand tolerance, after

reaching its maximum for any dose, falls rather rapidly during the early part of the course, and an interval of three to four days cannot be exceeded. But after the doses have reached a certain level, the interval can be lengthened. This is best illustrated by the final stage of a tuberculin course, when it is found that the maximum dose can be repeated at an increasing interval, up to a month or longer, without a return of reactivity.

The following is a summary of the intervals in the practice of various clinicians :—

Twice weekly for the smaller doses : Hamman and Wolman, J. B. Hawes, J. A. Miller, Wilkinson, Litzner, Möller, Neumann, Sahli ; increasing to a week or longer with the larger doses.

A shorter interval than half a week for the smallest doses : Bandelier and Röpke, Philippi, Römisch.

We advise starting with an interval of half a week and continuing with it until the reaction limit has been reached and passed. When there is clear sailing again and a dose of 10 has been reached the interval is increased to a whole week, returning always to half a week if difficulties are encountered. When the maximum dose has been reached the interval should be gradually increased to ten, fourteen and twenty-one days, and finally repeated once a month as long as the treatment is continued.

THE FINAL DOSE

In various contexts we have spoken of increasing the dose of tuberculin over a prolonged period, without arriving at any conclusion as to the size of the dose

which is to be reached in any particular case. The considerations determining the size of this final dose may be stated as follows :—

1. To continue to produce a series of adequate immunising responses over a sufficient time.

2. To produce a sufficient degree of tolerance to counterbalance any possible auto-inoculation.

3. To maintain this tolerance over a length of time sufficient to allow of an entire quiescence of the disease.

1. In many cases after an initial stimulus to the natural healing processes has been given by the tuberculin, these processes are adequate to cope with the disease and it is unnecessary to rise to a large dose at all. There are on the other hand sluggish processes which need repeated and prolonged artificial stimulation, and in these a larger dose must be reached before the course can be suspended.

2. The size of an auto-inoculation must vary within wide limits according to the extent of tubercular tissue and its relation to the blood stream. The amount of what we may call auto-tolerance is a rough guide to the size of the doses of auto-tuberculin which have been absorbed ; but, as we have seen, tolerance is a product of properly spaced and increased doses such as can hardly occur spontaneously except under the influence of " graduated labour." The measure of auto-tolerance is the dose at which reactivity is first encountered. And in disease with marked symptoms the point at which the symptoms first begin to improve (and the point may be a very definite one) marks the dose of injected tuberculin which has reached the size of an auto-inoculation. It would be helpful to know the

value of an auto-inoculation in terms say of **T**. Those with experience of the treatment of moderately severe and advanced cases find that improvement may sometime be delayed until a dose of **T** 100 or more has been reached.

3. It is obvious that tolerance should be increased a little beyond the immediate necessity of the moment, to have as it were some in hand for emergency ; and it would probably be a good rule to increase it to a dose tenfold that required to obliterate the effect of auto-inoculation.

Allusion is frequently made to an " optimum " dose in the course of specific treatment, meaning apparently a dose which produces satisfactory results without having to be increased, at all events for the time. In most cases this is probably the point at which reactivity is encountered and adequate immunising responses begin (*see* p. 98 and Chart XIX) ; and as we have seen it is then necessary to increase the dose more slowly, possibly even so slowly that a twenty basis is necessary ; but for all that it should be increased, tolerance is yet insufficient.

These considerations will generally give some clue to the final dose to be reached, but it is still necessary to fix some limit in those cases in which the course has indicated no point to stop before. This limit has generally been placed at 1,000 for either **T, BE** or **TR,** being 1 c.c. of the original solution. It is difficult to find any justification for this dose, which appears to have been chosen as the largest quantity of the stock tuberculin which can conveniently be administered without refilling the syringe. There is a very large consensus

of opinion that equally satisfactory results have been obtained with one-tenth this dose, or 100 ; and it is quite credible that the apparent extra advantage of the higher quantity may consist solely in the longer time during which the patient is under observation and control and tuberculin tolerance persists. It seems to the authors that these ends would be better secured by insisting in every case on keeping the patient under observation after the end of the course and on renewing the specific treatment if it seems desirable.

On this point Petruschky (Danzig) has always laid special stress. From his experience in association with Koch in Berlin he came to the conclusion that it is rarely possible to produce the maximum benefit from tuberculin in a single course ; although Koch spared no pains to assure this on account of the difficulty of keeping out-patients under observation for a second course of treatment. He accordingly worked out what has since been always known as the " Etappen " method, Etappe being a military term denoting a day's march ; the method consisting accordingly of a series of marches separated by halts. The maximum dose of any series he fixed at 50 to 100. Treatment and interval alternate, each of about three months' duration, and the whole course lasts some two years.

The writers consider that this serial method is not an aim in itself, but that the longer period of observation and control is very desirable ; and Petruschky's method may sometimes be the best means of attaining this.

Larger doses than 1,000 have been given by a few clinicians and for the most part abandoned again.

On the authority of his son's statement Götsch gave up to 6,000 or 8,000 of T ; and Schlossmann even gave 20,000 (20 c.c.) to children. It is not certain that any one injects more than 1,000 now ; and the tendency has been for those who give as much as this to reduce the dose rather than for others to come up into line with it.

Stating the practice of various authors categorically we find :—
More than 1,000, only Götsch, Schlossmann.
Reach 1,000 in nearly every case, Bandelier and Röpke, M. Wolff, Löwenstein (500), Cevey, Litzner, Wilkinson.
Reach 1,000 in many cases but strictly individualise and stop at the "optimal" dose in other cases, Hamman and Wolman, J. A. Miller, Möller, Römisch.
Stop at 50 or 100, Lüdke, Neumann, Turban.
At a smaller dose, 3 Wolff-Eisner, 1 Rothschild.

We conclude :—

1. That the dose should be increased until at least tenfold the quantity at which reactivity is first met has been given.

2. To stop at 100 where no indication has occurred to stop before.

3. Only to give more than 100 :

(*a*) in an advanced case where symptoms have not improved up to this dose,

(*b*) when the patient cannot be kept under observation.

4. Not to exceed 1,000 in any case.

DURATION OF TREATMENT

The length of a course of specific treatment cannot be foreseen. The average time given by most authors is

six to nine months. Of this time the first three months is the most important, as it is then as a rule that the difficulties occur and are overcome. Of the last 8 cases of Stadium I treated by one of the writers with **TBk** an average period of twelve weeks was required to increase from an initial dose of ·003 up to a mean final one of 96 ; the average number of injections being twenty-four and no general reaction occurring. The cases were all under close observation although not all of them in a sanatorium.

More advanced cases, or those of long-standing, will naturally require a longer period of treatment. In a recent case, the time from the onset of symptoms, or the probable time during which the disease has been active, may be taken as a rough guide to the time required for treatment.

The method adopted has a great influence on the duration of treatment. If reactions are ignored it is easy to reach the final dose with much greater rapidity than where they are utilised. Neumann for instance has given the duration of an ideal case as 37 doses @ 4 days = 148 days ; but adds that the ideal case never occurs in practice ! In the method of avoiding reactions many months may be passed before a real immunising dose has been reached ; and on the lines of Denys and Sahli the course necessarily lasts for years. In some cases this is an actual advantage in itself, in that observation and control are thus prolonged ; but L. Spengler points out that in other cases patients are liable under these conditions to inject themselves, and that in point of fact Denys acquiesces in this.

The duration of treatment on the method which

we recommend is intimately bound up with the attainment of the particular final dose which has been found desirable. Other considerations have guided administrators, and some of these may be found of help. They can conveniently be grouped under three headings :—

1. **Biological.**—Jochmann uses the obliteration of the cutaneous reaction of v. Pirquet as a test of the termination of treatment, finding that this sometimes was delayed until T 500 had been injected. Beninde also injects on Koch's recommendation until the cutaneous reaction is no longer given either with undiluted T or BE of threefold strength. It is difficult to see what these tests prove except that tuberculin is tolerated, which is already being demonstrated by the treatment ; it appears evident that if tuberculin is tolerated internally, it will be also tolerated by the skin. It is unlikely that help will be obtained in this way.

2. **Symptomatic.**—Treatment should be continued so long as symptoms continue to improve. This indication is vague but real. As long as there remains any sputum or any bacilli in it there is still a possibility of tuberculin doing something more. Schnöller in discussing this aspect of treatment with BF thinks that the length of time has more to do with the symptomatic indication than attainment of any particular dose.

3. **From Experience.**—Experience shows that it is wise to continue some little time after the sputum and other symptoms have disappeared. Latham says that as it is not known how long the immunity lasts after the injections are stopped it is well to continue after the apparent maximum of gain.

We may summarise thus :—

1. The duration of treatment varies from three months upwards.

2. It depends largely on the method ; if that of utilising reactions is adopted, the duration is the time required to reach the individual final dose and to maintain it as long as is necessary.

3. Treatment should continue as long as symptoms improve or active disease is present ;

4. And as a precaution for some time after.

REPETITION OF THE COURSE

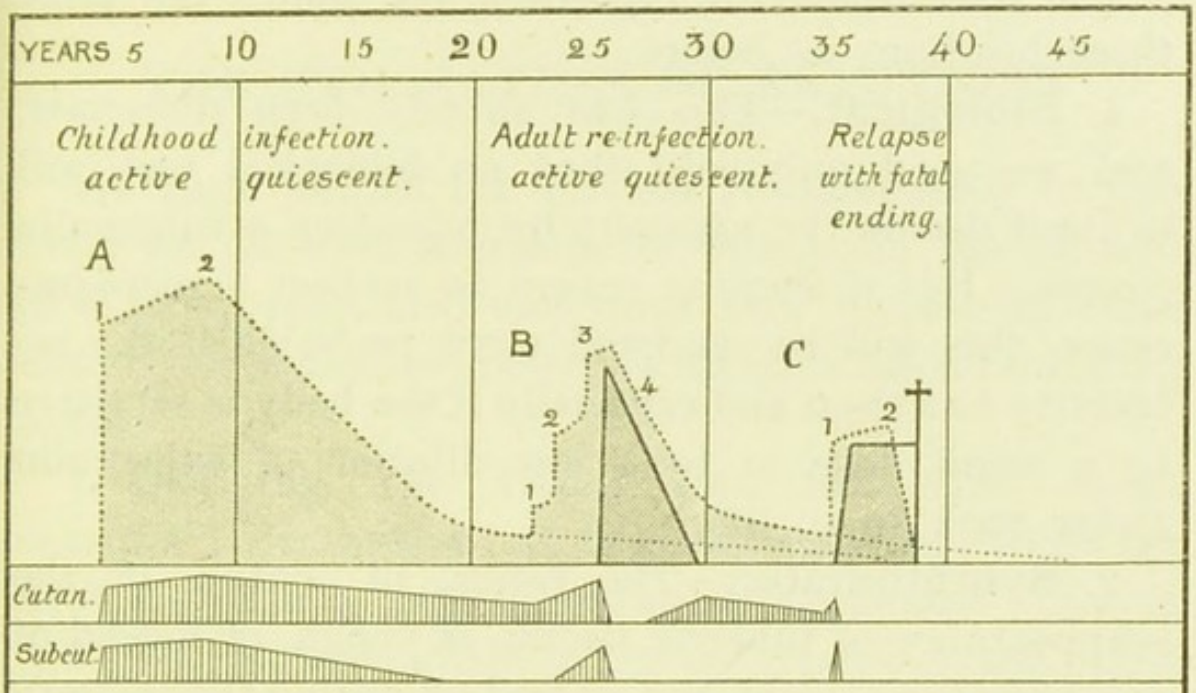
After the course of specific treatment has been finished, the case being still under observation, it remains to inquire what are the indications for a repetition of the course. We will assume that the primary course produced an adequate series of immunising responses and a degree of tolerance under which the disease became quiescent. After treatment ceases tolerance falls and on the rapidity of this fall depends the time at which reactivity to a moderate subcutaneous dose of tuberculin returns. At the same time, if the disease remains quiescent, sensitiveness falls likewise, and it is quite probable that in a favourable case the sensitiveness may fall nearly as rapidly as tolerance, and that the difference between them, or the reactivity, may never return to the extent of a positive subcutaneous test. But two other possibilities are present :

1. A recrudescence of the disease may increase the sensitiveness again and give rise to a return of reactivity.

2. Tolerance may drop so fast in relation to sensitiveness that reactivity returns without any recrudescence of the disease.

These alternatives are illustrated graphically by Chart XXI opposite, which shows the variations of sensitiveness and tolerance throughout life for an individual case of tuberculosis.

We cannot therefore follow those clinicians, and there are many who regard a return of reactivity as the criterion for the repetition of the course. Petruschky, for example, who is the father of the serial treatment, states that, where disease is active, reactivity returns in three months and that the specific course should then be recommenced. Bandelier, Möller, Röpke and Wilkinson give their patients a test dose of T 10 subcutaneously every three months and recommence tuberculin treatment where a reaction occurs. This procedure has the merit of simplicity and would replace the necessity of any exercise of judgment; but we regard it as certain, alike in theory and practice, that reactivity may return without recrudescence of the disease and without any necessity for renewed treatment. The converse is also equally true. Hammer cites a case of a woman of 25 in whom after a tuberculin course ending with T 1,000 the subcutaneous test remained negative, but who nevertheless broke down again after three years. And it is very probable that in chronic progressive disease tolerance is kept up by auto-inculation and its retention is not necessarily a favourable sign. Finally it is a matter of common knowledge that reactivity is lost where the organism fails to respond to a severe reinfection.



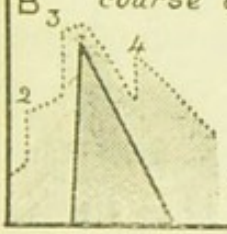
The cutaneous test is positive when as much sensitiveness is present as is represented by 2 mm. above the base line of the diagram; the subcutaneous test when 5 mm. present: and not neutralized by tolerance.

A. *Childhood Infection at 4 yrs. (1) Sensitiveness rapidly developed and rises while the disease is active until 8 yrs. (2) Then falls steadily until at 18 yrs. the subcutaneous test is negative, and at 25 yrs. the cutaneous, unless reinfection takes place (light dotted line)*

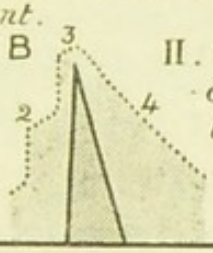
B. *Adult Reinfection in a series of relapses (1) (2) & (3) between 22 & 25 years. Subcutaneous test positive again until neutralized by the rising tolerance of a course of tuberculin treatment. At (4) tolerance has dropped sufficiently below sensitiveness for the cutaneous (but not the subcutaneous) test to become again positive.*

C. *Relapse (1) with sudden fall of sensitiveness (2) in the final stage when all tuberculin tests are negative.*

Illustrating return of positive subcutaneous test after course of tuberculin treatment.



I. *A fresh relapse (4) occasions a sudden rise of sensitiveness.*



II. *Without a recrudescence of disease tolerance falls more rapidly than sensitiveness.*

CHART XXI.—Illustrating the development and variations of sensitiveness during life, its relation to tolerance, and to positive cutaneous and subcutaneous tests.

The indications for repetition fall under the same three headings as before :—

1. **Biological.**—This has already been discussed, and we need only add that no biological test will in itself decide the necessity for repeating a tuberculin course. But if there is reason to suspect a recrudescence, this will be rendered more probable if the reactivity has risen and especially if the body is sensitive to a small dose or to a low dilution of tuberculin (refer back to p. 62).

2. **Symptomatic.**—The return of sputum or the reappearance of tubercle bacilli, of cough, or indeed of any symptoms which had passed off during the primary course, should suggest a secondary one. In those cases in which the primary course had apparently not exerted the maximum possible benefit, it should be repeated after an interval.

3. **From Experience.**—Clinical experience of those who have tried serial treatment is strongly in its favour. The family practitioner who can keep his patient under observation may bear it in mind as an alternative : and it certainly may have its place where for any reason the primary course has been suspended before the desirable final dose of tuberculin has been reached.

Method.—For the repeated course the lessons of the primary should be taken to heart. It will be known at what stage reactivity is likely to be met ; and the dose can generally be safely doubled up to this limit. After it has been reached progress can probably be on the six basis if the ten basis was used before and the whole course last perhaps half or two-thirds the time of the primary.

THE UTILISATION OF REACTIONS

We have termed the method recommended in this book for the administration of tuberculin the method of utilising reactions, and must now discuss in some detail how reactions are to be utilised in the immunising course.

1. **Utilising the Local Reaction.**—The local reaction is in itself of no importance except in so far as it indicates a local formation of antibodies; but it is a most valuable guide to the occurrence of the other reactions. The local reaction may be situated in the subcutaneous tissue where the tuberculin was placed by the syringe—known then as the depôt reaction, or in the skin itself—the needle-track reaction. The slighter grades of depôt reaction are only appreciable by picking up a fold of skin between the finger and thumb; but even these are of importance. The needle-track reaction is of less significance as it is the result of a trace of tuberculin remaining in the punctured skin giving rise to an intra-cutaneous reaction, known to be the most sensitive of all the tuberculin tests.

The occurrence of a local reaction of even the slightest grade should always be taken as evidence of the limit of tolerance being reached and of a therapeutic action being exerted. When it occurs the dose should not be increased, nor should the interval be extended, but the same dose should be repeated at a different site, when one of three things may occur :—

(1) The local reaction may be less or may be absent.

In this case repeat the same dose again and continue to do so once more after an injection has caused no trace of reaction; then increase in a ratio not greater than the ten basis.

(2) The local reaction may remain the same. In this case the same dose is to be repeated indefinitely. There need be no fear that time is being wasted, the local reaction is itself a certain indication that the dose is not inert. At the same time the lesion should be very carefully examined for evidence of focal reaction and this will in such cases often be found.

(3) The local reaction may increase and a general reaction occur. This is much the least common of the three alternatives and rarely occurs except at the very beginning of the course. In fact it may almost be taken as evidence that the proper dosage has not been found, and that probably the rise has been too rapid. Or some unnoticed intercurrent affection has reduced the reactivity which has again asserted itself. Measles is known to do this in a very marked degree.

And here we may usefully allude to the phenomenon of **hypersensitiveness,** described for the most part by adherents of the method of ignoring reactions, who assert that it is specially apt to occur with the repetition of the same small dose. They state that it is a serious complication, that it may detrimentally affect the general health, and sometimes render the further conduct of specific treatment impossible. The theoretical aspect of the question has already been discussed in an earlier section (*see* p. 23) where it was seen that the repetition of the same initial dose may produce an increasing sensitiveness with insufficient tolerance and

an increasing reaction; and further that this result was not produced on starting with a smaller dose and working up, when tolerance was developed *pari passu* with increasing sensitiveness. This so-called hypersensitiveness then is really a result of commencing with too large a dose and it does not occur when the principles of the method we recommend are understood and put in practice.

Denys' experience bears out these views; he finds the causative factors of hypersensitiveness to be :—

1. Beginning with too large doses,
2. Increasing the dose too rapidly,
3. Or increasing the dose after a reaction,

which are all conditions under which sudden alterations of sensitiveness are likely to occur. Of the deliberate use of this same hypersensitiveness in diagnosis mention has already been made. Koch observed that where a dose of tuberculin given subcutaneously for the purpose of diagnosis produced a slight local without general reaction, the repetition of the same dose was practically certain to produce a stronger reaction, and this sequence was of great significance in diagnosis. Rolly has found this hypersensitiveness occur when the interval between the injections was five to eight days, which is as we have seen too long a period for the satisfactory development of tolerance to small doses.

In discussing the local reaction mention should be made of the fact that there are certain **non-specific factors** in its production :—

(1) The volume of the fluid injected is not without influence : the same dose of tuberculin contained in

1 c.c. is more likely to produce a reaction than if it were contained in but five or two divisions. It is the other way with the general reaction and Sahli especially has shown the greater probability of this occurring with the same dose in a greater concentration. The writers have however not been able to confirm this.

(2) A big or a blunt needle is more likely to produce local reaction, and this is an additional reason for using fine platinum-iridium needles and keeping them sharp.

(3) Sepsis need hardly be mentioned. It is so easy to be aseptic and the precautions are so simple that no one would risk being anything else.

To sum up: We believe that if the local reaction be carefully studied in a therapeutic course of tuberculin properly dosed, it will lead to the avoidance of general reactions in any but exceptional cases.

2. **Utilising the General Reaction.**—After what has been said it will be evident that a general reaction is not a very frequent occurrence in properly conducted specific treatment. But a reaction is not necessarily manifested on the chart by a rise of temperature. Latham and Neumann have independently called attention to a characteristic flattening of the chart, occasioned by the obliteration of the normal daily variation for one day or sometimes longer. The latter has aptly termed this a "depressor" reaction and it indicates a dose which has been efficient and not excessive. Even under the old régime in 1891 Heron noted in one case a fall of temperature after some injections of the series. The depressor reaction cannot be counted upon as a clinical control, but when it is seen it gives an added sense of security.

On the other hand the febrile reaction requires :—

(1) Firstly, **rest.**—And it is safest to let the rest take the extreme form of " typhoid rest " recommended by Paterson in spontaneous reactions. The patient is kept absolutely to bed and not allowed to get up until the temperature has fallen again. This applies to all cases but *a fortiori* to reactions in advanced or febrile cases, in whom the rigid observance of this measure may make the whole difference between a helpful incident in recovery and a dangerous complication.

The writers are aware that both in Germany and in England closed cases of pulmonary tuberculosis are being treated in ambulant practice with dose after dose producing severe general reaction, for which the patient has lain up at home ; and that these cases for the most part do well and the practice appears to be unattended with risk. The evidence is not complete that there is no risk, even though it certainly is small. And if the severe febrile reaction were a frequent and necessary part of a specific course it could hardly be treated by typhoid rest. But, as we have said, the febrile reaction is the exception in properly conducted tuberculin treatment and can therefore be accorded exceptional treatment.

(2) Secondly, **reduction in the Dose.**—As soon as the reaction has completely passed off, a smaller dose should be given which it is quite certain will not cause a reaction. One-tenth of the reactive dose, i.e. the same quantity of the next dilution, will serve in most cases. The increase is then on the ten basis until the point is passed again.

3. **Utilising the Focal Reaction.**—It is rational to suppose that the local gives a fair clue to the occurrence of a reaction at the focus of the disease. Unless it is visible, it is only when the focal reaction attains some intensity that it is appreciable to physical examination ; and this is generally the case when a general reaction is produced. We know already that the latter is caused by about ten times the dose required to produce a well marked local reaction.

Hence with the method here recommended, a focal reaction giving rise to appreciable physical signs is uncommon, and it is much more frequently evident in an alteration of the sputum, generally a decrease followed by a more prolonged increase, and less often some blood staining (*see also* p. 132, evidences of success).

But what we may call the subclinical focal reaction, in the form of a gentle hyperæmia producing a freer lymph flow through the focus with more abundant antibodies, is one of the principal factors in the treatment, and it is towards utilising these beneficent reactions that all effort is directed and every precaution taken to prevent them becoming harmful.

THE REACTION AS A SOURCE OF DANGER

The **local reaction** may be a trifling inconvenience but cannot on the principles enunciated here be a serious discomfort, much less a danger.

The **general reaction**, which is principally a toxic effect on the central nervous system, cannot in the grade here recommended do serious harm. In a

brain of less than normal stability the reaction may of course produce unpleasant symptoms: an attack of migraine may be started, neurasthenic symptoms increased, a fit caused in an epileptic, and the like. Headache, insomnia or depression may be much accentuated in those liable to them. But all these are normal incidents of a slight upset of such a nervous system and can scarcely be regarded as serious dangers. Only occasionally will the nervous symptoms be severe enough to demand a suspension of treatment, but cases do occur in which the tuberculin, as Turban suggests, has an action on nerve tissue akin to that of tetano-toxin.

Other manifestations of the general reaction have been described as "complications" of tuberculin treatment. A rigor may precede the rise of temperature; during the fever there may be pains in the joints; jaundice or a purpuric or scarlatinal rash may appear; or albuminuria be present. These are all evidences of a severe toxic dose having been administered and point to a very faulty method.

An exception must be made however for transient albuminuria. Its great frequency in tuberculosis apart from specific treatment has already been mentioned, and the appearance of a trace of albumen after an injection is probably a very frequent occurrence. The practitioner should however always be on his guard and remember that this may be due to a focal reaction in a tubercular kidney.

The **focal reaction** is not only one of the principal factors in tuberculin treatment but it is also the one possible source of serious danger. On this danger it is necessary just to touch, since the borderland between utility and danger is not a broad one; although we believe that the precautions mentioned in the last paragraph, carefully and thoughtfully applied, will avoid the danger altogether.

The dangers which have been adduced are in general terms :

1. Mobilisation of the tubercle bacillus.

2. Local extension of the disease.

1. Virchow was responsible for the conception of the tubercle bacillus, previously lying quiet and inert in the lesion, being drafted out to various parts of the body as the result of tuberculin reactions ; the word " mobilisation " passing into common use as the term descriptive of this dreaded result. The conception is now scarcely more than of historical interest, especially since evidence has accumulated that tubercle bacilli freely circulate in the blood in all stages of the disease without giving rise to miliary tuberculosis.

We should not be too ready to attribute every misfortune occurring during treatment to the tuberculin itself. J. B. Hawes mentions the onset of meningitis two days after an injection of **BF** 1 and Denys a complementary instance of the suggestion of **BF** to a patient being followed by the same symptoms.

2. There is every reason to expect an extension of the disease when a violent reaction occurs in a focus surrounded by tissues of lowered resistance and invaded by inflammatory products when these tissues, besides being of low vitality, are deficient in protective antibodies. That these conditions, however, are seldom present is testified to by the rarity of such an extension even when focal reactions are carelessly caused. There are still living numbers of healthy exponents in their own persons of the fact that the most careless of all focal reactions in the era of 1890–1 led to delimitation and encapsulation rather than to extension of the disease. In the ordinary fibro-caseous form of phthisis it seems as though the focal reaction may be counted on to stimulate the fibroid process.

In practice two conditions should make the clinician hesitate before provoking a focal reaction of even slight grade :

1. The presence of much consolidation, which may or may not be of purely tubercular origin. The focal reaction appears to accelerate the softening of such areas and the formation of cavities. But even here the question of any causal relation is often in doubt,

since the breaking down may be the inevitable natural history of the process.

2. Where mixed infection is certainly present. To this subject a special section is devoted later on (*see* pp. 142–148).

In both these conditions tuberculin if administered should be by the method of avoiding reactions.

The **secondary general reaction.**—The focal reaction which has become a danger manifests itself generally in the form of a secondary general reaction. Instead of the short sharp swing of temperature so characteristic of the ordinary general reaction, the temperature with or without an initial oscillation rises for a number of days, or oscillates in a series of smaller waves before falling. Such a feature of the temperature chart is a warning in itself. Pottenger, Crowe and Hort have called attention to various aspects of it, and J. A. Miller has noted its serious significance in an out-patient practice. Denys gives interesting illustrations of charts ending in regularly hectic temperature, developed by neglecting these secondary general reactions. On the laboratory side this is the "prolonged negative phase" or frequently the "summation of negative phases," where no immunising response follows. It is not a feature of the tolerance method but a result of careless dosage.

Treatment of the secondary general reaction. If rest is the indication for the fortuitous primary general reaction it is tenfold indicated in the secondary general reaction and should be of the most rigid character. The general rest of the body should be supplemented by all known means of producing local rest of the reacting focus.

In accordance with Wright's observation that in the prolonged negative phase produced by a dose of tuberculin, the exhibition of a much smaller dose may raise the opsonic power again ; so Crowe and others have found that the correct treatment of the excessive focal reaction is the injection of a minute dose, it may be ten or a hundred times smaller than the original dose. This fits in well with theory, for tolerance has been reduced, not increased, by the excessive dose, and the successful smaller dose is not really below the reactivity limit but just enough above it to produce a satisfactory immunising response. C. Spengler called such a dose a " decoy."

THE COURSE OF TREATMENT : EVIDENCES OF SUCCESS OR FAILURE

Some contend that there is no risk in the administration of tuberculin in suitably selected cases, and that the course can be persevered with in spite of any difficulties. This is going too far, for to suggest that harm is impossible is rather to discredit the efficacy of the remedy altogether, since all potent drugs have certain risks and drawbacks to their administration. If a tuberculin has been so manipulated that it may be used without discrimination in any case, the question at once arises whether it has not lost its specific properties.

Something has been said under reactions about the evidences of success or the reverse, but there are other more general indications to take into account, and these

may be divided into—such as can be observed by the patient himself ; the results of clinical observation and measurement ; and certain laboratory methods.

1. **Subjective Evidences.**—It is remarkable what a beneficial effect on the **appetite** may be apparent at once from small doses of tuberculin ; this improvement doubtless coincides with the first adequate immunising response, and many patients can accurately outline their immunisation curve by their feeling of fitness or the reverse. On the other hand, loss of appetite with nausea or dyspepsia, if more than the temporary result of a particular injection, should give pause and lead to a reconsideration of the dosage. In cases with spontaneous auto-inoculation in which symptoms such as night sweats, headache, anorexia and the like are present, these should tend to improve under the treatment, even if slowly. Occasionally the treatment gives rise to mental depression, or an exaggeration of " nervousness " accompanied by an unreasoning dread of the injections. Under such circumstances the course should be broken off.

2. **Objective Evidences.**—The most easily taken measurement is the **body weight,** and this is the best of guides. It has often been the subject of comment, especially of late by Wilkinson and Neumann, how even a diagnostic injection of tuberculin, resulting in a marked febrile reaction, may cause an increase in weight. And where hygienic treatment alone has hung fire, an indication of the helpful influence of tuberculin is often given by an immediate increase in weight. This does not of course apply to patients who have already put on a heavy panniculus as the result of rest and

feeding ; but in general, and especially in cases of difficult nutrition, rise of weight is a most valuable indication of the success of the treatment.

Conversely **loss of weight** is always a serious symptom, and if persistent should lead to a reconsideration of the dosage and a careful review of the whole case. Möller relates as a not uncommon experience that the loss of weight does not prevent the course being carried through to large doses but that there is no clinical improvement to record. But this is on a method of ignoring reactions and it is probable that in these cases there is no adequate immunising response occurring ; the tuberculin injected is not even being activated. Such cases with deficient sensitiveness should not be treated with increasing doses of tuberculin but rather on hygienic lines ; and Neumann has seen them regain their reacting power with a course of atoxyl, after which the specific treatment could be resumed.

Another very favourable sign is a reduction in the pulse frequency, especially where the frequency has been a result of toxic absorption. Decrease of expectoration should be looked for, although at first there may be a temporary increase in quantity. It has often been noticed that when effective doses of tuberculin are being given, there is an increase in the number of bacilli in the sputum, and even in the amount of elastic tissue. We have noted this in the absence of any appreciable focal reaction, but it can hardly be explained except as a process of exfoliation in a minor degree. Any one who has systematically examined large numbers of sputums will have been struck by the length of time that the presence of elastic tissue persists, occurring it

may be months or years after complete quiescence of the disease.

Absence of disturbing complications is an important point. Bandelier remarks how in a large industrial sanatorium it was a matter of common observation that the patients undergoing tuberculin treatment kept about while a certain proportion of the others were constantly confined to bed by minor ailments. American authors note the disappearance of dysmenorrhœa, possibly as the expression of improved nutrition.

3. **Evidences from Laboratory Methods.**—We have dealt so far with observations involving clinical apparatus of a simple character. There are certain controls of a more elaborate nature which can only be dealt with in a well-equipped laboratory. If these are essential to the conduct of tuberculin treatment, it can only be carried out by the clinician who is also an expert pathologist, or by the two in combination. In either case their prolonged and frequent use would tend to make the treatment more costly and more difficult, and to restrict the scope of its application.

(*a*) The **observation of phagocytosis** in the sputum offers a fruitful field of research on the existence of antibodies in the pulmonary secretion. Löwenstein first called attention to the presence in the sputum of leucocytes containing tubercle bacilli, finding them principally in chronic cases running a favourable course, and during tuberculin treatment. One of us made the observation, confirmed by examination of the sputum from cases under many forms of tuberculin treatment, that phagocytosis was constantly present during the positive phase of the immunising response and absent during the negative; and that its presence might be taken as an indication of a successful course of inoculation.

To demonstrate this phagocytosis the technique is very simple. The film is fixed and stained with fuchsin and methylene

blue in the ordinary way, care being taken not to overheat the preparation and to obtain an adequate counterstaining of the protoplasm of the phagocyte. With these precautions good films may be obtained although a less basic stain such as malachite or methyl green is more certain.

The examination of the sputum must in any case be undertaken at intervals during specific treatment, and it is certainly worth while to spend the small additional time required to determine the presence or absence of phagocytosis. In cases so uneventful as to raise the doubt in the administrator's mind as to whether it is really tuberculin that he is administering, this ocular demonstration will be a satisfaction.

On the favourable import of the phenomenon apart from specific treatment recent work of Pfeiffer and Adler has thrown doubt.

(*b*) On the **opsonic control** the writers can speak with a certain amount of decision as they have both worked at the method in tuberculosis from the time that Sir A. E. Wright introduced it, obtaining consistent and in more than one respect interesting results. One of us first made the observation that the large majority of cases of chronic pulmonary tuberculosis undergoing treatment, as of local forms of tubercle, have a subnormal opsonic content of the blood plasma. Both of us have used it as a guide to specific treatment and have learned much from it of dosage and interval ; but, having applied the knowledge so gained, regard it no longer as an indispensable aid, but in the light of a help in doubtful cases and the clue to difficulties. Latham puts it that the opsonic control has been in the nature of a tutor whose lessons carefully heeded bear fruit after he is no longer required. The opsonic control has shown us that a dose of the highest dilution of Beraneck's tuberculin, producing clinically no apparent result, raised the tuberculo-opsonic index from 0·7 to 1·3 and was the beginning of a successful immunisation. At a later stage of tuberculin tolerance a dose 1,000 or 10,000 times as large produced a very similar immunising reaction with a shorter negative phase ; affording an entire justification of the method of increasing dosage given by observation of the opsonic index. Many more instances could be given of the value and interest of the control ; but the aim of this book is to apply the results of this and other research work to methods of clinical control of wide applicability, whilst admitting that there is still scope for the opsonic control where it is practicable to employ it and specially in the solution of difficult problems.

(*c*) Of other immunity tests the agglutination value served a useful purpose in establishing the efficacy of new tuberculin as an immunising agent, but has proved of no service as a clinical control. Estimation of antibodies by means of complement fixation is yielding interesting results, but the practical bearing on specific treatment has not yet been shown.

We may therefore conclude that, interesting and valuable as are the laboratory controls to tuberculin treatment, there is now a sufficient amount of accumulated experience to make the clinical control sufficient in the average case.

TUBERCULIN IN FEBRILE CASES: ITS ANTIPYRETIC EFFECT

Opinion has long been divided with regard to the employment of tuberculin in febrile cases of phthisis, both as to safety and utility. The decision turns primarily on the origin of the fever, and to a less extent on its degree and duration.

Nature of the Fever.—It would carry us too far to analyse in detail the various types of raised temperature in phthisis and to explain their causation. But it is essential to distinguish as far as may be between pyrexia due to the tubercular process itself, to absorption of its own toxin; and that caused by superadded infections or other accompanying conditions. The distinction will be clearer if the fever is classified somewhat.

1. **Early Fever of Slight Grade.**—In the case of early pulmonary disease as it is wont to come first under observation, there is generally a slight continuous elevation of temperature, amounting frequently to less than 1°F.; in the vast majority of cases this pyrexia yields

within a period of days or weeks to complete rest. Whether tubercle bacilli are present in the sputum or not—in other words whether the disease is open or closed—this pyrexia is due to the tubercular toxin, as can easily be shown by examining a series of opsonic indices during the period of rest. In such a case it would be entirely inappropriate to give tuberculin. There is already a sufficiency of auto-toxin present in the circulation; this is being reduced by the rest; and the time is soon coming at which it will cease. After the temperature has become normal is the time in such a case when tuberculin treatment will have to be considered.

2. **Fever of Higher Grade.**—Certain types of pyrexia are generally held to be indicative of mixed infection, and some authors have suggested that any considerable or persistent elevation is due to other than the tubercle bacillus. It is however most likely that the tubercular toxin by itself may give rise to temperature of continuous, remittent and intermittent types. Hence other criteria than the mere form of the chart must be taken into consideration. Clinically we find that the pure tubercular pyrexia is more amenable to rest and as a rule not associated with other severe symptoms, as headache and sweating. The presence of other organisms in the sputum, especially if in abundance and constant from day to day, will be a valuable indication, but it may be impossible to distinguish with certainty except by examining the blood for signs of antibodies against the one or the other infection.

(*a*) **Continuous Fever.**—It has been shown by Landouzy for his "typho-tuberculose" that a high con-

tinuous temperature may usher in a pure tubercular infection, but we believe that a similar high temperature occurring during the course of phthisis is more commonly due to a pneumococcus mixed infection.

(*b*) **Remittent or Intermittent Fever.**—The distinction in these cases may be very difficult or impossible. The hectic type with daily oscillations of 4°F. or more is probably always due to a secondary streptococcus infection, but slighter grades of intermittent fever are often seen in quite early cases of closed phthisis where the probability of a superadded infection is very remote, and there is rather a direct action of tubercular toxin on the heat regulating centre.

In all these cases of more considerable fever the element of duration is a most important one. In the first instance all other measures will be exhausted that can reduce the temperature before resorting to tuberculin. Landouzy's cases all defervesced without, and it can never be too strongly emphasized what a tremendous influence for good the most rigid application of rest has in these febrile cases. The treatment of mixed infection when there is a reasonable possibility of it being present is dealt with in a succeeding paragraph.

Duration of Fever.—It is generally accepted that an elevation of temperature which has persisted for three months in spite of hygienic treatment is not likely to come down at all with merely prolonging treatment on these lines. And not only does this justify resort to other methods, even if in the nature of a forlorn hope, but affords a very clear field to demonstrate their efficacy. Some of the most careful and painstaking clinicians are confident that in a large proportion of these

prolonged febrile cases the temperature can be brought down to normal by means of very small doses of tuberculin, while others have recorded striking, almost dramatic, defervescence after larger doses producing reactions. At the end of the book are reproduced two charts illustrating defervescence by the two methods.

Type of Temperature equivalent to Fever.—The inverse type of daily variation of temperature, with the highest reading in the morning, is clinically equivalent to fever, and fever of a specially intractable kind. Rothschild mentions that such cases have their maximum temperature in the night, when it can easily be missed, and this surmise has been confirmed by F. Junker with the aid of specially constructed maximum thermometers of such small size that they can conveniently be retained during night in the rectum and read off in the morning. This type of fever is always to be regarded as a warning signal, and where it persists or develops during treatment it is a hint to desist. Latham quotes J. K. Fowler that twenty-eight out of thirty cases who showed this type of temperature at Brompton Hospital died in the hospital or shortly after leaving it. Latham adds that where tuberculin has been of use it has resulted in an immediate alteration of this type of temperature.

Method in Febrile Cases.—Nearly all workers have preferred to use endoplasm tuberculin and there seems special reason in these cases for using a form of tuberculin less readily absorbed than **T** or **TO**, in order to reduce the liability to focal reaction whch is, as we have seen, to be specially avoided where much inflammatory tissue is present.

An exception to this is found in Philippi, whose large experience in febrile cases makes his method worthy of special study. Out of 90 cases of phthisis in all stages, who had had fever for an average period of five and a half months before the commencement of specific treatment, 65 became afebrile with tuberculin. In cases of Stadium I an average of 24 days was required : in Stadium II, 28 days ; and in Stadium III 56 days. He used **TO** beginning with ·0000005, that is to say a dose two thousand times smaller than the initial dose of ·001 suggested in the text for routine use. The dose was increased twice weekly until one having an appreciable effect on the temperature was reached, and this optimum dose then repeated. The highest dose required to produce a definite antipyretic effect was ·00003. A careful watch was kept all the time for evidence of focal reaction.

We shall however hardly do wrong in preferring the bacillus emulsion or the still more insoluble **TR** in these cases, as we shall obtain with these preparations an effect at once more gentle and more prolonged. Philippi's dose of half a millionth of a c.c. requires a dilution of a thousand times greater than the lowest that we have given, and demands two further stages in preparing it. Of **BE** the initial dose may be ·0002 or two divisions of (6) increased very slowly at intervals of seven to ten days up to a maximum of ·001. Jannsen in four carefully recorded cases of reduction of fever of several months' duration used doses of **BE** from ·0002 to ·0008. Turban, Möller and Römisch have all obtained good results in some proportion of cases on the same lines. Sahli lays stress on combining the tuberculin in febrile cases with reduced nourishment and salicylates ; this might be tried as a temporary expedient.

We would suggest for the treatment of febrile cases a scheme somewhat as follows :—

1. A period of complete (typhoid) rest in bed, combined if necessary with small doses of antipyretics, of

which pyramidon and cryogenin most deserve a trial, until the temperature falls below 100°F.

2. Then a trial of small doses of **BE** or **TR** as indicated above. It may be added that **Tp** has been highly recommended for this purpose.

3. If unsuccessful in producing any effect after three or four weeks, a careful examination of the sputum for evidence of mixed infection. If found this should receive particular attention (*see* p. 144).

4. If absent rather larger doses of **TR** or **BE** should be tried experimentally for a depressor effect (*see* p. 124); and if this is obtained the same dose repeated after the effect begins to pass off.

5. Finally, a trial of horse-serum in some form, given by the mouth or rectum. It is a striking fact that as good results have been reported by competent observers with non-specific sera, as with so-called specific ones, and the conclusion is very plausible that it is in each case the normal untreated horse-serum which is the potent factor. On the method of its action the work of E. C. Hort and others on anti-trypsins may throw light. But the serum can at present hardly be administered other than empirically, and has generally been given in doses of 5 or 10 c.c. by the mouth, whether combined or not with the oral administration of tuberculin. The tuberculin given in this way may be less liable to cause a focal reaction (Latham and Inman).

Drastic Method by the Production of Reactions.—We reproduce at the end of the book a chart, No. XXVI, of an aggravated febrile condition where the temperature was brought to normal by the production of a series of severe reactions.

The case was under the care of Litzner at Schömberg and had been febrile for months with temperature varying between 100° and 102° and physical signs of extensive catarrh of both upper lobes. Ten doses of **BE** during a period of eight weeks brought the temperature down to normal, after which the patient returned to his work as an official (Details kindly supplied by the author). The method was a sequence of doses beginning with one already large and proceeding by jerks up to one a hundred times as great. The actual doses in this case were 0·4 (twice) 0·8, 1·6, 3·2, 8, 20 (twice), 40 (twice). Apropos of his method Litzner quotes with approval Cornet's remark that in avoiding the dangers of the first tuberculin era the striking successes had also been eliminated.

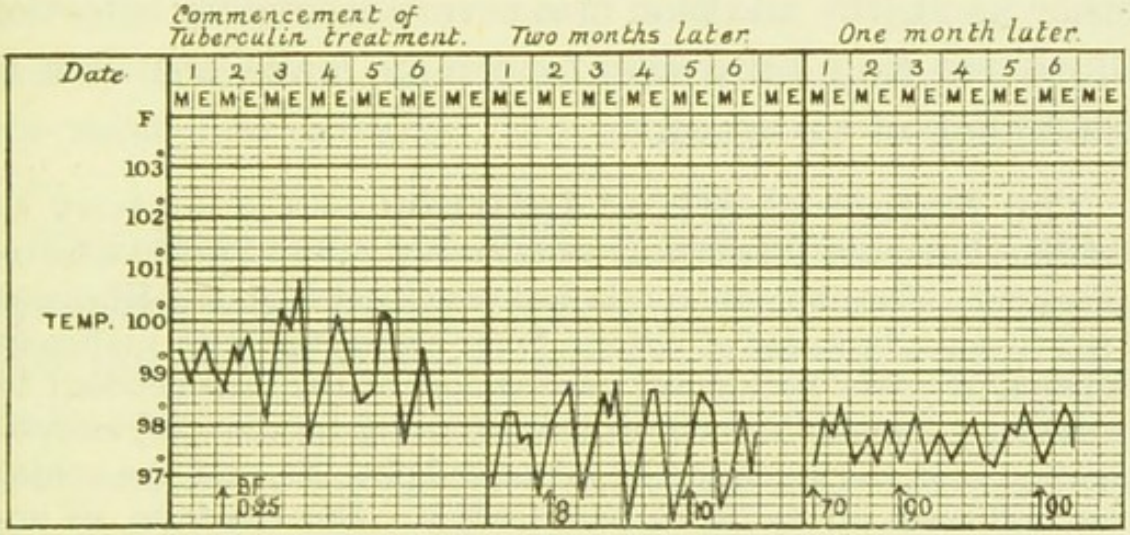


CHART XXII.—Effect of tuberculin in diminishing first the raised mean temperature and then the daily oscillation. (From Denys' *Le bouillon filtré*, p. 50.)

The writers would add therefore to the scheme—

6. In persistent cases of considerable pyrexia in which no result has been obtained by other less drastic methods, it is justifiable to try the effect of large doses of tuberculin producing reactions. But the danger must then be faced of producing focal reaction which cannot be controlled.

In contrast to this case is reproduced a second chart, No. XXVII, taken by permission from Krause (Hanover), where doses of ·005 to ·015 were given and a complete defervescence resulted. A third one (Chart XXII) from Denys illustrates the similar effect of **BF.**

TUBERCULIN IN MIXED INFECTION

Allusion has been made under the treatment of febrile cases to the part which other organisms play in phthisis. The subject is a difficult one but it cannot be dismissed from a book dealing with tuberculin treatment, because on the one hand it is often a secondary infection which first calls attention to the existence of tubercular disease and leads to its specific treatment; and on the other hand, the addition of a severe secondary infection to an existing tubercular one may make any line of treatment of no avail.

The Nature of Mixed Infection.—It is not every co-existing infection in phthisis which can rightly be called a mixed infection. The expression was first used by Brieger and Ehrlich in 1882 to describe a case of enteric fever associated with malignant œdema, a mere accidental association of two independent infections. Babes in 1888 called attention to the polymorphic character of the infection in advanced phthisis, and the subject was followed up by Koch and Gaffky. But the term as now used denotes something more than the occurrence simultaneously with tuberculosis of another bacterial infection; we should not now call the association of pulmonary tuberculosis and gonorrhœa a mixed infection; nor even phthisis developing in the subject of a chronic bronchial catarrh. The latter would be in the language of C. Spengler an attendant infection.

For a mixed infection the two germs must be present, not merely at the same time, but also in the same place, and a mixed infection in phthisis is one in which the tubercular tissue becomes secondarily the settling ground of other organisms. When this is the case, the two organisms are present in the sputum in such intimate relation that the smallest particle of sputum con-

tains both, and neither can be removed by washing the sputum in relays of running water.

But even if this latter condition is fulfilled, it does not follow that the secondary infection, any more than the tubercular itself, is active, and it is a common experience to find tubercle bacilli and catarrhal cocci associated together in the washed sputum without any clinical ground for supposing that the latter are producing any symptoms. It is a matter then of considerable difficulty to decide in a particular case whether a mixed infection is present or not; and as it has a very practical bearing on the administration of tuberculin we must first consider the diagnosis of mixed infection.

The Diagnosis of Mixed Infection.—(*A*) **From Symptoms and Clinical Course.**—We have seen above that the persistent intermittent type of fever with great daily variation, generally called hectic, is probably always due to a secondary infection with streptococci, but rarely as Jochmann has shown to an actual septicæmia. Another characteristic type of fever noted by the writers is a periodic elevation generally ushered in by a slight chill and often attended by catarrhal signs in the upper air passages, the attacks occurring at regular intervals. This condition is so conspicuously amenable to vaccine treatment with the offending bacterium, generally a catarrhalis-like organism, that there should be no hesitation in thus dealing with it.

Help is often afforded by a study of the antecedents of the pyrexia. No doubt will arise where a catarrhal infection has passed from member to member of a household, or where a patient is laid low during an epidemic

of real or pseudo-influenza. Many mixed infections arise from careless and unnecessary contact with catarrhs. In other cases one of the organisms already present but latent in the respiratory tract has become virulent, or relatively virulent, from the diminished resistance of the body to it; and a history of previous similar attacks may be obtained. A febrile attack occurring when the patient is at work, especially in a large town, is much more likely to be due to a secondary infection than at home or in the country; while an attack coming on in a sanatorium, except where a catarrh has been imported, is quite improbably due to this cause.

(*B*) **From Examination of the Sputum.**—In the washed sputum alongside the tubercle bacilli will be seen the other bacteria in larger or smaller number. In the writers' experience their order of frequency is: pneumococcus, catarrhalis, streptococcus, Friedländer, staphylococcus, tetragenus. As we have seen their mere presence does not necessarily denote pathogenicity, but experience has shown that streptococcus and Friedländer when present are almost certainly actively harmful; catarrhalis (which probably stands for a whole group of organisms) very frequently not; pneumococcus of significance when abundant and not when in small number; staphylococcus an occasional saprophyte in cavities. The finding of them engulfed in phagocytes would be an indication that the plasma was actively hostile and their presence not merely accidental. Much more research on these lines is desirable.

(*C*) **From Certain Blood Tests.**—Organisms with which the body is in conflict excite the production of antibodies whose presence can be demonstrated. The

method of demonstration is however, as we have seen, very laborious, and the diagnosis of mixed infection must commonly be based on a careful collation of other indications. It might sometime be possible to indicate the existence of a secondary infection by a method analogous to the cutaneous reaction for tubercle.

The Treatment of Mixed Infection.—Avoidance. The treatment of mixed infection can hardly be discussed without touching on what is even of greater importance, its avoidance. If it were only realised how important is the matter and how the addition of a secondary infection may turn the scale against recovery, more precaution would be taken in this respect. A tubercular lesion of the lung which has become open should be isolated from catarrhal infection as scrupulously as a wound from septic infection. The patient who has had the misfortune of a tubercular focus breaking through into a bronchiole should be at once sent away into a sanatorium, or otherwise into pure air until the focus has closed again. Such an elementary precaution would in most cases prevent further mischief. This constant risk of secondary infection is the great drawback to the ambulant treatment of open phthisis, and justifies the existence of sanatoriums for isolation from catarrhal infections as long as town life presents the risk of these. The open-air life is not merely out of reach for the time being of catarrhs but hardens against subsequent infection. If it is impossible to remove the patient from the neighbourhood of secondary infection he should wear an inhaler charged with some volatile antiseptic, and so keep his mouth closed and his friends as well as catarrhal organisms at a distance.

Treatment Proper.—Having decided that a mixed infection is really present what should be the line of treatment ? In our opinion undoubtedly to get rid of the secondary infection before treating the primary one, in every case where this is possible.

The **general treatment** consists in placing the patient where he breathes only pure air and has his powers of resistance raised by hygienic measures, being at the same time isolated from the risk of reinfection and hardened by exposure against the liability to relapse.

The **special treatment** consists in inoculation with a vaccine prepared from the infecting organism. The vaccine must be autogenous ; of most of the organisms isolated from sputum it is only possible to say that they are members of a certain group ; a stock vaccine can only by a happy coincidence have been prepared from the particular organism of the group actually present. Hence in the majority of cases a stock vaccine will be perfectly useless and only bring discredit on the vaccine treatment. For some time past one of the writers has prepared a vaccine from the sputum of every case which still shows evidence of secondary infection after a month of sanatorium treatment, and the results have certainly justified the trouble involved.

Of other special means the inhaler has already been mentioned, and it is certainly of service in restraining mouth breathing and preventing free intercourse with catarrhal subjects. The writers have not been able to satisfy themselves that it does more than this or has any greater influence than pure air in the treatment of mixed infection.

To assist the general measures in severe cases of

mixed infection, the injection of colloidal metals, e.g. collargol, introduced by Crédé, has been tried and the writers have seen it of apparent benefit in severe influenza. In cases of hectic fever, the resistance of the body is generally so much reduced as to preclude response to an active form of immunisation. Pawlowsky and others emphasize the hopelessness of any attempt in the presence of the streptococcus infection; and it is here that any measure giving prospect of raising the general tone should be given a trial. Möller whilst confirming the malignant character of the streptococcal mixed infection makes the interesting suggestion that the sarcina and some cocci may be beneficial, as in these cases there are generally but few tubercle bacilli in the sputum.

Tuberculin.—If the mixed infection has been successfully dealt with, then is the time to commence tuberculin treatment. But supposing that success has been partial or wanting, is it safe or is any useful purpose to be served by administering tuberculin? The answer depends on the method of administration; if reactions are produced they are probably a source of danger in a tissue in which secondary germs are present; in this C. Spengler, Wilkinson and Möller agree. But if tuberculin is being given by the method of avoiding reactions there appears to be no increased risk in the association with mixed infection. Where fever is present the principles stated in the last paragraph should be borne in mind. The treatment on these lines may be continued at the same time as that with vaccine or whatever other means is considered appropriate. But the writers' preference is to deal first with the mixed infection where-

ever this is practicable. Shortness of time or external considerations may of course stand in the way.

TUBERCULIN AS SYMPTOMATIC TREATMENT

It is still unfortunately true that a large proportion of cases of pulmonary tuberculosis by the time they present themselves for treatment are beyond the reach of anatomical cure or even of permanent arrest. And there are in addition those in whom even timely treatment cannot arrest the disease. These cases have in the past been discouraging alike to doctor and patient ; and especially for the reason that there was nothing to do but watch the downward course without any helpful activity. It is now quite certain that in these cases the induction of tolerance by means of tuberculin injections is likely to be of sufficient use in the relief of symptoms to justify its employment. J. A. Miller regards this as the most useful sphere of specific treatment. And over and above this it provides the opportunity of a weekly or half-weekly visit ; wherein is contained, as Möller says, the helpful element of suggestion ; the patient feels that something active is being done for him, and is encouraged rigidly to carry out instructions that he would otherwise be tempted to neglect. Hence the value of tuberculin in what have been regarded as hopeless cases.

Detre admits the fact of the relief of symptoms but believes that there is a " symbiosis " established between the body and the bacillus owing to the development of tolerance, and that

the latter continues to develop unchecked. This view appears to be based on the supposition that sensitiveness is abolished when tolerance is developed, and that what we have called " policing " is no longer carried out. But there is reason to believe that this protective bacteriolytic function is increased rather than diminished by the tuberculin, and that it is tolerance which prevents the activated tubercular toxin from producing unpleasant symptoms. The symptomatic improvement is we believe attained without any sacrifice of immunising action. From the practical side much comparison of treated and untreated cases would be required to establish Detre's view, and we strongly incline to the belief that the objection is groundless, and that the relief of symptoms and the regular observation are really important factors in advanced cases.

Regarding method there is little more to add to the general lines already set forth. Tuberculin tolerance is as a rule already considerable although insufficient, and the dose may have to be rapidly increased to a high level before any appreciable effect is produced. In so doing evidence of focal reaction must be looked for with care, and a reaction, however slight, treated with absolute rest. After this point has been reached the dose will be repeated or increased very slowly, according to circumstances. When fever is present, what has been said under febrile cases applies here also.

TUBERCULIN IN PREGNANCY

The effect of pregnancy on the course of phthisis is not a constant one. In many cases, perhaps the majority, there is an increased sense of wellbeing and a loss of some of the more troublesome symptoms during the early months. Although this improvement may persist and the final result be to the good there is

unfortunately a tendency towards relapse, and that of a severe character, after parturition ; and this tendency is much increased by the strain of lactation if undertaken. It is not uncommon too for an unsuspected tubercular lesion to make its presence felt at this time. The risk is often so serious that the question of induction of abortion has to be considered. Of the comparative immunity of the period of pregnancy no explanation has been offered, but Bar and Dessaigne have made the interesting observation that the reactivity to T diminishes during pregnacy, to increase again after labour.

Petruschky was the first to advise tuberculin in these cases ; in his experience, not only was tuberculin well borne but it considerably reduced the indication for induction of labour. Hammer and Scherer confirm this, and the former observes that the mother has repeatedly pointed out to him how the child born during the specific treatment has been stronger and more robust than previous offspring. He further relates the case of a woman with chronic phthisis, who had twice aborted and who went to full term with a healthy child after a course of tuberculin. Illustrative cases do not carry conviction to others, but there appears at any rate very good ground for a thorough trial of tuberculin during pregnancy in women with active tubercle, or in whom a lesion has recently been active and fears are entertained for the effect of labour.

AUTO-TOXIC DISEASE IN CHILDREN

When we come to the consideration of tuberculosis in children (p. 175), we shall find that cases divide themselves readily into two main groups, namely those of infancy on the one hand and later childhood on the other. Tuberculosis at these different age periods presents different features, and to the latter division may be attached a further collection of cases, namely tuberculosis of adult type occurring in early years. We thus have three groups in which to consider the possible applicability of tuberculin treatment with the production of tolerance.

Infancy.—During the first year of life resistance to infection by the tubercle bacillus is at a minimum ; indeed it was held by pathologists till recent years that signs of healing were not demonstrable in tubercular lesions of infancy, and though this view is no longer tenable yet mortality and morbidity keep strikingly near together at the outset of life. The glands offer the first and best defence, and when these are superficial softening may occur without harm, and recovery follow. When, however, less accessible glands, as the intrathoracic or intra-abdominal, suffer the disease tends to spread beyond them to adjacent organs, or to disseminate into remote parts of the body. The extent of this spread in any particular case, at any particular moment, is extremely difficult to gauge, but in any such case the question of tuberculin treatment and its possible value may arise and have to be decided. Tuberculosis in infancy tends to be acute, and in such cases it is obvious that tuberculin treatment has nothing to offer ; the

same must be said for cases of more chronic course but in which widespread disease is obviously present—a protracted broncho-pneumonia or a general tuberculosis of chronic form. There remain only cases where somewhat doubtful evidence of disease of internal organs occurs—signs suggesting tuberculosis of bronchial glands with some amount of spread into the lung, the diagnosis being confirmed in most cases by a positive cutaneous tuberculin test which is of considerable value during the first year of life. For such cases tuberculin is certainly indicated, but different conditions obtain to those in adults, and these must be shortly considered.

Tuberculosis in infancy is characterised by certain peculiarities. In addition to the low resistance to spread of disease another fact has been remarked on—namely the comparatively slight intoxication accompanying the presence of widespread lesions. In addition, the production of natural tolerance generally fails—the tuberculin reaction remains—and also, as pointed out by Bauer, there is a failure of production of antituberculin in the blood. On account of these peculiarities two views have arisen as to the requirements of tubercular children *qua* tuberculin. There are those who say with Escherich that Nature, which has provided sensitiveness and omitted tolerance, should be followed, and hence small doses given with the maintenance of sensitiveness ; there are those, on the other hand, who follow Engel and Bauer in the artificial production of tolerance and antituberculin by the administration of tuberculin in rising doses.

The true indications probably lie sometimes with one

school and sometimes with the other, according to the nature of the case. It is highly irrational to suppose that the differences observed between the reaction to tuberculosis of infants, and older children or adults, can be differences in kind ; it is fairly sure that they are but differences in degree. The absence of tolerance and of antituberculin in the blood and also the mildness of intoxication observed in these cases all point to a difficulty in attacking the tubercle bacilli present in the tissues. Soluble tubercle products, such as tuberculin, can however be dealt with so that tuberculin reactions are obtainable, and we hold on this account that tuberculin treatment as a means of rousing resistance is even more necessary in infancy than at any subsequent age period. Whether the immunising response obtained should or should not be accompanied by the production of tolerance must necessarily depend on the need for this in the individual case (*see* p. 18). This fact has generally been ignored, and the German literature quoted below is concerned with cases many of which we should consider eminently suitable for the small dose method, that is, immunisation without tolerance. When, in infancy, disease has spread beyond this point it is generally of hopeless outlook, and so it happens that, at this age, the realm of the method of immunisation with tolerance is a very narrow and highly unsatisfactory one. A reference is here desirable to the very interesting literature of tuberculin treatment in infancy.

Ganghofner (1906) was the first to describe the treatment of young children with tuberculin ; he followed the careful method of rising dosage recommended (but hardly practised) by Götsch but advanced with still

more caution and to the maximum avoidance of reactions. He encountered great sensitiveness in infants and in them achieved no success, though he did no harm.

In 1908 Engel and Bauer, working in Schlossmann's clinic, showed that tolerance to tuberculin was easily obtainable in young children except where considerable and progressive disease was present. They recommended the use of large doses on the grounds that only on these doses does antituberculin appear as the result of treatment ; their plan was to repeat the same dose till reactions ceased to appear and then to rise higher, the final dose given being 2,000 to 5,000 even up to 20,000 c.mm. of old tuberculin. Among seventeen infants treated nine were under one year of age and all, contrary to expectation at this period of life, kept their health, and their lesions, whether of joints, bones, or lungs, improved. In 1909 Schlossmann confirmed the successes claimed by Engel and Bauer and described two cases on infants of six and eight months respectively, one with tuberculosis of knee and finger and " suspicion of the lung," and the other diagnosed as tuberculosis of intrathoracic glands and lung and both progressing to recovery. He gave old tuberculin in doses beginning with ·1 c.mm. and, when a reaction occurred, as frequently happened, the same dose was repeated (up to twenty-eight times in one case) on alternate days until tolerance was established.

Attempts by others to emulate the successes claimed for the Engel-Bauer method have not led to similar results. Escherich (1910) indeed, and also Paul Rohmer (1910) saw increased resistance as a result

of treatment in a case or two, but they did not save their patients from death. Moreover the former attributes softening of thoracic glands in some of these to excessive tuberculin reactions, and concludes that this method is not suitable to the treatment of tuberculosis in early childhood.

The difficulty of reconciling these conflicting results depends on the difficulty in assessing the material under treatment. We have already recorded our impression that many of the cases were more suitable for small dose treatment ; in some, perhaps, the production of tolerance was indicated. The results are strikingly contradictory. On the one hand is the cautious administration of Ganghofner causing no harm but doing no good ; on the other hand the striking claim of Schlossmann and his pupils for large doses and large reactions. Against these claims must be put the undeniable fact that marked reactions lead in infancy to softening of tubercular areas with its attendant dangers. Whether the chance of success in a few balances this very definite risk is a matter where room exists for difference of opinion.

Where the signs point to disease of intrathoracic glands and little more we hold that the method of immunisation without tolerance is indicated, and would refer the reader to the treatment of occult glands (p. 219). Where the disease is more widespread the chance of life is in infancy extremely narrow under any line of treatment, and the argument for the Engel-Bauer method, which in our opinion should be greatly modified, may be stated as follows—

1. Such cases are fatal if left to themselves.

2. There is evidence that the resistance of the tissues may be increased by tuberculin administration, though the chance of complete success is remote.

Under such circumstances it is obviously our duty to put the matter clearly before the parents of such a child so that the remote chance may be given them if they elect to take it. At the same time it must be borne in mind that to discredit tuberculin may be to deprive of this treatment some other child (perhaps of the same household) who might have derived more certain benefit from its administration.

Childhood.—In children of school age the resistance to the tubercle bacillus is considerable, and two stages may be recognised in its progress. The first arrest is in glands and it may never pass beyond. In its second stage it appears at some further point either in surface structures, as so called surgical tuberculosis, or in internal structures, such as the lung or abdominal organs. Hilum phthisis, where the disease spreads from the glands into the lung, will be considered with apical phthisis in children. There remain a group of cases for which the method of small doses at long intervals is in the main suitable (*see* Part III). It happens sometimes, however, in these cases mainly localised that disease has spread so far as to lead to very definite auto-inoculation, and the question of establishing tolerance during treatment will then arise.

This is especially apt to occur in cases of tubercular peritonitis and in disease of large joints such as the hip. In such cases, however, symptoms can usually be controlled by enforced rest, and in the case of tubercular peritonitis excellent results are obtained on the small

dose method even where some amount of fever and general symptoms are present.

There remain **Hilum Phthisis** and true **Apical Phthisis** of adult type to consider. Hilum phthisis, where the disease spreads into the lung from glands about its root, belongs to an earlier age and is of generally less hopeful outlook than primary apical disease. Since, however, the two are sometimes difficult to separate clinically, and since the principles of treatment are similar in both they may here be conveniently grouped under one heading.

Apart from initial dosage the specific treatment of phthisis in the child is, with all its indications and contra-indications, identical with that in the adult and needs no separate chapter for its description. An initial dose small enough to avoid a reaction must be chosen, and this is best calculated by the relative weight of the child, a child of three or four stone being given one-third of an adult dose. The final dose is no more fixed than in the adult and differs according to the rapidity of increase and the time over which treatment is spread. There is a fair consensus of opinion as to the value of tuberculin with the production of tolerance in selected cases of lung tubercle above the age of infancy, and the reader is referred to the foregoing pages for the details of its administration.

AMBULANT TUBERCULIN TREATMENT OF PHTHISIS

Something has been said under other headings (pp. 74 and 76) of the conditions under which specific

treatment is carried out : whether in the sanatorium, by the practitioner in the home, or at some institution to which patients come up for treatment. These various external conditions have been borne in mind in considering the details of treatment throughout. Administration in sanatorium or private practice does not call for special consideration, but there are certain points in what we prefer to call the ambulant treatment that demand attention. We use the word " ambulant," coined on the German model, to cover the whole ground of the treatment of patients coming from their work or their homes for treatment, whether in the out-patient department of the hospital or at special institutions for the purpose ; assuming in any case that the administration of tuberculin will be co-ordinated with the other factors of prevention and treatment in a disease of so many-sided a character as tuberculosis.

The class of case attending for such ambulant treatment may be either—

1. The early case of closed phthisis where there is no danger of mixed infection and no reason for sacrificing occupation or leaving home : primary ambulant treatment.

2. The case which has been at a sanatorium but in which the tuberculin treatment has not been completed ; consecutive ambulant treatment.

3. The case which really demands sanatorium treatment but in which social or family conditions render this impracticable ; makeshift ambulant treatment.

4. The advanced case where tuberculin is being continued as symptomatic treatment.

We shall consider first how far ambulant treatment as thus defined is a novelty ; then whether it is a safe proceeding and what are its advantages and drawbacks ; touching finally on the methods special to this mode of administration.

Ambulant Treatment no Novelty.—Although in England the ambulant treatment with tuberculin on any large scale is new and principally due to the initiative of Wilkinson, elsewhere it is no novelty. It was practised by Koch in his " ambulatorium " where men like Petruschky gained their experience ; and in 1903 the latter could cite three centres (Danzig, Breslau, Stettin) for specific diagnosis and treatment ; while Friedeberg and Kayserling described their successful ambulant treatment of workers in Berlin. Denys published in 1905 the results of specific treatment of more than 1,000 out-patients at the Bacteriological Institute in Louvain during the preceding eight years, calling special attention to the fact that in the majority of cases the hygienic conditions of the patients left much to be desired.

At the annual gathering of the German tuberculosis specialists in 1907 B. Fränkel (Berlin), who presided, stated that he had been the first to combine the sanatorium and specific treatment ; had practised the latter also in private and out-patient practice since 1891 and was in favour of its ambulant use except for cases with arduous employment. Hammer reported on its use in the polyclinic at Heidelberg.

Three years later, in 1910, at this gathering a whole session was devoted to ambulant tuberculin treatment,

and of fourteen speakers eleven were in favour of it, some with reservation.

Under Trudeau's inspiration, centres have been established in the great cities of the United States dealing with ambulant tuberculin treatment ; of these may be mentioned the Phipps Dispensary of the Johns Hopkins Hospital, Baltimore, under Hamman and Wolman ; in New York under J. A. Miller ; in Boston under J. B. Hawes and C. Floyd.

In Bukharest Mitulescu has treated hundreds of ambulant cases since 1906.

Safety of Ambulant Treatment.—Of the safety of ambulant treatment sufficient time has perhaps already elapsed to constitute a clinical proof. The conclusion of the Johns Hopkins workers is to the effect that "tuberculin may be used on a large scale in the dispensary without danger and under the most satisfactory control." M. Wolff has recently reported on a hundred cases among out-patients in all of whom 500 or 1,000 was reached without a single bad result. Those who have expressed the most anxiety over the dangers are probably unaware of the extent to which the method has already been practised by many clinicians in various lands.

Advantages of Ambulant Treatment.—The advantages of ambulant treatment are obvious at sight.

1. It enables the patient to remain at home. It does not remove him to artificial conditions of life away from his usual occupations, and in many cases with the addition of financial anxiety. There is no question of a subsequent return to less hygienic con-

ditions with consequent liability to relapse ; if cured at his work and under the conditions of his home-life the cure should be lasting.

This is not the same argument as the one frequently employed, that climatic treatment should be under conditions as nearly as possible resembling those of the patient's home. If a change of environment is necessary, it should obviously be that change which brings the maximum benefit in the available time. And this change is often the very reverse of the climatic surroundings of the patient.

2. He can remain at work, unless this is in itself of unsuitable character, and thus combine the tuberculin treatment with the normal auto-inoculations of his daily life. There is in this respect again no return to conditions so different from sanatorium life as to court a breakdown.

3. The patient can, as we have seen, continue the course of specific treatment begun in the sanatorium, and have the treatment also when he would be unable to leave home or when the disease has become chronic and it would not be worth while for him to do so.

Drawbacks of Ambulant Treatment.—The drawbacks of ambulant treatment also need a little consideration.

1. It has been urged that there is insufficient control of the patients and that symptoms cannot be watched with the accuracy necessary to form the basis of treatment. There is something in this objection, but it has not been verified in practice, granted that certain conditions discussed in the next section are present.

Hamman and Wolman state that the requirements on the part of the patient are—

Some degree of intelligence in order to take reliable observations of temperature and other symptoms.

The willingness to undergo a long and tedious cure.

A certain loyalty and cooperation with the physician, so that symptoms may be fairly reported and instructions faithfully carried out.

It is the experience of many besides the writers that these postulates are realisable in ambulant as well as sanatorium practice. Even in sanatoriums patients have been known to fake their temperature charts.

2. Stress has been laid by some authors on the inability of obtaining rest after an injection in ambulant patients. Röpke points out with justice that the importance of this rest has been much exaggerated, and the writers agree with him in not prescribing a routine day of rest following an injection, being content with enjoining no unusual exertion on this day. This provision covers the worker also.

3. In the case of arduous occupations there is the great difficulty of regulating auto-tuberculinisation, and this is liable to interfere seriously with the conduct of a course of injections. Ritter and Brecke doubt the expediency of giving tuberculin at all under these conditions, and where autotoxic symptoms are marked it is obvious that the patient should not remain at work. Ritter finds for this reason better results with officials, merchants and especially women, in all of whom auto-inoculations are less likely from the nature of their employment. When it is imperative to give tuberculin to a patient at arduous work it should be done, as Röpke suggests, on Saturday afternoon.

4. Perhaps the greatest drawback to ambulant treatment is that it leaves the tubercular patient exposed to all kinds of secondary infections. Hence

wherever the disease is both open and recent, every effort should be made to place it under hygienic treatment for a time, and if possible until it has become closed again.

Methods of Ambulant Treatment.—The methods of ambulant treatment must be modified to meet the particular case. The following is the routine of the Phipps Dispensary—

(*A*) The newcomer is referred to the visiting nurse, who instructs the patient in the taking of temperature and pulse and recording his symptoms. A sufficient record is obtained before treatment is started.

(*B*) The patient is supplied with a special record book, with printed directions on the cover, on the lines suggested by Lawrason Brown.

Some exception has been taken to the use of such record books on the ground that it tends to make the patient too introspective. The writers on the other hand consider the book of the greatest possible value to ambulant treatment, and would hardly care to undertake it without some such record. Both the chart and the instructions on the cover are copied from Lawrason Brown with certain alterations and abridgment.

(*C*) On the day following, the nurse visits the home and advises as to the conditions of the sleeping room, as to taking milk and extra nourishment. She gives instructions regarding remaining in bed until the temperature is normal, and at any time during treatment if occasion arises.

(*D*) The nurse's visit is repeated at first every day, then at increasing intervals.

(*E*) If necessary the C.O.S. is asked to assist in providing suitable sleeping accommodation and extra nourishment.

Record Book for Ambulant Tuberculin Treatment.
(Taken with modifications from Lawrason Brown, *Tuberculos*
A Treatise by American Authors, edited by A. C. Klebs.
Appleton & Co., 1909.)

This record book is intended to aid your doctor in giving you tub
culin. He has to depend upon your accuracy, which is therefo
closely connected with the benefits that you will receive from this li
of treatment. Put down no statement that is not, to the best of yo
belief and knowledge, true in every particular and not in any way m
leading.

The list of symptoms should be carefully scanned and the sig
+ or 0 used to denote **present** or **absent**. If your back or ar
wherever you receive the injection, does not attract your attentio
put down 0 opposite **local symptoms**. Otherwise indicate wh
symptoms you have at this spot. If you feel as usual and ha
none of the general symptoms, indicate this by an 0 opposite **gener**
symptoms. Otherwise put + opposite each symptom that occu
Do the same for **focal symptoms**. When cough or expectorati
are said to be increased, it means in comparison with the usu
amount.

The **temperature** should be taken carefully in the way in whi
you have been instructed and at the times stated on the cha
In any case the morning temperature should be taken before getti
out of bed. When your temperature reaches 100° you should
to bed, unless your doctor has told you otherwise ; also if you f
bad or have any pronounced symptoms.

The **weight** should be recorded once a week, and the **pul**
noted only when it varies from the usual rapidity.

Under routine, **in bed** means whether you have spent the da
morning or afternoon in bed. **Exercise** means how many hours ea
day you have spent in walking. On the day of the injection a
the day following, you may take your usual exercise, unless t
doctor has told you not to, but you must not do anything ext
or unusual.

Be perfectly frank and honest with your doctor. Tell him of a
act of over-exertion, and if any symptoms occur which are mention
in this book, be sure to call his attention to them. It is only by mut
confidence that the best results are obtained. You are both partn
in the most serious business of your life, and partners should disc
every detail of their affairs, but they should not divulge them to the r
of the world.

AME

hart for week beginning	SUNDAY.	MONDAY.	TUESDAY.	WEDNESDAY	THURSDAY.	FRIDAY.	SATURDAY.	REMARKS.
UBERCULIN Dose								
OCAL SYMPTOMS—								
Pain								
Tenderness								
Swelling								
ENERAL SYMPTOMS—								
Headache								
Pain in limbs								
Pain in joints								
Malaise								
Sleeplessness								
Fatigue								
Restlessness								
Nervousness								
Indigestion								
Nausea								
Vomiting								
Chilliness								
Rash								
Enlarged glands								
.....								
.....								
CAL SYMPTOMS—								
Oppression in chest								
Cough : increased								
decreased								
as usual								
Expectoration :								
increased								
decreased								
as usual								
Stich in side								
Shortness of breath								
.....								
.....								
MPERATURE—								
Morning								
Midday								
Evening								
Night								
LSE								
petite								
ength : increased								
decreased								
as usual								
UTINE : in bed								
hours up								
exercise								
at work								
ight on urday	SUNDAY.	MONDAY.	TUESDAY.	WEDNESDAY	THURSDAY.	FRIDAY.	SATURDAY.	REMARKS.

Much stress is naturally laid on the work of the nurse or health visitor with whose assistance all the other curative factors are brought into play. Besides this the American workers emphasize the necessity of instruction to the patients attending, and some years ago Pratt of Boston started weekly "tuberculosis classes" at which the physician met the patients and discussed with them the lines of treatment and their special difficulties. In London this was done also by the late S. B. Atkinson. M. S. Cohen, of Philadelphia, elaborated the classes further into lectures and demonstrations.

The **equipment** for the dispensary may be of a very simple character. The records should cover a long period, say three months, at sight, and all the necessary information can be compressed on to the chart with the temperature. Such a three months' chart is used to reproduce the temperature records at the end of this book. The nurse or clerk who receives the patient writes up the chart from the record book and notes the weight. The patient is examined if desirable; the dose given and entered on the chart. On the principle of a weekly or half-weekly dose, attendance can be limited to two afternoons a week; but as we are considering patients who follow their occupation, latitude of time must be given and in many cases evening time. For reasons already mentioned Saturday afternoon should be one of the times of attendance. A summary of the requirements of a dispensary with a description of a building designed for the special purpose, is given by Mearns Fraser.

RESULTS

The writers have decided to give no statistics of the results of tuberculin treatment in phthisical patients. This self-denying ordinance has been dictated by several considerations. In the first place it has been done recently and well by Latham and Inman. In the second, statistics of cure are of very questionable value in a disease such as phthisis, in which there is so strong a tendency to spontaneous arrest, and in which even the necessity for any sort of treatment is difficult to assess. And in the third place there are certain available statistics of a different but more convincing character.

During the last ten years, which have seen the development of the sanatorium movement, there has been a steady numerical increase in the proportion of those which have combined specific with hygienic treatment. In Germany, where it is largely a question of public institutions, the percentage in 1905 was 29, in 1907 it was 57, in 1910 the figure is about 70. For many years the names of Meissen and Schröder were associated with a sceptical attitude towards the value of tuberculin; now both of these clinicians whose experience of hygienic methods extends back over a period of twenty years or more, have published results favourable to its use. In any considerable resort of phthisical folk it would be difficult at the present time to find a practitioner who was not giving tuberculin in some form or other. An analysis, made for the purpose of this book, of the views of twenty-four continental clinicians with large personal experience

of the treatment of phthisis, showed eight enthusiasts, eight in favour of an extensive but not universal application of the remedy, four in favour of its employment with reservations, and only four who regarded it with disfavour. At the annual gathering of German tuberculosis specialists the value of tuberculin may be regarded as an accepted fact since 1907, and three years later the discussion turned not on its remedial value but whether this could wisely be employed in ambulant practice. One of the writers, in reply to a request for information as to personal experience with tuberculin, received replies from sixty English-speaking practitioners who had used tuberculin more or less extensively, and of these thirty-six had formed a favourable opinion of its action in phthisis. These figures speak for themselves.

But statistics apart, certain results may be said to be well established by clinical experience. The first and most striking of these is that phthisis treated with tuberculin before it has become open, i.e. before it has been exposed to the risk of secondary infection, remains closed. The importance of this fact, on which there is practically unanimous opinion, can hardly be exaggerated. It is true that the same result has been claimed for hygienic treatment : Bandelier regards the fact as being so well established that he refrains from giving tuberculin to these patients because it is unnecessary. It is also true that the *vis medicatrix naturæ* unfettered by art would have had the same result in a large proportion of cases—the Paris Morgue (quoted by Huggard) gives 68 per cent. of cures without the bias of any pet remedy ; but there remains a proportion, it may be

small, of closed pulmonary tuberculosis which will not get well, and with these tuberculin has been shown to be competent to deal. Early diagnosis—that is to say, *really* early diagnosis, before tubercle bacilli appear in the sputum—combined with specific treatment, insures completely against a breakdown.

We believe that statistics have already shown the ability of tuberculin to increase the percentage of those who lose their sputum, or the tubercle bacilli contained in it, during hygienic treatment, and to extend the expectation of working efficiency after hygienic treatment; but we are content to leave this to a more rigid demonstration. Of all these matters the tubercular patient is the final judge, and misled as he was by the disasters of 1890–91 there is no doubt that his experience of tuberculin under the new conditions is making him willing, and sometimes even anxious, to submit himself to treatment with the remedy.

PART III

THE METHOD OF IMMUNISATION WITHOUT TOLERANCE (WRIGHT)

THE TREATMENT OF LOCALISED TUBERCULOSIS

CONTENTS

PART III

THE METHOD OF IMMUNISATION WITHOUT TOLERANCE (WRIGHT)

THE TREATMENT OF LOCALISED TUBERCULOSIS

THIS, the last section of the book, deals with the method of immunisation by tuberculin without the production of tolerance. This method is suitable for the treatment of localised tuberculosis, for under these conditions auto-inoculation is absent and hence no tolerance is needed to overcome it. Such localised disease is *par excellence* the tuberculosis of childhood, and so it comes about that the following section deals mainly with disease in children and its problems are largely discussed in terms of the child. Immunisation without tolerance means tuberculin at long intervals so that the tolerance of each injection may wane before the next is given. It also means tuberculin in small and equal doses since, in the absence of tolerance, each dose will attain its full effect. Hence the method of tuberculin administration without tolerance may be summed up shortly as the small dose method, at long intervals, suitable to localised tuberculosis, and especially to tuberculosis in children.

OUTLINE OF THE METHOD

Tuberculosis in children being the special province of this method of administration, it has seemed suitable to precede it by a short discussion of this very special subject. It is highly essential that the frequency of early infection should be appreciated, and that the influence of age, and the spread of the disease by stages should be grasped in the interests alike of prognosis and treatment. Having touched on this subject we shall then pass on to the selection of cases suitable for this method of administration, the conditions under which treatment may be given, whether at home or elsewhere, and the means we have for the observation and control necessary to attain a satisfactory result. The principles which guide us in the administration of tuberculin by the small dose method next claim our attention, and we shall pass from these to their practical application under the headings—Choice of Tuberculin, Initial Dose, Optimum Dose, Indications of Success or Failure, Duration of Treatment, and Repetition of Treatment. The administrator of tuberculin cannot afford to ignore any helpful contributory influences, and a short résumé of auxiliary treatment claims the next place, to be followed by consideration of the subject of mixed infections. Lastly will come a section devoted to disease of Special Regions—Tuberculosis of Glands, of Bones, Joints, Skin and Connective Tissue, of Serous Membranes, the Eye and the Kidney and Bladder, all save the last of these groups belonging especially to the realm of tuberculosis in childhood.

TUBERCULOSIS IN CHILDREN

This subject is so intimately bound up in the method of tuberculin treatment without tolerance that it seems to form the natural introduction to this section of the book. Its problems differ widely from those of adult tuberculosis, and their consideration here is important because recent investigations have tended considerably to alter and enlarge our views. This has been so especially with regard to the prevalence of the disease, for the more subtle our diagnostic methods become, the wider do we find is the spread of the tubercle bacillus in the early years of life.

There are two methods by which the prevalence of tubercular infection can be estimated, namely by examination after death, and by specific tests during life. Now ordinary post-mortem statistics represent a hospital population where, necessarily, an artificial concentration of tubercular material occurs. Our aim, however, is to estimate the incidence of infection in the living, and some amount of evidence on these lines is forthcoming from among healthy children dying of acute diseases. Hamburger gets over the difficulty in another way, namely by recording, among ordinary post-mortem material, only those cases where tuberculosis was not the cause of death. By these means he obtains the following percentage incidence for tuberculosis at various ages.

At 0–3 months	0% tubercular
„ 4–6 „	0% „
„ 7–12 „	4·5% „
„ 1–2 years	17% „

At 3–4 years	. . . .	30% tubercular
„ 5–6 „	. . . .	34% „
„ 7–10 „	. . . .	35% „
„ 11–14 „	. . . .	53% „

These figures are sufficiently striking and would be still higher, Hamburger explains, if microscopic examination had been added to ordinary observation.

Far higher, indeed, is the percentage of children found

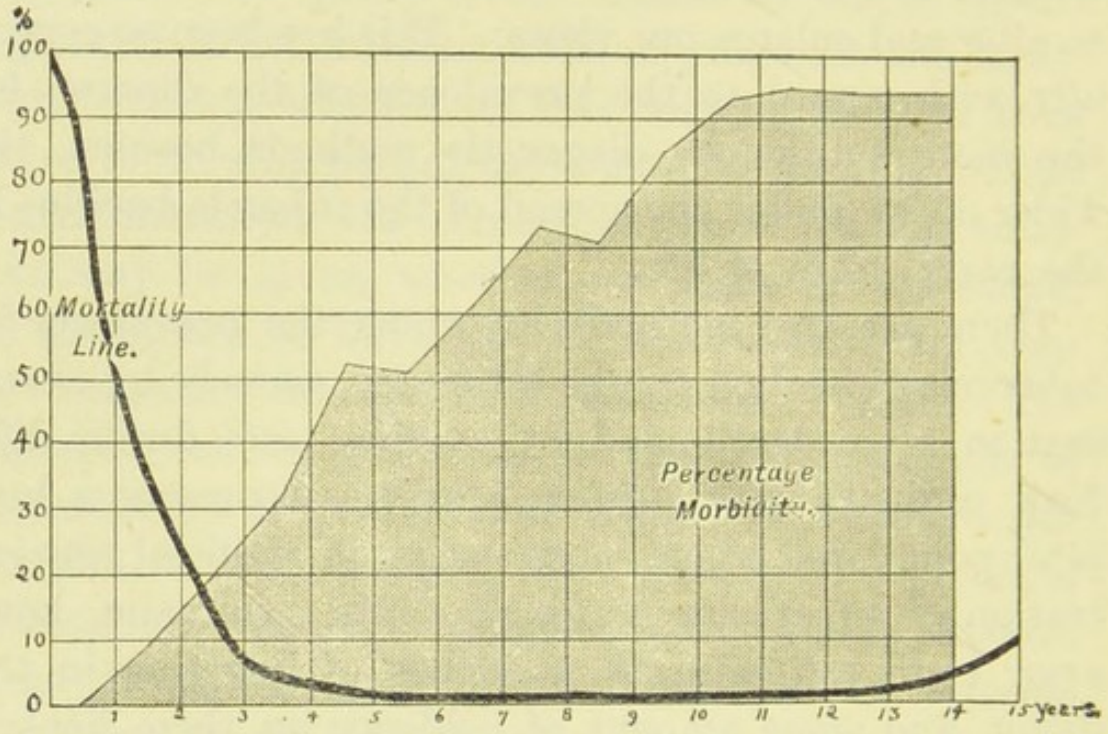


CHART XXIII. (after Escherich. *Wien. med. Wochenschr*, 1911 lxi. 115). Shows the percentage morbidity after Hamburger and Monti, and also the percentage mortality on these figures calculated from the tuberculosis mortality tables of Vienna for the same year (1909).

to react to tuberculin during life. This is well exemplified in Chart XXIII, prepared from the results obtained by Hamburger and Monti by the use of the cutaneous, reinforced by the subcutaneous, local test among 509 school children in Vienna. Startling as are these figures they cannot be said to overstep the facts. Closely

comparable are the figures obtained by Nothmann for Düsseldorf, Mantoux for Paris, Petruschky for Danzig, Ganghofner for Prague. Where lower percentages were obtained, as by Engel and Bauer for Düsseldorf and Moro for Munich, the discrepancy may be fairly attributed to the lower delicacy of the test employed. The reliability of these tuberculin tests has been often verified in individual cases by post-mortem examination, and Hamburger records how, in cases at first negative, prolonged search always resulted in the discovery of some small and often calcified focus of disease.

It must be remarked that the figures of Hamburger apply to a poor school population in a large city. A lower incidence of tuberculosis was found by Schlossmann among his private patients and also by Hillenberg under conditions of village life. Such a contrast under different conditions of life would be expected, but Römer points out that the low percentage of Hillenberg might be attributable to the weak tuberculin he used for his test.

The figures given above, then, point clearly to a steady rise in the incidence of infection as the ladder of time is ascended, and teach us that nearly all become infected with tubercle bacilli before school life is over.

In striking contrast to the morbidity curve is the mortality curve of tuberculosis (Chart XXIII). At the outset of life mortality keeps pace with infection, infection spells death, but when the first few years of life are past the striking fact about tuberculosis is its recoverability. The disease is of mild aspect up to the end of school years, when phthisis of early adult age begins to take toll of life. Such a period of relative immunity in the light of the morbidity curve given above suggests to us strongly that such immunity is acquired, and depends on the presence of a hidden focus, probably

in the lymphatic glands, the outcome of an earlier mild infection.

From the **clinical** aspect the two important points to realise about tuberculosis in childhood are the following :

1. That the resistance to invasion by the tubercle bacillus is at a minimum in infancy but gradually increases with age.

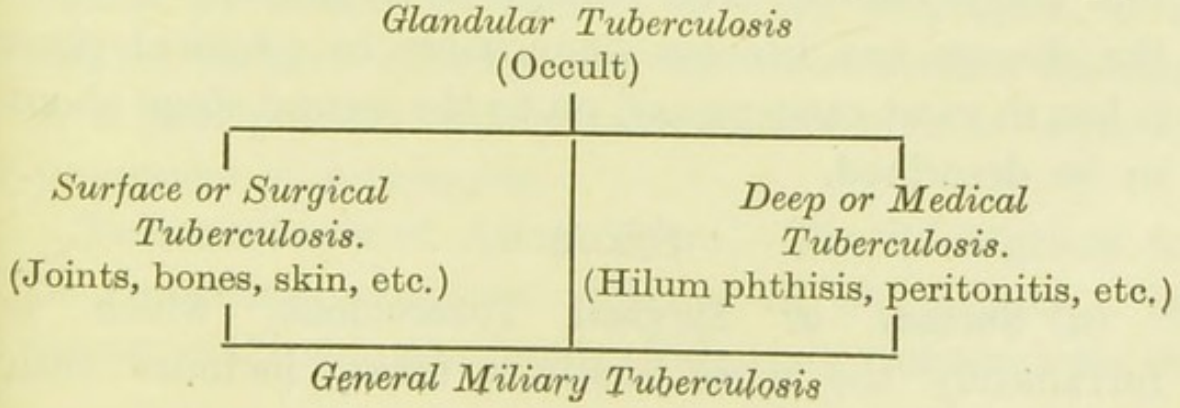
2. That tuberculosis in children tends to spread by lymphatic channels and is therefore (from the clinical point of view) nearly always primary in lymphatic glands.

These two facts give the clue to prognosis and treatment ; they also supply materials for a convenient classification of tuberculosis in childhood. The first suggests the main division of the subject into age periods, the second supplies indications for the subheadings of these groups. In addition we must take into account the fact that in later years of childhood tuberculosis of adult type begins to appear, though still somewhat modified by conditions peculiar to early life.

Infancy Group.—Here we have children with little or no resistance to the tubercle bacillus ; their main defence is at the lymphatic glands, the organs best fitted to cope with infection, but even here resistance is, as a rule, too small to arrest the passage of disease. The tubercle bacillus enters the glands (cervical, thoracic, or abdominal) from the mucous surface of the respiratory or alimentary tract, but the glandular barrier is quickly broken through and a general spread through the surrounding organs tends to occur. If, by good fortune, only cervical glands are infected, these may soften but the child recover ; if, on the other hand, deep

glands are involved a tubercular broncho-pneumonia is likely to follow or a massive blood infection give rise to miliary tuberculosis. Either of these conditions may run an acute course, or this may be more or less protracted with wasting as a prominent feature. It is only when the disease is confined to glands or when but slight involvement of the lung is added that tuberculin treatment offers any hope in infancy (p. 153). This age group may be said to extend from birth up to three or four years, but it must be noted that resistance is rapidly increasing throughout this period, so that the child of four years is in a much stronger position as regards tubercle resistance than is the young infant (Mortality line, Chart XXIII).

Childhood Group.—No hard and fast line separates this from the infancy group, but for convenience we can place under this heading children from four years old upwards. The bacillus is still arrested in the glands, and now the general resistance, and especially the resistance of the lymph glands, being greater, these are able to limit the disease in many cases, and in more and more as age advances. Hence, among this group at least two stages must be recognized: (1) The stage of localised disease in the glands. (2) The stage where the disease has passed beyond these into other organs.



From this table it will appear that the further stage of tuberculosis in childhood, once the barrier of the glands is overstepped, may show itself in two groups according as external and comparatively unimportant structures, or internal and comparatively vital organs are attacked.

STAGE 1.

Glandular Disease (manifest or occult). In most cases the portal of entry is the buccal, respiratory, or intestinal mucous membrane, the clinical focus appearing in the **cervical, intrathoracic,** or **intra-abdominal** glands. When the first occurs we have the common cervical adenitis. Intra-abdominal glands are sometimes discoverable to palpation but in many cases these, as well as the intrathoracic glands, have to be grouped under the heading **occult tuberculosis.** Here the disease may remain quiescent, and with considerable involvement of intrathoracic glands the child may remain fat and rosy. Under such circumstances the condition is unsuspected unless some accident, as tubercular meningitis, supervenes. In a proportion, however, the disease manifests itself by general symptoms such as wasting, slight fever, and characteristic cough, and these may lead to an attempt at diagnosis which, even with the assistance of a skiagram, is at this stage difficult and sometimes impossible. When the disease has become diagnosable by physical signs it has in most cases passed on to the second stage about to be described.

STAGE 2.

(*a*) **Surface or Surgical Tuberculosis,** which is fortunately the more common form, includes such

conditions as joint disease, dactylitis, subcutaneous abscess—in short all the common and often multiple tubercular lesions which occur within easy reach of the surgeon's knife. Such conditions are mostly benign in their course, and comparatively amenable to treatment, but the underlying occult disease from which they sprung must not be forgotten.

(*b*) **Deep or Medical Tuberculosis.**—This term may be applied to those cases where the spread takes place into adjoining organs instead of through the blood to distant parts. Thus arises that form of tuberculosis of the lung conveniently described as hilum phthisis; also disease of the pleura, of the peritoneum, or of both these membranes together. Hilum phthisis is a very serious condition and of worse prognosis than is apical phthisis in the child. This may be so partly because the disease is not recognised till it is anatomically well advanced, the presence of a few tubercles in the lung where the bronchial glands are tubercular, being, probably, a common and recoverable condition. Tuberculosis of pleura and peritoneum, where serious disease of the underlying organs is absent, is a condition very favourable for tuberculin treatment. The possible accident (if one may so name it) of tuberculosis in all its stages, whether glandular alone, or glandular accompanied by disease of surface or deep structures, is a sudden massive infection by the blood stream leading to a fatal general miliary tuberculosis with or without symptoms of meningitis.

Tuberculosis of Adult Type.—The third group to be considered concerns children of older years. In young children, as already indicated, tuberculosis of

the lungs tends to be secondary to tuberculosis of the intra-thoracic glands and to spread inwards from these, but from the age of 7 or 8 years upwards true apical phthisis, a fibro-caseous tuberculosis of chronic type starting at the apex of the lung, begins to appear. In these early years it is a rare disease, but it becomes more and more frequent as age advances. Now the striking point about this phthisis in children, in many cases, is its mild aspect ; occasionally it is virulent and rapidly fatal, but as a rule it runs a more benign course than in adults and recovery from quite advanced stages may occur.

We know that, auto-infection apart, there exist two paths by which the tubercle bacillus may travel to the lung—the respiratory path of the old standing inhalation theory, and an alimentary path of more recent discovery. Now alimentary infection—through the intestinal wall, by the lymphatics and thoracic duct into the systemic veins, and so through the heart to the lung—gives the child a mechanical advantage over the adult owing to the much greater filtering power of the lymphatic glands in early years ; the bacilli tend to be arrested in these. But when infection occurs through the respiratory tract this advantage no longer tells. We find, however, that there is a further reason, other than mechanical, why phthisis in children tends to run a mild course towards recovery. For such comparatively mild character and non-lethal course is a conspicuous feature of all forms of tuberculosis occurring in later childhood. Children of school age, to put it shortly, show a very decided immunity against tuberculosis and thereby present a striking contrast to the great suscep-

tibility of infancy and, to a lesser degree, of early adult years.

The removal of the most susceptible during the first year or two of life is, no doubt, a factor but to it must be added, we think, an acquired immunity due to a previous mild infection. The reaction to tuberculin tests in such cases not only points to the presence of a focus of disease, but also indicates the sensitiveness through which this affords immunity against further infection. Just as in immunised cattle, so in these children a mechanism is present whereby they are protected against the dangers of a fresh invasion (*see* Chart XXI, page 119). As years pass over such immunity is gradually lost till, in eary adult life, phthisis becomes the common and severe disease which it is at this period.

SELECTION OF CASES—INDICATIONS AND CONTRA-INDICATIONS

The question of suitability for tuberculin treatment can only be decided for the individual case, but a few guiding principles may be put forward to help the doctor in his selection. In the first place it may be said that there is only one **indication** for treatment—namely uncured tuberculosis. Admitted that spontaneous cure is common, it can never be foretold that any particular case will recover without treatment, consequently the indications are to treat all cases of uncured tuberculosis unless contra-indications exist. Such **contra-indications** may be of two kinds: (1) unsuitability of the method of small doses here discussed; (2) contra-indications against tuberculin in any form.

1. **Unsuitability of the small dose method** depends solely on the question of auto-inoculation. It has been already pointed out (p. 18) that where autotuberculin is supplied in large quantity from the patient's lesions the action of small doses from outside can never be equal and efficient. Cases where such auto-inoculation cannot be controlled are unsuitable for this method of administration, and must be treated on rising dosage with the production of tolerance.

2. **Contra-indications to Tuberculin Treatment in general.**—These arise in the main from the acuteness, or too advanced spread of the disease, under either of which conditions tuberculin is unsuitable. Since such contra-indications are those of autotoxic disease there is no need to consider them further at this point. There remain, however, certain relative contra-indications under the small dose system which may reasonably be considered here. Of these **emaciation** is that which most commonly comes under consideration, and there is no doubt that where this is present in marked degree tuberculin is generally useless. As a rule the condition points to widespread disease, and in young children such may exist with very equivocal signs, and almost no other evidence of auto-inoculation; in other cases the trouble is one which affects nutrition through the alimentary tract—widespread involvement of mesenteric glands or intestinal ulceration. In all such cases the outlook is highly unfavourable, and if tuberculin is given at all it should be given in minimal doses. The state of nutrition is a factor which controls very greatly the administration of tuberculin; even conditions of flabbiness and want of tone imply a reduced power of

response, and dosage should be kept low till a higher state of nutrition can be achieved.

Another condition where response to tuberculin is reduced or altered in marked degree is the condition of **infancy.** As is well known the resistance to tuberculosis is at a minimum during the first year of life (p. 177), and the effect of tuberculin treatment is always relatively disappointing. Tubercular areas, at this age, show little tendency to productive inflammation and much proneness to softening, and tuberculin confidently administered is only too likely to encourage the latter. On the other hand no other remedy but tuberculin is available, and in its absence the outlook is highly unfavourable. Infancy therefore does not constitute a contra-indication to tuberculin treatment but only an indication for its very cautious administration, covered by a very guarded prognosis as to the outcome of the trouble.

A further relative contra-indication to treatment lies in the inability in some cases of obtaining reliable data for its control. This will depend on the carelessness or ignorance of the patient or his friends. Tuberculin then becomes highly difficult to administer, and it may be impossible to treat such cases unless a reliable nurse can be obtained, or they can be moved into an institution.

CONDITIONS OF ADMINISTRATION—HOME OR ELSEWHERE

Under the method of immunisation without tolerance suitable for the treatment of localised tuberculosis,

the conditions are peculiarly well adapted to home treatment. The injections are given at long intervals, and, when the suitable dose and interval are discovered, but little change may be needed over many months of treatment. A reliable nurse, or the mother, must be trained to watch for the special indications required in regulating dosage, and often the latter is the more subtle observer of the slight changes marking the appearance of a negative phase, and the change of this to a positive phase. In addition, a temperature chart must be kept and dressings may need application. It is only under conditions where special observation or surgical measures are required that home treatment ceases to be convenient. There exist, however, hygienic grounds for alteration of home surroundings and sometimes removal from them in many cases of localised tuberculosis. These may be considered under two headings—Removal of source of tubercular and removal of source of mixed infections.

Removal of Source of Tubercular Infection.—In all cases of tuberculosis of children the source of infection should be investigated. In adults and older children this attempt is generally futile on account of their constantly changing environment, but in young children and infants this is by no means the case. Their surroundings are relatively fixed, and their relation to those surroundings very close and intimate. Consequently parents, nurses, servants, all in short who come into near contact, must be suspected as possible tubercle bacillus carriers, and any case of ill-health, wasting, or cough in the household must be investigated. It was pointed out by Hamburger that in the case of tubercular

infants the presence of open tuberculosis in some member of their immediate circle could nearly always be demonstrated, and it is obviously foolish to direct all one's attention to the soil and neglect the constantly falling seed.

Removal of Source of Mixed Infections.— Not only does tuberculosis by leading to ulceration open the door to other infections, but in addition other micro-organisms prepare the soil for the tubercle bacillus (*see* Glands, p. 221). Under either alternative it is fully proved that tuberculosis spreads more rapidly, and more quickly gets out of control in the presence of a mixed infection. Such being the case, our utmost endeavours must be directed to eliminating or avoiding the growth of other organisms. Their treatment when present will be considered under the heading of mixed infections, our purpose here is to consider their avoidance. This may be accomplished both actively and passively—actively by rigid asepsis and, in the case of glands, by the strict exclusion of all cases of mucous-membrane catarrh, whether called influenza, or masquerading as an ordinary "cold;"—passively by the adoption of an Open-Air Régime. The avoidance of mixed infections is not the smallest item in the value of open-air treatment. Its effects on general health are not denied, but the isolation from infections which it accomplishes is the marrow of its application. Even in towns it can be carried out with complete satisfaction, given a space sufficiently dry, and open to light and air to allow of its adoption. In most cases of localised tuberculosis, however, at some time or other in their course a change to seaside or country is indicated. In

this case isolation from infections is still more complete, and in addition is added the striking effect of mental change and skin stimulation on processes of nutrition. The spirits brighten, the appetite increases, and corresponding progress is made. Especially valuable in this respect is the air of the Kent coast for localised tuberculosis in children. The authors can vouch for the remarkable effects of this air on nutrition, probably through the increase of nervous energy produced by its stimulating effects on skin and surface structures. This increased nervous energy leads to increased efficiency of bodily functions, including the very important ones subserving alimentation.

OBSERVATION AND CONTROL

It is obvious that in the home treatment which generally suffices for cases of localised tuberculosis, observation must be in part the work of the nurse or mother of the child. The information required by the physician may be put under the following headings—

1. **Evidence of Auto-inoculation or its Absence.**—This will be derived mainly from the temperature chart, but also to a certain extent from observation of symptoms such as malaise, loss of appetite, headache, following unusual exertion.

2. **The Immediate Effects of Tuberculin Injections.**—This comprises all the phenomena of the negative phase, and their duration. A local reaction must be watched for, general symptoms recorded, and the changes in the area of disease estimated. The

doctor should arrange to see the case himself during this phase on some occasions at least. In addition the "rebound" to positive phase and its accompaniments must be looked for and recorded.

3. **The Rate and Extent of Progress.**—These can only be gauged over comparatively long periods of time, and must be estimated by accurate records taken at the beginning of treatment and at convenient intervals. General progress is best estimated by increase of weight and a corresponding accession of nervous energy. Local improvement is measured with the eye and touch, generally assisted by the probe, tape measure, and other instruments.

The means whereby we obtain the information above outlined as necessary for the control of treatment are mainly the following—

Temperature.—This is best taken in the rectum, for reasons given on page 83. A chart should be kept, and for this purpose the three months' chart illustrated at the end of the book is to be recommended. On it should be recorded, in addition to the temperature, the weekly weight, and each injection of tuberculin. The temperature should be taken at first every four hours, and later morning and evening (6 p.m.) and, in addition, at any time when unusual symptoms suggest the presence of fever. The pulse record is of little value in children.

Weight.—Cases should be weighed at the same hour and in the same clothes once weekly and the result recorded on the temperature chart. Changes of weight are of especial value when the original home conditions are maintained during treatment.

Observation of General Symptoms.—Observers vary in their skill, but much can be accomplished by training. Observations should be recorded daily, and for this purpose a chart such as that on page 165, is very valuable. By this means the amount and duration of negative phase phenomena are accurately measured, and these form an essential guide to the adaptation of dose and interval.

Observation of Local Symptoms.—In the forms of tuberculosis coming under our present section there is generally some visible or palpable lesion present. It is very important, as has been mentioned elsewhere, that the doctor should provide himself with a very accurate record of the local conditions at the beginning of treatment so that he may be in a position to justly estimate the presence or absence of progress and, in the former case, its amount. The tape measure, the probe, and convenient standards of size and shape must be pressed into service, and in cases of bone or joint disease the skiagram is almost essential. Observation of the focal reaction must be directed to such points as swelling, colour changes, increase of discharge, and the length of time over which such changes are present.

Special Investigations.—Under this heading there remains only opsonic determination to consider, for other special means of observation and control are at present lacking. If the reader turns to the section "Principles of Administration" (p. 191), it will be obvious to him how much the small dose system of tuberculin administration relies for its application on the work of the opsonic school, but having learnt the principles we can as a rule dispense with this guide.

Mention may be made also here of the use of the opsonic index before and after exercise as a test of autoinoculation or its absence, and hence of cure, in cases of disease brought to an apparently successful issue.

PRINCIPLES OF ADMINISTRATION

These depend upon our knowledge of the action of tubercle products on the tubercular organism, and especially of the influence they exert on the focus of disease.

The Immunising Response.—The whole therapeutic effect of a dose of tuberculin may be spoken of as the immunising response, and our understanding of what takes place is derived partly from clinical observation, but very largely from the work of Wright and his followers on what is known as the opsonic power of the blood. This is a property of the serum whereby it prepares the bacilli exposed to it for phagocytosis by the leucocytes and, presumably, also by the fixed cells of the body ; opsonic power is probably a by-product effect of antibodies possessing other functions and, since it is comparatively easy to measure, it forms a convenient indication of the amount of general antibody formation in the body.

The injection of tuberculin affects the opsonic content in a characteristic manner. A suitable dose is followed by a fall of opsonic power commonly spoken of as the " negative phase " of immunity, and this is followed by a rise called the " positive phase " which, after the " high tide " of immunity has been passed, gradually falls again till the original line or one slightly

higher is reached. The value of this immunising response depends on the fact that in localised tuberculosis the opsonic content of the blood (representing antibody formation in general) is below normal, and is especially low in the tubercular areas themselves. Tuberculin raises the antibody content over a definite period of time ; but it does more. For as a result of clinical observation we discover other effects accompanying the immunising response. The negative phase corresponds to a period of malaise, loss of appetite, and general depression, and also to congestion and increased exudation in areas of local disease. These are no other than the " general " and " focal " elements of the familiar tuberculin reaction, though here exhibited on a mild scale, and the latter of these is of no little utility in localised tuberculosis as a means of directing the blood stream into the diseased areas. This focal effect can be increased at will as we shall see later, by the application of local derivatives. The positive phase of opsonic content is also found on careful observation to have its clinical accompaniment—a general increase of well-being and waning of symptoms on the one hand and, on the other, improvement in the local area of disease following the temporary hyperaemia.

Application of the Immunising Response.—When we turn to a consideration of how the elements of the immunising response should be applied to the treatment of local tuberculosis we find the following indications stand out most clearly :—

1. To keep the opsonic power of the blood at a high level for as long a period as possible.

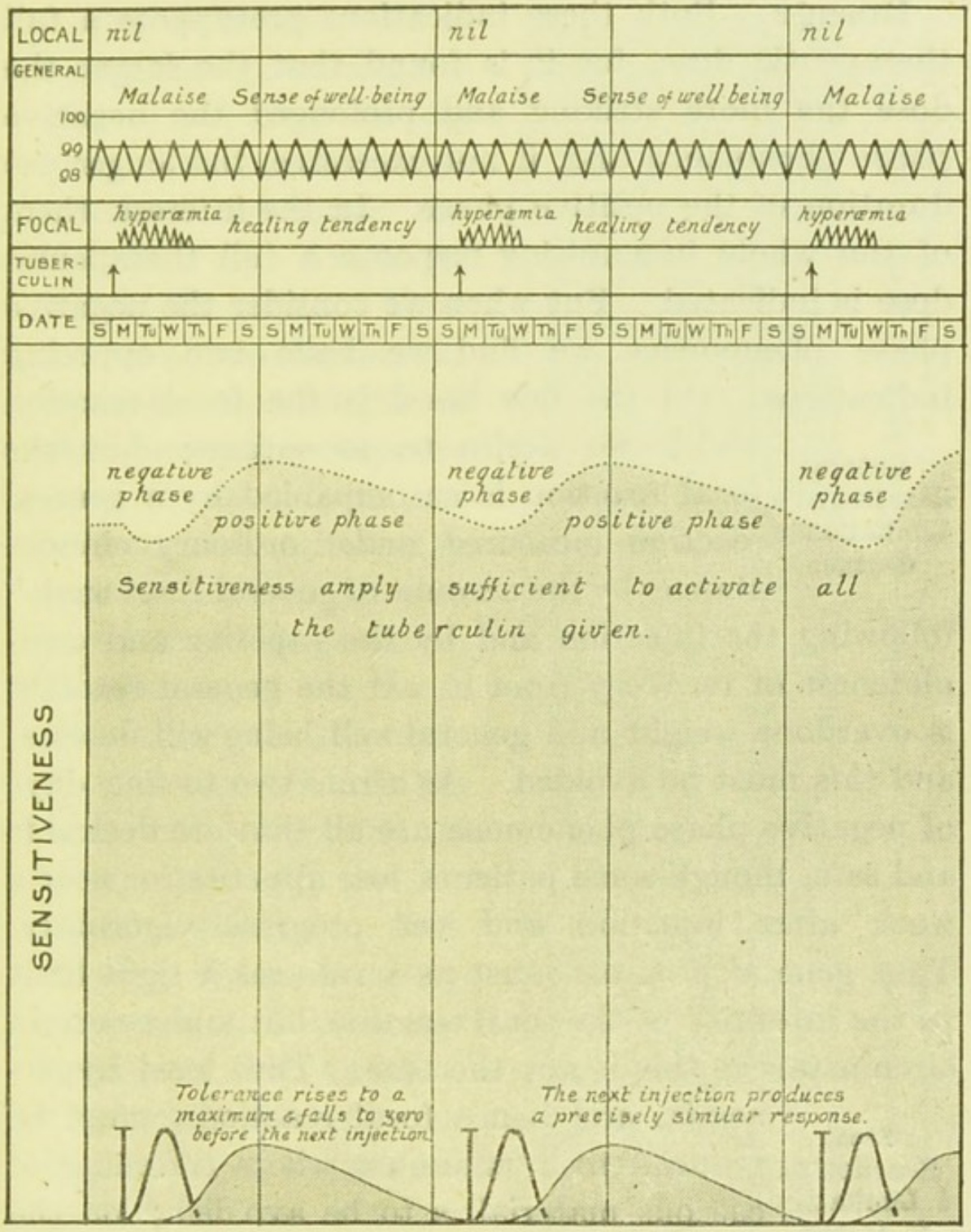


CHART XXIV.—Method of immunisation without tolerance; a second equal small dose is given when the response to the first is over.

2. To obtain and control the focal reaction occurring during the negative phase with a view to flushing the tubercular areas with blood.

Dosage.—Both these indications presuppose a full therapeutic dose, for it is found that the larger the dose the more striking and prolonged the negative phase phenomena and, if not excessive, the longer the duration of the positive phase. In the interest, then, of the whole immunising response a full therapeutic dose is indicated. But when we consider the negative phase phenomena we find we have two opposing indications. On the one hand is the focal reaction which we desire to encourage; but the focal reaction is accompanied by a general reaction measured under ordinary circumstances by the amount of general "set back" following the injection and by the rapidity and completeness of recovery from it. If the general reaction is overdone weight and general well being will decline, and this must be avoided. As a rule two to four days of negative phase phenomena are all that are desirable and safe, though some patients lose appetite for near a week after injection and yet progress vigorously. Thus general progress must as a rule set a rigid limit to the intensity of the focal reaction, but under certain circumstances this is not the case. Thus local hyperaemia, and hence focal reactions, must be reduced to a minimum where softening of caseous material is to be avoided; on the other hand where a local lesion does not respond, more vigorous treatment, even to the losing of weight from excessive general reaction, may be for a time desirable in a well nourished patient, though this measure can only be advised on occasion and in the hands of the experienced.

General Reaction as a Limitation to dosage.

Focal Reaction as a Limitation to dosage.

The Interval. — The indications governing the size of the dose having been mentioned it remains to determine the interval at which it should be given. Here we have two factors to consider, the length of the immunising response —for it should be our purpose to give the opsonic positive phase as much scope as possible; the length of the wave of tolerance to tuberculin (p. 13)—for till this has waned a reinjection of equal size will not be equally efficient. Fortunately the immunising response and tolerance wave run side by side, and our indications for the spacing of dosage can be derived from either or both sources of information. As regards the immunising response we can by the determination of the opsonic index directly find its

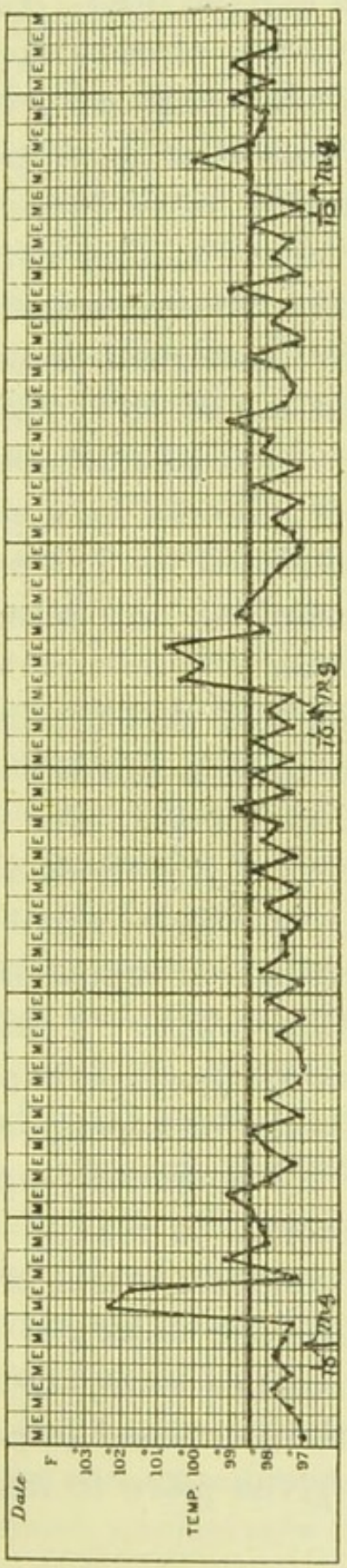


CHART XXV.—(From Latham and Inman, *Lancet*, 1908, ii. 1280, by kind permission.) Shows that after a very effective dose (subcutaneous) tolerance has not waned in three weeks since repetition of the same dose produces a lessened response.

length on a given dose. In absence of this we can use our knowledge, already derived from this source, that the response varies with the size of the dose; on a minimal dose it is short, perhaps ten days, on a large dose it is long, three weeks or over. On the side of the tolerance wave similar evidence is forthcoming; the quantitative cutaneous test has shown that sensitiveness returns to its original point within fourteen days on a dose about one-tenth of that capable of giving a general reaction. That a full therapeutic dose giving a marked reaction is followed by a prolonged tolerance wave is well exemplified by Temperature Chart XXV, where sensitiveness has not returned to its former level in three weeks.

Thus we find that the interval must depend on the size of the dose, and it is obviously of equal importance with the dose itself. For if reinjection is left too late time is lost; if it is made at too short interval the dose is ineffective. If maximal response is aimed at, as in the treatment of lupus, the intervals must be long, perhaps three weeks; if small doses are given the intervals should be short, perhaps ten days. On the average doses suitable for average cases an interval of fourteen days is very commonly appropriate. The suitability of the interval is readily gauged by the equality in effect of the doses. If it is too short irregular response will occur—one dose will be inefficient because given on the tolerance wave, the next may lead to a reaction because the shortened response following an inefficient dose has given place to fresh reactivity.

CHOICE OF A TUBERCULIN

We have already indicated the essential oneness of action of all the tuberculins (p. 36) ; with almost any preparation success may be achieved, the main requirement being thorough familiarity with the brand in use. We have, nevertheless, pointed out that certain differences also, depending on Solubility, Toxicity, and Strength are to be found among tuberculin preparations. These differences separate especially the extract tuberculins, represented by **T**, from the endoplasm tuberculins represented by **TR**. The former contains the soluble products of the bacillus ; the dose is quickly absorbed and sharp reactions are readily produced. It is also, on account of the manner of preparation ; more toxic (p. 38). Endoplasm preparations, on the other hand, are very insoluble and hence are but slowly absorbed ; their effects are gradually produced, and reactions tend to be mild and prolonged.

When we consider the indications for treatment in localised tuberculosis we find that the insoluble preparations offer obvious advantages. Our aim is to produce mild but prolonged focal reactions ; a good immunising response with minimal disturbance of general health. This seems best achieved by the endoplasm preparations, and these appear to us to possess the additional advantage that more subtle gradation of dosage can be achieved than with the more soluble preparations. The endoplasm tuberculins are also recommended by custom and experience, for it is with these preparations almost exclusively that the small dose treatment rose into prominence in the

hands of Wright and his followers. We would then recommend the use of **TR** or **BE** as standard preparations in the treatment of localised tuberculosis, and our feeling is that the former, which contains the endoplasm alone, is, on this account, more especially suitable. In the treatment of autotoxic tuberculosis we have for convenience reduced the initial dosage of the tuberculins to a common figure. Under the method of immunisation with tolerance this is a safe and highly rational practice, since the initial dose is minimal and in all stages the relation of one dose to the next is of far higher importance than the actual quantity administered. On the method now described, however, it is the actual dose which tells ; the initial dose is larger because there is less risk of harm and sensitiveness is more easy to gauge. Hence it is of real importance on this method that the relative strength of the preparations used be known as accurately as possible. Unfortunately no real comparison can be made between **TR** and **BE** and only clinical experience can deduce their relative potency. On these grounds it is the custom of the writers to consider **BE**, for purposes of administration in cases of localised tuberculosis, two or three times stronger than **TR** on the old system of measurement by milligrams of solid substance used, and consequently of nearly equivalent strength, volume for volume. In the present section the dosage is given in terms of **TR** as this preparation is representative of the endoplasm tuberculins and gives excellent results in practice.

INITIAL DOSE

At the beginning some dose has to be chosen on which to start treatment and, with experience, the optimum dose will often be struck with no further trouble at the outset. The dose, as would be expected, is more easy to gauge in localised tuberculosis, where tolerance is never present, than it is in cases of autotoxic disease. For cases of phthisis sensitiveness has been shown to vary among individuals up to the proportion of 100 : 1, but it seems highly unlikely that this can apply to cases of localised tuberculosis. The quantitative cutaneous test (p. 64) by which this result was obtained in the hands of White and Graham seems likely to prove of great utility in the future as a means of determining the initial dosage. In the absence of such a test we are reduced to the method of giving an "average dose," or such dose above or below this as our general impressions lead us to believe that the individual case will require.

Our own plan in cases of localised disease is to consider ·05 c.mm. as a probable dose for an average adult and to calculate children's doses from this according to their weight. Thus a child of $2\frac{1}{2}$ to 3 stone will start with a quarter of an adult dose, and a child of $3\frac{1}{2}$ to 4 stone with one-third of such dose, and these will be found as a rule rather below than above the optimum dose in average cases. In the case of infants, however, in whom disease is generally active and sensitiveness high, a further reduction in dosage is wise at the outset.

Having started in this manner the result will ob-

viously be success, or failure, and the means whereby the optimum dose is attained by a study of the general and local effects of treatment must now be considered.

THE OPTIMUM DOSE

General Indications of Success or Failure.—When things are as they should be the weight begins to rise, often at the rate of 1 or 2 lb. per month. The rise is accompanied by increased appetite and a general feeling of well-being, so that the child takes more notice of his surroundings and more interest in his toys. This general improvement is commonly broken by a slight "set back," corresponding to the negative phase and representing a slight tuberculin reaction, for a day or two immediately following each injection. At such times the child becomes languid, loses appetite, and may even vomit. The temperature is seldom affected, but if previously raised it may drop to normal for a few days. Such general symptoms are compatible with a suitable dose; if they are absent the dose is too small for an average case (it may be kept small for special reasons), if they are not quickly recovered from the dose is too large and must be reduced. In measuring these negative phase phenomena in a child care must be taken that they are not overlooked or underestimated by unobservant friends; parents and nurses differ widely in the amount of skill they acquire in gauging the amount and the length of set back following a tuberculin injection; it is best to supply them with a chart for daily observations so

that the nature and duration of any symptoms may be available to the doctor at his next visit.

When the dose is too large improvement, both general and local, ceases and the child begins to look tired and cheerless, becomes flabby, and the appetite wanes and weight is lost. This is a condition which must on no account be allowed to come about, and the dose must be quickly altered for its avoidance. In a strong, well-nourished child with strictly localised disease a slight temporary loss of weight may be allowed when this is accompanied by local improvement as the result of focal reactions.

When the dose is too small no effect either general or local is observed and the indications are to increase it.

Local Indications of Success or Failure.—Local lesions may be either hidden, as for instance tubercular thoracic glands, or manifest. When they are manifest they may be either visible or only apparent to examination with special instruments such as the stethoscope or laryngoscope. Since it is especially with more or less visible lesions that we have to deal in the small dose system of tuberculin administration, we will consider local lesions as they appear to the eye as in a tubercular sinus.

Corresponding to the general set back accompanying the negative phase of opsonic power certain changes are observable in the area of disease. The tissues become swollen and congested, and any discharge present is temporarily increased. This is the focal reaction, whose main attribute is a local hyperaemia. Following this and corresponding to the positive phase of opsonic power, a marked improvement occurs which may

proceed to a temporary healing of the focus by the end of a week or a fortnight. Unless final healing is near, however, the disease again relapses, and this alternate relapse and improvement follows each injection till at last the conditions are suitable for permanent closure.

Dangerous Focal Reactions.—General and local conditions must always be considered together when indications for tuberculin dosage are sought. At the beginning of a course of treatment special consideration must be given to the improvement of the general condition unless this is already excellent. When this point has been assured the local needs must then be more closely studied. General and local improvement commonly run hand in hand, but it may happen that local needs render inadvisable a dose which would otherwise suit. For the focal reaction carries with it under certain conditions an element of danger; the increased blood supply is in many cases a stimulus to healing processes, but in some cases it leads to softening of tubercular areas. This is especially apt to occur in infants, in whom the resistance to the tubercle bacillus is at a minimum, and at almost any age where large amounts of caseous material are present. Such softening in certain situations, as in the intrathoracic or intra-abdominal glands, may lead to very serious consequences, and even in superficial areas is generally undesirable. Under such circumstances the indications point to avoidance of marked focal reactions and hence restrictions of dosage. With such dosage a ten days interval may be sufficient, and no such striking general improvement can be expected as in cases where a more ample immunising response can be permitted.

It is however wiser to achieve a moderate but sure improvement than to run the risk of initiating a process we cannot check. It has been mentioned elsewhere, and may be here again insisted, that negative phases in excess or under contra-indicating circumstances, are just as great a danger under the small dose system of Wright as they are when called "tuberculin reactions" under the system of rising dosage suitable for cases of auto-toxic tuberculosis.

Opsonic Control.—We have seen how in the general and local conditions we have ample indications to supply us with the necessary guides to treatment. If more than these are needed a careful study of the opsonic index may be of assistance. The authors have already expressed their indebtedness to the study of this method (p. 134) and highly recommend it as a means of "learning the ropes." With experience, however, the opsonic index becomes unnecessary and we can derive the information required for rational treatment from other sources.

DURATION OF TREATMENT

This may be considered from the prognostic and from the therapeutic point of view. The **prognosis** as regards length of treatment is of the utmost importance on account of the natural impatience which is liable to overtake the patient and his friends during the long-drawn-out healing of tubercular processes. If the matter is explained at the beginning it is less likely that the doctor will be blamed, or that a satisfactory cure

will be interrupted through the ignorance of the sufferer. In cases of bone and joint disease a skiagram will sometimes help to convince the friends that the gaps so clearly visible cannot be filled in a few days or weeks. The authors are in the habit of warning patients that the cure is likely to take at least as much time as the disease has already lasted ; this prepares their minds for the long struggle with disease and anticipates the disappointment of hope deferred.

From the **therapeutic** point of view treatment in localised tuberculosis must necessarily be continued till the local lesion is healed and, for safety, for several months beyond this. A cure is admittedly difficult to gauge, and relapse is very liable to occur if treatment is omitted too early ; this is especially the case in lupus, where relapse constitutes the most unsatisfactory feature of its treatment. But another reason exists in cases of localised tuberculosis for prolonging treatment after the local disease has healed. This is the presence in all such cases in children of an occult primary focus in glands, whether of the abdominal or the thoracic chain, and, in the latter case, of a lung lesion besides in nearly all cases. Such glandular lesions are slow of healing and a year's treatment is by no means too long to cover the risks due to this primary focus. The treatment in its later stages involves but little trouble either to the doctor or the patient for, in many cases, the same dose may be given at the same intervals without change over long periods of time. At the end tuberculin may be given at longer intervals while the case is kept under occasional observation to prevent relapse.

REPETITION OF TREATMENT

The treatment of localised tuberculosis is directed to cure, and if the directions given in the foregoing section are followed it is unlikely that any repetition of treatment will be required.

AUXILIARY TREATMENT

Tuberculin is no passive immuniser to neutralise the poisons of disease. Its action presupposes a power of response on the part of the body ; it is a stimulus to the defensive mechanism, a call for active effort on the part of the tissues. Consequently no measures must be neglected which may help to put the body in the best possible condition to respond to this call. Some go so far as to withhold tuberculin in cases where malnutrition is marked whilst hygienic-dietetic measures are directed to improving this. We think rather that such measures should go hand in hand with specific treatment, but also that auxiliary treatment is, on occasion, of such vital importance that tuberculin cannot be given without it. Here we have spoken of auxiliary treatment in the restricted sense of treatment directed to improvement in the general condition of the patient, but it will be obvious that this is only one side of the picture. We must, in addition, consider under this heading auxiliaries to the tissues actually fighting the bacillus—the so-called diseased area or focus of disease. We shall take the subject therefore under two headings—those measures which influence

the general condition, and those which influence the local condition.

General Auxiliary Treatment.—This, save for the special subject of auto-inoculation to be immediately considered, amounts in practice to hygienic-dietetic treatment. It aims at the full efficiency of all the bodily functions, the improvement of general nutrition and therewith increased power to fight disease. In addition to open-air régime and change to sea or country which have been already discussed, it includes such items as clothing, baths, and sleep, which do not concern us in this volume.

Control of Auto-inoculation.—Under the heading of general auxiliary treatment must come also remedies directed to the control of toxin-supply from the seat of disease. For the successful use of the method of tuberculin administration we are discussing auto-inoculation must be eliminated or reduced to a minimum, and this is achieved mainly through the provision of rest for the diseased part. Any movement leading to symptoms of auto-inoculation, whether fever, loss of weight, or failure of tuberculin treatment, must be controlled, and it is obvious that the necessity for this will vary greatly with the nature of the disease. Thus in a large joint, such as the hip, auto-inoculation readily occurs, and complete rest must usually be insisted on as a *sine qua non* to tuberculin treatment. In the small areas concerned, however, in a tubercular dactylitis no such measures may be necessary; the conditions are those of a local disease solely. The application of the principle of rest necessarily varies according to the part diseased; thus a tubercular

peritonitis must obtain rest by recumbency, a diseased elbow with a splint, a hip joint with some form of extension apparatus or a Thomas' splint.

In many cases, consequently, the elimination of auto-inoculation needs for its accomplishment the use of apparatus forming part of the surgical treatment so often necessary in localised tuberculosis.

A further matter for mention at this point is the power we appear to possess of relieving undue congestion of inflamed areas, and thereby improving the blood supply, by the exhibition of certain salts (citrates, etc.) either by their effect on elimination of tissue fluids by diuresis, or, perhaps, in reducing coagulability of the blood.

The opposite action is claimed for the soluble salts of calcium, which are said to increase blood coagulability and limit auto-inoculation; the authors have not satisfied themselves that they have obtained the latter clinical effect in any cases they have treated.

Local Auxiliary Treatment may be divided into—(1) local measures which tend to increase the efficiency of the focal reaction; (2) surgical treatment.

1. **Aids to Focal Reaction.**—Of these the most readily obtainable is **heat.** This may be applied to areas of local disease as fomentations, hot sand or salt bags, or hot water bottles, and these may be protected from open wounds by a layer of dressings. Of somewhat similar action are the **light rays** (as Finsen lamp) used with success as an auxiliary to tuberculin in the treatment of lupus (p. 231). Other means of inducing hyperaemia in the area of disease are those employed by Bier and generally associated with

his name. **Bier's hyperaemia** is obtained in the limbs by application of a bandage, or in other parts by the use of suction apparatus. Bandage hyperaemia, a true passive hyperaemia, is obtained by applying several turns of a rubber bandage at the proximal end of the limb; the test of its proper application lies in the fact that the limb becomes congested, but that there is no pain and the extremity remains warm. The bandage is worn from one to three hours daily, longer application being found to lead to the development of cold abscesses; œdema is to be avoided. Suction hyperaemia, a mixture of active and passive hyperaemia, is applied by cupping glasses furnished with a rubber ball. They are applied for three-quarters of an hour daily, five minutes on and three minutes off and, in the case of open wounds, are used daily till the granulations have become red and firm, and after this less often. Cold abscesses can be cleared at intervals by the use of suction glasses. When open wounds are being treated the surrounding skin must be cleaned with benzine or ether and smeared with vaselin; the glasses must be boiled and kept in antiseptic solution. A further aid to the focal reaction remains in gentle **movements** of the diseased part. Where the tubercular area is of wide extent this is not permissible, but with small lesions a certain amount of movement is not only harmless but advantageous and markedly aids the healing process, doubtless through its effect on blood supply.

All these remedies act by the production of hyperaemia, and this should be judiciously applied. It must be remembered that in inflammation the blood stream

diminishes after a transient acceleration, and this natural process should be imitated. Agents which usually induce active hyperaemia produce, in inflamed parts, only passive hyperaemia as the blood stream is slowed, but even this in excess does harm. A moderate induction of hyperaemia is a valuable aid to tuberculin treatment in open ulcers or sinuses ; to a less extent in early tubercular lesions. Where caseous material is present more certain and rapid softening of this is induced than would have occurred without, and such action may be a disadvantage or the contrary according to the circumstances of the case.

Other measures useful to aid the focal reaction in open ulcers and sinuses may be mentioned under the headings **hypertonics** and **decalcifiers.** They increase the flow of plasma through the open surface by their local action. The former act by increasing the osmotic pressure, and are represented in practice by a 3 to 5 per cent. solution of sodium chloride applied to the wound ; the latter hinder the coagulation of lymph on the surface and are commonly applied as a ·5 to 1 per cent. solution of sodium citrate. These adjuvants were introduced by Wright, and are conveniently used together in a simple solution. The surrounding skin must be protected with vaselin, and the solution should be applied on lint covered with guttapercha tissue.

2. **Surgical Measures.**—These have in the main two aims. To remove dead tissue and to correct deformity.

The **removal of dead tissue** when present in any quantity is a necessary auxiliary to tuberculin treatment. When such dead tissue is inaccessible, as in caseous thoracic glands, encapsulation is all that can be hoped

for, and caution must be taken that focal reactions do not lead to rapid softening. When, however, accessible parts, as neck glands, are under consideration the indications are different. If a small caseous focus is present the gland will retrogress, though slowly and incompletely, under tuberculin treatment. The gland does not disappear but it remains quiescent. When a large caseous core is present this is best removed. On the other hand it may be allowed to soften, as is likely to occur under tuberculin, and be subsequently aspirated. In all conditions of delay in healing investigation must be made into the possible presence of dead material requiring removal. A skiagram will sometimes show that in such cases suspected of harbouring dead tissue the real cause of delay is the large amount of destruction which needs repair, and this must always be borne in mind. In all cases where surgical measures are required these should be timed to coincide with the high tide of immunising response, that is with the second week after a tuberculin injection ; moreover an operation should stand in lieu of the injection which would otherwise follow it, since a free introduction of autotuberculin may be presumed to result from it.

The correction of deformity needs no comment here. It is obvious that in disease of joints, and to a less extent of bones, the prevention or correction of deformity forms a very vital element in treatment and must be relegated to suitable hands.

MIXED INFECTIONS

The course of localised tuberculosis is vitally bound up in the question of mixed infection; indeed the ultimate issue depends in some cases solely on the possibility or not of excluding secondary infection with pyogenic organisms. This is the case especially where large collections of dead material, so-called tubercular abscesses, develop in connexion with such lesions as spinal caries or hip disease. The subject of mixed infection may be conveniently considered under two headings, namely in closed lesions and in open lesions.

Closed Tubercular Lesions.—The striking point in these cases is the acuteness which a tubercular abscess may show without the presence of any pyogenic organism. As a rule closed tubercular lesions as long as they are covered by healthy skin are found to be sterile. Petroff found no organisms in forty-nine cases fulfilling these conditions. In eight cases where organisms were present either a former puncture, or the vicinity of excoriated skin, remained a possible source of infection.

Open Tubercular Lesions only too readily become the home of other organisms. Among forty-four cases examined by Petroff three were negative and the remaining forty-one showed infection with the following organisms—

23 Staphylococcus (16 albus, 6 aureus, 1 citreus).
18 Streptococcus.
8 Pseudo-diphtheria bacillus.
4 Bacillus pyocyaneus.
2 Microc. tetragenus.
1 Bacillus coli communis.

besides a few saprophytes and organisms of unknown nature. The streptococci appear to bear a higher proportion among these lesions than in cases of acute suppuration where Jakowski among 827 cases found 605 due to staphylococci and 154 due to streptococci.

The Results of Mixed Infection are, in the case of wide tubercular areas, disastrous. Much depends upon whether the resulting inflammation takes an acute or chronic form. In the former case a septicaemia may result, and it was the fear of this which led to the conservative treatment of tubercular abscesses before the days of aseptic surgery. An acute suppuration is especially apt to occur where the abscess wall has been damaged, where an incomplete operation has been performed, or the opening is too small and becomes blocked. A streptococcus infection is more to be feared than that with staphylococcus. If, in addition, putrefactive organisms obtain an entrance a very serious condition of sapraemia may be set up.

Not only is the pyogenic organism, however, a danger in itself but it opens the door to further inroads by the tubercle bacillus. It has been shown by animal experiment that much greater destruction occurs in a joint infected with tubercle bacillus plus pyogenic organisms, than with tubercle bacillus alone. But, in addition to this, such ulceration appears to remove a barrier to the generalisation of the tubercle bacillus, for in these cases of mixed infection tubercular areas appear in the lungs at an early stage.

Treatment.—This must be directed in the first place to the most scrupulous asepsis in all matters dealing with tubercular areas. In the case of a psoas abscess

or hip joint sinus this may be a matter of life or death to the patient, and in all tubercular areas is of the highest importance. When a mixed infection has occurred special efforts must be made to keep it in control.

(*a*) **Surgical Measures** will be directed to ensuring efficient drainage, and perhaps counter-drainage, and opening up tracking sinuses or pockets.

(*b*) **Tuberculin Treatment** is by no means contra-indicated on account of mixed infection in localised tuberculosis. By treating the tubercular infection one appears to improve the patient's power of attacking the pyogenic organism. This is exemplified in the case of infected psoas abscess described on page 226, where tuberculin alone was sufficient to restore the patient to health.

(*c*) **Vaccine Treatment.**—The same case exemplifies also how greatly the effects of tuberculin are accelerated in such a case by the addition of a vaccine against the secondary infection. This fact is supported by a consensus of opinion, and in all cases of mixed infection where a large area is involved it is best to investigate the infection and give the appropriate vaccine in addition to tuberculin. In the case of small areas the presence, nearly invariable, of a second organism is no necessary indication for a vaccine and tuberculin alone will generally achieve the desired results.

TUBERCULOSIS OF SPECIAL REGIONS

LYMPHATIC GLANDS

The lymphatic glands are of such essential importance in childhood, where they form the main, and at times

the sole, defence against the tubercle bacillus, that we shall discuss this variety of tuberculosis in terms of the child though the adult is not entirely exempt. Not only is manifest tuberculosis of lymphatic glands common in childhood but it must be remembered in addition that tubercular disease of other parts is nearly always secondary to a hidden glandular focus. Indeed it may fairly be said that all tubercular children possess foci in their lymphatic glands. But the matter may be looked at from another point of view also ; we find in practice that a majority of children, especially of the poorer class, show chronic glandular enlargement mainly in the cervical groups. Volland among 628 school children between the ages of 7 and 9 years found 97 per cent. so affected. Not all such glands are tubercular, but it has been shown that no less than three-quarters of these enlarged glands removed for inspection show tubercular changes to the microscope. Thus we see that tubercle bacilli are frequently arrested in the glands, that the changes to which they give rise are often slight and strictly local, and that only in a proportion of cases does a condition clinically recognisable as tubercular lymphadenitis arise.

Tuberculosis of lymphatic glands may be considered for our present purpose under two headings—Manifest and Occult.

1. **Manifest Tubercular Adenitis.**—For convenience we will consider cervical adenitis as the manifest form because it is the commonest. The conditions we are likely to meet are threefold. (*a*) Glands which are enlarged but in which a diagnosis of tubercle is doubtful. (*b*) Enlarged glands which on account of their

size, consistence, and prolonged presence are judged to be caseous but are not softened. (*c*) Softened glands with or without a sinus.

(*a*) **Enlarged but not Caseous Glands.**—In cases where glands are enlarged but not evidently tubercular it is especially important that the effect of removal of all sources of infection (p. 221) and complete rest of the parts be given an adequate trial. If these fail tuberculin may be used with a good chance in these cases of complete resolution.

(*b*) **Caseous Glands.**—Where a caseous core is present the conditions are very unfavourable for tuberculin treatment. Such dead material is outside the blood stream, and the effects of tuberculin can only be exerted on the surrounding glandular tissues. Healing can then take place only by encapsulation and a very slow shrinkage, but not by complete disappearance. Such a process, where the amount of material is small, practically amounts to "cure" though it is not strictly such. Where caseous material in large quantity is judged to be present it is best got rid of by coreing the gland through an incision or, if the gland is really single, a rare condition, by complete removal.

Where tuberculin treatment alone is elected in these cases considerable patience is required. Improvement is bound to be slow owing to the very slight exchange in these firm glands between their contents and the body fluids outside them; any attempt to accelerate the process by obtaining marked focal reactions, and by the production of hyperaemia through the application of heat or suction is apt to be followed by further enlargement and softening. In infants, indeed, such softening

can only be avoided by the most restricted tuberculin administration, all negative phase phenomena being avoided and attention directed mainly to the increase of general nutrition.

(*c*) **Softened Glands.**—When the glands are already softened the indications for tuberculin treatment are greatly altered. If a sinus is present the resulting drainage draws a good flow of blood fluids through the tubercular tissues and the very best conditions for healing are present. Tuberculin may then be used with marked success if the following points are studied. Firstly to give such doses as will cause slight focal reaction and negative phase phenomena lasting a few days and repeat these doses at about two weeks' intervals, and secondly to see that discharge through the sinus is free and to help it if necessary by the application of heat and hypertonic solutions.

If the softened glands are not yet opened the dead material must be removed. Where the skin is still uninvolved in the inflammatory process an attempt should be made to remove the contents with a large exploring needle entered somewhat from the side through healthy skin. The gland then fills with plasma, and this interchange of fluid leads in many cases to cure without further interference. This manœuvre may be repeated if necessary, but mere refilling of the gland is not an indication for this apart from further enlargement or lack of improvement. Western squeezes out the contents through an opening made from healthy skin with a tenotome, and this method may be adopted where the exploring needle fails to draw. When the skin is involved the gland must be evacuated through an inci-

sion, the process being advantageously followed up by clearing with a flushing curette. Whatever operative measure is adopted it should be timed to hit off the high-tide of tuberculo-opsonic power, and this is present during the second week after a suitable tuberculin injection. It must be borne in mind also that operative measures lead to considerable auto-inoculation, and it is best to omit the usual dose of tuberculin following the operation and let this auto-inoculation stand in lieu of it.

Multiple Glands.—Hitherto we have written as if but a single gland was concerned, or all glands (if more) were in the same stage of inflammation. This is by no means the case in practice when, more commonly, glands in all stages are present and have to be treated. When this is the case that member of the group most likely to give trouble, namely the large gland not yet softened, must receive special consideration. If tuberculin is given freely, or heat or suction applied in the interests of a neighbouring sinus, it must be remembered that such a large gland will probably respond to it by softening, especially if the patient is young. The points for and against permitting this must be duly considered in each individual case, and treatment varied accordingly. It has been our experience also that any rough operative measures such as the use of a Volkmann, or the needless probing of a sinus, also tend to promote enlargement and softening in contiguous hard glands.

Results of Treatment.—As regards the prognosis of tubercular adenitis under tuberculin treatment it may be said to be good where a fair opportunity is given. Sinuses from glands, as indeed all tubercular sinuses, heal with great certainty and comparative rapidity

under suitable tuberculin administration ; periadenitis and thickening of scars are, moreover, very favourably influenced. Caseous glands when still within reach of unassisted tuberculin treatment slowly grow smaller, and there is an accompanying improvement, often well marked, in general nutrition. When such glands however have sunk to the size of a lentil, or even a broad bean, and are hard, no further change is to be expected of them and they will probably remain quiescent. In cases where the disease has been of but short duration before treatment was commenced the diseased glands may disappear. In such cases their tubercular nature is not always evident. There is no doubt that the age factor is a very vital one in the prognosis of tubercular adenitis. The marked lack of resistance to tubercular disease in infancy is well exemplified in glandular tubercle, for in the glands if anywhere healing processes should be active. In these children, however, rapid softening generally occurs, unrestrained or but little restrained, by the administration of tuberculin. In them the slightest focal reaction increases the local disease, and tuberculin should be given in minimal dosage (p. 199) with the object of increasing general nutrition, and tiding them over to the second year when more notable resistance is to be expected. There appears, also, to be some diminution of resistance to tubercular disease about the age of puberty, and, in the St. Mary's Hospital inoculation department, the least satisfactory results were obtained in children between the age of 10 and 15 years. Among these 50 per cent. showed great improvement, 20 per cent. moderate, and 30 per cent. no improvement.

Analysis of the whole St. Mary's Hospital material (79 cases) led Carmalt-Jones to the conclusion that among any eight cases of tubercular adenitis five will show marked improvement (with two or three cures), two will improve slightly, and one or two will fail to improve. It must however be remarked that the cases analysed were of an exceptionally unsuitable character since no less than half of them had been operated upon, and in a quarter of them more than one operation had been performed. In private practice better results are certainly obtainable in cases of this nature.

2. **Occult Tubercular Adenitis. — Diagnosis.** — It happens unfortunately that the glands in which the tubercle bacillus is most commonly arrested, namely those draining the mucous membranes of the respiratory and intestinal tract, are entirely out of our reach. So much is this the case that it requires a distinct mental effort to keep them before us as the probable primary focus in cases of surgical tuberculosis in children. Much more certainly are they overlooked when they constitute the sole focus of disease for, until symptoms such as wasting, fever, and characteristic cough appear, there is nothing to direct our attention to the condition. This is particularly disastrous in practice, for it is at this, clinically the first, stage of tubercular infection in childhood that specific treatment is likely to be successful, and there is no doubt that fatal disease would often be avoided if tuberculin could be used before the glandular barrier is passed. For this reason the utmost effort must be made to discover such cases early, so that they may be treated while the disease is still localised.

Treatment.—When abdominal glands are involved

they are occasionally palpable and their resolution may be watched, but when tracheal or bronchial glands are tubercular the success of treatment must be gauged mainly by improvement in the general nutrition and the waning of symptoms. It is fortunate that the deep glands do not show the same tendency to softening as do those in the neck, but still such an accident occurs not infrequently and leads, in the chest to caseous consolidation of a large area of lung, or in the abdomen to peritonitis or abscess formation. The possibility of such softening must be kept always in mind, and the great probability of hastening it if careless and needless tuberculin reactions are permitted to occur.

The Small Dose versus the Large Dose Method.—The method of small dosage at long intervals is that best suited to the treatment of tuberculosis of lymphatic glands and fulfils all requirements; considerable success has nevertheless been obtained in occult tuberculosis by a mild and limited intensive treatment in the hands of German investigators. Petruschky was the pioneer in this line, and to him is due the credit of insisting on the importance of attacking the disease at this stage while it is still curable. Five such cases were treated by him with success between the years 1893 and 1897 when he first published the results. He used various preparations, including **T** up to 50 c.mm., and gave his treatment in stages with intervals between. Following his lead with equally satisfactory results came Escherich who used **TR** in doses of ·05, rising to·2 c.mm. given once or twice weekly, and Raudnitz who used old tuberculin in weekly doses rising from ·001 c.mm. and given in courses of six months' treatment with three to

six months' country holiday between, after the serial method of Petruschky. Though there is nothing unsuitable in the use of a rising dosage carefully administered in these cases, yet the method of equal doses at long intervals is more rational since there is no indication for raising tolerance. Such small doses give as good results, are more easily administered, and offer more certainty of avoiding reactions which may be harmful. The beneficial effect of tuberculin on nutrition apart from tuberculosis described by certain writers in this country suggests the probability that they were unconsciously treating for malnutrition some of these undiagnosable cases of occult tuberculosis.

Auxiliary Treatment.—In the treatment of tubercular glands no blind attention must be fixed on tuberculin to the exclusion of other measures. The tubercle bacillus generally follows in the path of other infections and settles down in a gland already inflamed. Consequently there exists, clinically, a stage before its presence is suspected, then a stage of suspicion, and finally one of certainty.

Avoidance of Mixed Infection.—In the stage of doubt all sources of infection must be promptly and adequately removed, but in the stage of certainty also the tubercular gland must be protected from added secondary infection Consequently the area draining to the gland or glands, its watershed so to speak, must be carefully investigated and any source of infection removed. Thus in the case of cervical glands the skin, the teeth, the mucous membrane of nose, mouth, middle ear, and throat, and especially the state of the tonsils, must all be investigated and any condition of catarrh so commonly present in the

"scrofulous" must be carefully treated. In the case of the intra-thoracic glands bronchial catarrh must be looked for, and with intra-abdominal glands intestinal catarrh, for these all add a burden to the resistance of glands already in jeopardy. Not only must infections already present be removed however but, in addition, the patient must be protected from any fresh sources of infection; "catarrh" and "influenza," must be kept at a distance.

It is on this account, largely, that an open-air régime is so valuable in these cases, and to it may be added with the greatest advantage in many cases removal to the country or sea. Especially is this important in infants, where resistance is small and the balance readily turned, and also in cases of older children suspected of caseous thoracic glands. The success in Germany of tuberculin in occult tuberculosis was closely bound up with the country holidays which interspaced the courses of treatment; too early return to school life was found to lead only to relapse. It is for these children that the Open-Air School offers such a chance of benefit.

In addition to the removal of sources of infection it may also be necessary to combat a secondary infection already present. All tubercular sinuses are the home of other organisms besides the tubercle bacillus, and such mixed infection in some cases delays or prevents healing, and may necessitate the use of a second vaccine in addition to tuberculin.

Rest.—Lastly, in the case of inflamed neck glands, especially in early stages where many are involved but their tuberculous nature doubtful, it may be necessary to limit movements of the part by the use of a poroplastic splint or occasionally of sand bags.

Illustrative Case.—A girl aged 10 had suffered with enlarged neck glands for years, and one under the chin had been growing rapidly some 3 or 4 weeks. She appeared well nourished, there were nits in the hair but no other source of irritation. Enlarged glands were present in the right posterior triangle, one as large as a cherry; there was also a softened sub-mental gland of similar size. The opsonic index was ·8. Tuberculin **TR** ·025 c.mm. was given on September 5, 1906, and caused 2 or 3 days of negative phase symptoms; later the opsonic index rose to 2 and 1·4. Three weeks after injection the softened gland was unchanged, the other large gland was reduced to one-half of its former size. The softened gland was opened on October 6, and required a further scraping on December 28. Meanwhile on doses of ·025–·03 c.mm. the other glands gradually dwindled in size, and by January 22, 1907, the disease was quite stationary. Tuberculin was continued to April, and when seen again at the end of June the glands remained shotty and the disease quite inactive.

Steps in Treatment.—1. Remove source of tubercular infection where this is discoverable (p. 186).

2. Investigate and purify "watershed" of infected gland — treatment of catarrh, enlarged tonsils, etc. (p. 221).

3. Hygienic-dietetic treatment.—Open-air and good food. Change to sea or country (p. 188).

4. Remove dead material if present in bulk—aspiration, incision, etc. (p. 216).

5. Give tuberculin according to directions (pp. 191—203).

6. Maintain local hyperaemia with heat, hypertonics, etc. (p. 207), caution as to caseous glands and infants (p. 202).

7. Continue treatment up to cure if successful. If unsuccessful, in the case of a sinus, investigate secondary infection and use a second vaccine.

BONES

Tuberculosis of bones, a chronic osteomyelitis or occasionally a periostitis, is best exemplified in the common disease of children called tubercular dactylitis, where the small bones of the hand or foot are attacked, and in Pott's disease where the process starts in the bodies of the vertebrae or the intervertebral discs of the spinal column.

Tubercular dactylitis, often part of a more generalised surgical tuberculosis, may attack many toes or fingers or arise in foot and hand at the same time. The parts being superficial sinuses are early present, and the prognosis, especially as to duration of disease, is dependent on the amount of bone destruction that has occurred before the patient comes under treatment. If a sequestrum is present no healing can occur till this has come away. Where, also, wide loss of bone has occurred, a slow process of contraction of parts, and of new tissue formation to fill up the gap, will delay over months or years the closing of the sinus.

Tuberculin should be given by the method of immunisation without tolerance suitable to localised disease (p. 191–203), mild focal reactions being aimed at. In an early case the results of treatment are often striking; the wound may close after the first injection, but generally opens again to close finally a few weeks later. With widespread disease doctor and patient must possess their souls in patience, for, though tuberculin will hasten healing, yet the course is likely to be tedious if uneventful. In such cases a skiagram will often demonstrate the futility of expecting a rapid result.

Lesions of the hands and feet lend themselves very conveniently to "bandage hyperaemia" after the method of Bier, though the authors have not found this a valuable accessory to tuberculin treatment. On the other hand, a dry sinus may, in these cases, be irrigated with hypertonic solutions (p. 209) with very useful results. Excessive movement of the part must be forbidden; a splint for the hand is often needed, and in the case of the foot walking only does harm; in both extremities, however, some amount of passive movement may be actually of advantage. In cases where tuberculin appears to have no effect, and we have not yet met such a case, the possibility of a syphilitic dactylitis, which we think must be very rare, is to be borne in mind.

Illustrative Case.—A boy aged 1 year 10 months, whose mother had died of phthisis, was brought with the following history. At the age of 10 months a finger was removed for tubercular bone disease and soon after this the disease appeared in both feet and the left elbow. After a year's ordinary surgical treatment the following conditions were present—bone disease of the left foot with a sinus showing much redness and swelling, an abscess on the right foot, a partly healed sinus over the left olecranon process, and a few scars of superficial abscesses. Tuberculin treatment was started in November, 1908, doses of ·017–·02 c.mm. being given at 2 week intervals, with the result that 8 months later all these lesions were completely healed and his weight had risen by 5 lb. He has continued to gain weight since, and in May, 1911, remained quite well.

Spinal Caries.—Tubercular dactylitis was representative of long bones, the metacarpals and metatarsals, as well as short bones, in their relation to tuberculin treatment; spinal caries may stand for bones of mixed structure. But little has been written on the effect of tuberculin in these cases; nothing, so far as we know, in

regard to uncomplicated spinal caries. The following case exemplifies its value where abscess and sinus were also present in a case of Pott's disease, and especially the effect of tuberculin, when persisted in, even where a mixed infection leading to marked pyogenic poisoning was present.

Illustrative Case.—A girl aged 5 years suffered with spinal caries and psoas abscess 3 years previously and had worn a spinal jacket ever since. In March, 1906, a second abscess formed and burst and an open sinus remained. By July her condition was so desperate from the surgical point of view that she was handed over for inoculation treatment. She was then wasted and anaemic with a profusely discharging sinus 6 inches long and a mass of enlarged abdominal glands. Her tuberculo-opsonic index was ·7–·8 and the sinus contained a staphylococcus aureus. Under **TR**, given in doses generally of ·025 c.mm., her general condition rapidly improved and by December the discharge had greatly decreased. A year later she was fat and well with a sinus 1½ inches deep but no trace of glandular enlargement remaining. Then for the first time a dose of vaccine from her staphylococcus, long held over, was given and a month later the sinus was healed. Tuberculin was continued at long intervals, she has continued well, and 5 years later is at school and in perfect health.

Steps in Treatment.—1. Remove sources of infection (pp. 186–187).

2. Place under the best hygienic conditions—open air, good food (p. 187).

3. Facilitate removal of dead bone. Allow time for the replacement of loss of material by contraction of surrounding parts, and formation of granulation tissue. Keep sinuses clean and encourage hyperaemia. Allow some movement but not full function.

4. Give tuberculin according to directions (pp. 191–203).

5. If healing is slow a vaccine from other organisms

present may be tried, and in the case of dactylitis the question of possible syphilitic disease considered.

JOINTS

In no variety of tuberculosis is the effect of tuberculin treatment more difficult to gauge than in joint disease. The slow progress of these cases and the consequent difficulty in following them to a finish ; the great variety, moreover, in the results obtained under any form of treatment renders a personal estimate of the value of tuberculin somewhat open to fallacy. Nevertheless its acknowledged use in other forms of bone tubercle, together with the approval of certain surgeons of experience who have had the opportunity of judging, makes its value in joint disease indubitable.

In the treatment of tuberculosis of large joints great attention must be directed to the question of auto-inoculation. This readily occurs, and must be reduced to a minimum by the application of rest, and often some appropriate apparatus, before the administration of tuberculin begins. Otherwise no success will follow the treatment, which should be that directed to produce immuni ation without tolerance (pp. 191–203). In addition to the provision of local rest, surgical measures for the removal of dead tissues may be required, and the use of a second vaccine where mixed infection appears to exert an important influence on progress.

The results obtained in the out-patient department at St. Mary's Hospital, and investigated by Maynard Smith, give some indication of the efficiency of tuberculin administered by the appropriate small dose method. The patients were provided with the necessary splints,

plaster, or Scott's dressing, and a few were treated with hyperaemia after the method of Bier in addition to tuberculin. Three cases treated from the beginning of their illness were cured, two with complete function and one with some remaining deformity. Of sixteen cases which had been already treated with splints for twelve months, and were handed over to the inoculation department because the result was unsatisfactory, no less than twelve were cured with complete, or nearly complete, function, and four improved and remained under treatment. Even among a further fifteen cases of more prolonged duration six were reported cured. In eight cases with sinuses all these healed except in one who ceased to attend for treatment. Many of these cases were treated for years (up to three years) and give good example of the patience required, but also of the very adequate reward that is likely to follow it. Rapid results cannot be achieved where destruction of tissue leaves large gaps to be filled by the slow processes of repair.

H. M. W. Gray of Aberdeen has found the prognosis in tubercular joint disease greatly improved by the use of tuberculin, especially with regard to the recovery of complete function. He thinks also that where tuberculin is used the period of immobilisation of the joint may be safely shortened, and recommends passive, and also gentle active movement of the limb two to four weeks after all tenderness has disappeared.

He remarks that sinuses would less often appear if tuberculin were more consistently used, but in the treatment of such sinuses he finds much more rapid results follow the combined use of other vaccines with

tuberculin than the use of tuberculin alone. He employed **TR** in doses of ·11 c.mm. for all cases above the age of 3 to 5 years and gave it at intervals of ten (and sometimes fourteen) days. Other writers, as Painter, bear witness to the great value of other vaccines to combat the secondary infections, generally staphylococcus, present in sinuses and abscesses in connexion with joint disease. Maynard Smith describes the use of such a vaccine in the case of one only of his patients.

Illustrative Case.—Dr. George Western in the *Lancet* (1907, ii, 1375) describes the case of a boy of 6 years who came under treatment for pain in the knee of two years' duration. Tubercular arthritis had been diagnosed, and a Thomas splint worn without improvement, so that in April, 1906, there was enlargement of the joint, thickening of the synovial membranes, and pain on movement. The temperature fluctuated daily between 98° and 102°F., and there was much night sweating. The opsonic index was ·8. Tuberculin treatment was begun on April 4, and by May 19, the pain had gone, and fever and sweating ceased. In December the synovial membrane still showed slight thickening, but there was free movement of the joint to a right angle and great improvement in the general health.

Steps in Treatment.—1. Remove sources of infection (p. 187).

2. Place under the best hygienic conditions—Open air, good food (p. 187).

3. Fix the joint according to surgical requirements (extension, splint, plaster, etc.). It is important from the point of view of tuberculin treatment that auto-inoculation be reduced to a minimum.

4. Aspirate abscesses, remove dead tissue, keep sinuses clean, and ensure efficient supply of plasma with hypertonics, etc. Use extremest caution to avoid secondary infection.

5. Give tuberculin according to directions (pp. 191–203).

6. In cases of abscess or sinus where improvement hangs fire prepare and administer vaccine from organism responsible for mixed infection.

SKIN AND CONNECTIVE TISSUE

Lupus.—The visible nature of Lupus Vulgaris has constituted it rather a convenient field of demonstration for the value of tuberculin. During the first tuberculin era intense reactions were obtained, and rapid results expected, so much so that a commission of Paris physicians in 1891 considered one month's trial sufficient evidence on which to base a highly unfavourable report of its value. Saner views, however, led to more satisfactory estimates, and a large body of German opinion pronounced in its favour. Thus Rosenthal found marked healing effects in all forms of lupus ; von Bergmann obtained great improvement; Brieger, among eighteen cases of lupus of mucous membrane, obtained healing in one case, improvement in others. All had the same story to tell—great improvement but generally not progressing to healing. William Levy of Berlin, discoursing on the two first lupus cases to be treated with tuberculin, described less favourable results. Very severe reactions were permitted in these cases and he attributed fresh tubercular lesions which appeared in bone to the action of the remedy. In this country Squire and Leslie Phillips both found improvement result from a modified application of Koch's programme.

With the advent of the New tuberculin **TR** in 1897 the profession obtained a remedy less likely to

lead to overdosage and the failure which results from it, and a chorus of approval from Bussenius, van Hoorn, Doutrelepont, Gerber and others greeted its application to cases of lupus. Since this time good results have continued to be obtained by many, but the want of special knowledge of tuberculin treatment has tended till late years to retard its progress as a remedy for this variety of disease. Moreover the introduction of treatment by Finsen light and X-rays have directed attention away from tuberculin treatment towards these remedies.

The effects of Finsen light on lupus were found to be good but somewhat uneven, and in 1905 Bulloch pointed out that this discrepancy corresponded to the opsonic content of the blood, those cases which did well having a high tuberculo-opsonic index, and vice versa. This contention was supported by Western from independent observation, and the Finsen light found its useful and more suitable place as a means of flushing the diseased focus by stimulation of the local blood supply.

Stanley Griffith has lately shown that Finsen and Kromeyer rays also inhibit the growth on artificial culture media of tubercle bacilli obtained from cases of lupus. It has not been shown whether this is due to true bacteriotropic action or results from change produced in the culture medium.

Western was able, moreover, by the addition of tuberculin treatment to carry to cure cases of lupus which had been treated for three to five years with Finsen light without benefit. In the treatment of **dry lupus** he extols such combined use of tuberculin and Finsen light, and this opinion appears to receive general support. In **moist** and **ulcerated lupus,**

on the other hand, tuberculin alone, or with the addition of vaccines for other infections, will generally cure. This is in full correspondence with our experience of tubercle elsewhere, the flow of lymph through an open surface forming a peculiarly suitable condition for cure by tuberculin. For lupus it was pointed out as long ago as 1897 by Malcolm Morris, who treated six cases of virulent lupus with **TR** with the best results, and especially so, he remarked, where the disease was active and ulcerating. The healing process takes place, according to him, in the following order—

1. Diminution of surrounding redness.
2. Shrinkage of the lupus nodules.
3. Healing of the ulceration.
4. Diminution of thickening, and softening of the scar.

Choice of a Tuberculin.—That success with tuberculin is not bound up in a particular preparation is exemplified in the variety of these recommended. McCall Anderson achieved the happiest results with **T** in dosage rising from ·25 up to 1000 c.mm., at intervals of four days. He considered the obtaining of well marked focal reactions as essential, and directed that this should be done with as little general reaction as possible. Bulloch used **TR** in his cases; Western found **TR** and **BE** equally efficient.

Method of Dosage.—Our present knowledge then teaches us that tuberculin is a most valuable remedy in lupus. The disease being localised there is no reason for raising tolerance, but if judicious focal reactions are obtained a lupus may be cured by immunisation with tolerance if desired. Better than this, however, is the use of equal and fairly large doses at long inter-

vals. A definite focal reaction is to be aimed at but only to moderate infiltration and redness and not to loss of weight and general well-being.

The most successful dosage for lupus is certainly higher than that for other forms of localised tuberculosis; it must be pushed till some definite effect is secured. If a dry scaly lupus is present hyperaemia is to be helped by the addition of Finsen light, fomentations, or hot sand bags. If the surface is moist and ulcerating, these may not be required, but in such cases a secondary infection may be aggravating the trouble, and a vaccine from this prove necessary. Cases of lupus are especially prone to relapse and, to avoid this, tuberculin is best continued at regular intervals, with or without local hyperaemia, many months after healing is accomplished. In addition such cases must be under occasional observation for a long period, so that any recrudescence may be promptly met.

Illustrative Case.—Skin. Dr. William Bulloch in a paper read before the Royal Medical and Chirurgical Society in November 1905, described the case of a patient aged 23, who had had lupus of the left cheek for 20 years. Two hundred and eighty-nine applications of Finsen light were made at different times and the patient was apparently cured in 1904 but relapsed repeatedly. Tuberculin was begun in August 1905, ·2, ·3, ·5, ·3 c.mm. being given. She was discharged apparently cured but to be kept under observation. She returned in January 1906 with two fresh nodules in the scar, which was otherwise sound.

Mucous Membrane.—Dr. George Western described in the *Lancet* (1907, ii. 1449) the case of a man aged 38 who had suffered with lupus of the soft palate for two years. X-rays, cautery, and scraping were unsuccessful and perforation threatened. The lesion consisted of several small localised ulcers on the palate and on either side of the uvula. The opsonic index was ·7 in December 1904 and ·73 in December 1905. Tuberculin **TR** was commenced December 20, 1905, with a dose of ·1, and

later ·08 c.mm., and by January 31, 1906, the ulcers were healed, but treatment was continued till the end of April. In July a recurrence occurred with fresh healing in six weeks under the influence of tuberculin. After this an occasional injection was given and there was no relapse up to November 1907.

Steps in Treatment.—1. Tuberculosis elsewhere, which might contra-indicate drastic dosage, must be looked for.

2. Place the patient under good hygienic conditions as regards fresh air and good food.

3. Give tuberculin according to directions on pages 191–203, and push till well marked focal reaction is obtained, but with avoidance of disturbance of general health.

4. If improvement is not marked—

In **dry** lupus increase blood supply with Finsen light, application of heat (fomentations, hot sand bags, or salt bags).

In **moist** lupus cultivate secondary organism, generally a staphylococcus, and use a vaccine from this.

Other Tubercular Skin Lesions.—It appears that all those skin lesions suspected of connexion with tuberculosis, including the tuberculides, react to subcutaneous injections of tuberculin, except only Lupus Erythematosus. This being the case it might be expected that tuberculin would find a therapeutic use among them, and this has been so at least as regards Erythema Induratum. Whitfield described two cases of this condition which improved under tuberculin, and Western cured two cases, each of two years' duration, although the standing which their occupation entailed, and on which the local congestion peculiar to these

cases in part depended, had to be continued throughout. At this point may be mentioned the fact that certain skin lesions may appear during the use of tuberculin ; thus Little and others described the appearance of Lichen Scrofulosorum in patients under tuberculin, and Cranston Low (reporting from Neisser's clinic) mentions the occurrence besides papular, of macular, haemorrhagic, and urticarial lesions.

Scrofuloderma.—Tubercular ulceration of the skin and subcutaneous tissue generally spreads from disease elsewhere. Very commonly the lymphatic system is the source, softened glands which have burst or been scraped, or areas of tubercular lymphangitis ; sometimes the disease has started with a sinus leading to bone, or a subcutaneous abscess ; the edges of operation wounds are often attacked with spreading disease. Such ulcers often defy ordinary methods of treatment for years, but their exuding surface, and free blood supply renders them peculiarly suitable for tuberculin treatment. The success of this, even in cases which had resisted other treatment for periods as long as twenty years, was especially insisted on by Wright and Western and is generally admitted. Cure is the rule. Moreover Wright points out, in the case described below, that the surface became covered in with soft elastic skin, not scar tissue, and McCall Anderson also commented on the " soft and pliable " surface left after such healing. Dressings of lint soaked in hypertonic and decalcifying solutions (p. 209) may be applied when necessary in these cases, and secondary infections are likely here and there to call for treatment by a second vaccine.

Mention may here be made of the satisfactory effect of tuberculin treatment on the skin and mucous membrane thickenings, and catarrhs so typical of the scrofulous child. Escherich, who regards scrofula as a tubercular intoxication, describes how, under such treatment, the typical scrofulous facies, phlyctenular conjunctivitis, and eczema all disappeared; to appear again after treatment was discontinued, but again to improve under fresh treatment, and again relapse.

Illustrative Case.—Sir Almroth Wright described, at a meeting of the Royal Medical and Chirurgical Society in November 1905, the case of a man aged 30, who, in the autumn of 1902, developed tubercular glands on the left side of the neck, and a tubercular abscess on the point of the left shoulder. He was operated on in January 1903 and, the wound becoming invaded with tubercle, further operations, six in all, were undertaken. Each time the wound became reinfected, and by December 1903, the whole area from the point of the shoulder to the base of the ear formed a single deep eroded ulcer. The lobule of the ear was half eaten away, and immediately beneath it was a deep, ulcerated crater, threatening to break into the oesophagus. The axilla was occupied by a gland the size of a pigeon's egg, and the patient was haggard and very emaciated. After 8 months' treatment with new tuberculin, supplemented by a staphylococcus vaccine, and the local application of formalin g(latin, the crater was quite filled up, the axillary gland no longer palpable and the ulceration nearly healed over. Three months later the wound was entirely closed over by soft elastic skin. He returned later with freshly developed tubercular glands which were again successfully treated with tuberculin.

Steps in Treatment.—1. Place under good hygienic conditions—open air and good food.

2. Protect the ulcer from contamination, and stimulate if necessary with lint soaked in hypertonic and decalcifying solution (p. 209), the skin round being protected

from the action of these with vaselin. Remove dead material if present.

3. Give tuberculin at intervals according to directions on page 195.

4. Cultivate secondary infection and, if progress is not rapid, prepare and use a vaccine from this.

SEROUS MEMBRANES

It is remarkable how scanty is the reference, both in English and German literature, to the tuberculin treatment of tubercular serositis, for this is one of the most satisfactory chapters in tuberculin therapy. In no form of tuberculosis are more striking results achieved than in cases of tubercular peritonitis.

Peritonitis.—Tuberculosis of the peritoneum is practically always secondary to disease elsewhere; Borschke found but two cases primary out of 226 examples of the disease. Infection may be direct from the Fallopian tubes or from rupture of a mesenteric or retroperitoneal gland, or indirect by the lymph stream from intestinal ulceration, or by the blood stream from a distance, as from bronchial glands or lungs. Once planted on the peritoneal surface the tubercles grow and coalesce, and exudation in variable amount appears. According to the stage of disease and the proportion of these inflammatory products the picture varies, and a convenient classification of cases into ascitic with much fluid, and plastic with thick exudation, can be made. In addition some writers describe an adhesive variety where exudation is very scanty and matting of the bowels is the characteristic feature.

In the **Ascitic** form we have an early and sometimes acute infection of the peritoneum, often combined with tuberculosis of the pleura as a multiple serositis. In many cases spontaneous recovery ensues; failing this drainage of the peritoneal cavity through an incision has been a common treatment in the past, the resulting hyperaemia often leading to cure. A study of Case 1, however, will show that equally good immediate, and perhaps better ultimate results may be obtained by specific treatment.

The **Plastic** form may follow on the former or begin insidiously, and in practice the term is often used to cover a variety of abdominal lesions.

In addition to the peritonitis with its inflammatory masses, thickenings, adhesions and, in many cases, fluid, caseous glands may be discovered and intestinal ulceration is sometimes present. Especially confusing are cases where mixed infection is present, and where high fever and rigors with a dry brown tongue point to the formation of peritoneal abscesses.

Prognosis.—It is often of the greatest difficulty in cases of tubercular peritonitis to attempt any prognosis at the outset. The presence or not of intestinal ulceration is generally difficult to decide but it is present, we think, much less frequently than would be expected. The exact local conditions are often so greatly masked by abdominal distension that a mere guess at the extent of the disease is alone feasible. Especially must caution be exercised both in the prognosis and treatment of children of 3 years old or under, for in these the abdominal condition is often but part of more widespread disease. The suspicion of this may be confirmed by the

presence of glandular enlargement in remote parts of the body, especially the neck, and experience teaches that the younger the child the less likely is such a condition to proceed, even on the most careful treatment, to a successful issue.

Treatment.—The manner in which peritoneal masses of quite tumour-like extent will melt away under tuberculin treatment is as striking in its way as the disappearance of a gumma during an antisyphilitic course. In some cases, nevertheless, the results of treatment are disappointing, and these not cases where the presence of intestinal ulceration made the outlook of necessity desperate. It must be borne in mind that it is in abdominal tuberculosis that a bovine source is notably frequent, the results of the English Commission showing 53 per cent. for abdominal glands and the German Commission 65 per cent. In cases, therefore, where a patient trial of tuberculin leads to no result a change to the bovine preparation is worth considering. In tubercular peritonitis tuberculin dosage must be entirely gauged by general symptoms since we have no means of measuring the focal response. A wasted child should begin on a minimal dose (p. 184), and this should be cautiously raised but kept short of definite general symptoms, a rise of weight and general well-being furnishing the immediate goal. At a later date, or in a more robust child, definite negative phase symptoms covering a day or two should be aimed at (p. 194). In the treatment of tubercular peritonitis some amount of recumbency is nearly always indicated. We cannot give the bowel rest, but violent or sudden body-movements may certainly do harm, and the same applies in

our opinion to the old-fashioned treatment by abdominal manipulation. We have seen a fresh spread of disease follow a slight fall in a case otherwise quiescent and progressing favourably.

Pleurisy.—The common form of pleural effusion, though always or nearly always tubercular, is so successfully combated by the older well recognised methods that tuberculin has, so far, not found a place in its treatment. On general grounds however tuberculin is strongly indicated in these cases especially in their after treatment, since other foci, especially in glands, are nearly certainly present, and it is common knowledge that such cases are often but the early warnings of a lung disease which manifests itself later. That tuberculin is of value in such cases must be believed both from their analogy to peritoneal tubercle, and also from the effects of tuberculin in such examples of multiple serositis as Cases 1 and 2 specially picked out to illustrate its effects in both peritoneal and pleural disease.

Meningitis.—Since T. meningitis is generally only a part of a general miliary tuberculosis but little result is to be expected from tuberculin treatment. Nevertheless such treatment has been attempted and a few cases of recovery have been recorded, notably two out of four cases treated by Nathan Raw. It must be the occasional fortune of all with experience of children's practice to see cases of limited general tuberculosis and tubercular meningitis which proceed to recovery ; to be sure in some cases such recovery is but temporary, and is followed later by a fatal relapse. But on the chance that the distribution of tubercle bacilli through the blood stream may be minimal it would seem at least

rational to try the effect of a few injections of tuberculin in any case of this description.

Illustrative Case 1. Ascitic Peritonitis and Pleurisy.—A boy, 9 years of age, gave a history of cough and wasting for 12 months, and abdominal pain of 4 days' duration. On August 30, 1906, some free fluid was found in the peritoneal cavity, and by September 5 considerable ascites and a small pleural effusion on the left side were present. The opsonic index was ·86. **TR** ·025 c.mm. was given, and by September 19 both peritoneal and pleural cavities were practically free of fluid. By September 26 a gain of 1 lb. in weight was recorded though all the fluid had gone. No second injection of tuberculin was given, and though the opsonic index kept about 1· there was a return of fluid in both pleural and peritoneal cavities by October 13 when a second injection of ·025 was given. Ten days later the chest and abdomen were again practically normal and remained so, tuberculin being continued till the following May 1907. Four years later, in May 1911, the boy was well and had shown no return of disease.

Illustrative Case 2. Plastic Peritonitis and Pleurisy.—A girl aged 5 years 1 month. The onset of symptoms dated from 6 months before she came under observation; abdominal masses had been discovered 3 months; there had been no fever. She was treated by sea air, and tuberculin with horse serum by the mouth. No improvement followed but continued loss of weight. When seen on April 27, 1910, the abdomen showed distension with free fluid, and bands of thickening, especially across the middle line in the region of the great omentum. Examination of the chest revealed dry pleurisy over the right back, and impairment in the interscapular region. Tuberculin **TR** was given in doses of ·02 and ·025 c.mm. and continued throughout treatment at intervals of 14 days. Each dose caused malaise and some digestive disturbance followed by loss of appetite for a week; occasionally she vomited. By July 18 there was a gain of 3 lb. in weight and distinct improvement in local conditions. By September 8 the signs in the lungs were but slight and the mass in the abdomen was hardly palpable, but there was still some fluid. By October 24 the abdomen showed neither fluid nor thickening but appeared to be quite normal. The abdominal wall was now thick and fat where at the beginning it had appeared feeble. The chest only showed slight impairment and feeble breath sounds at the right base. The child

looked well and there was a further gain of 3 lb. since July. By January 12, 1911, she had gained altogether 10 lb. in weight since the beginning of treatment, an average of over 1 lb. per month; the abdomen was normal and the chest practically normal. By this time she was walking about the house, and, moderately, out of doors. In April she vomited for two days, a localised patch of abdominal inflammation appeared, and a little fluid at the base of the right pleura. An attack of diarrhoea reduced the weight somewhat, but by July the fresh disease had cleared and her general health was excellent.

Steps in Treatment.—Remove source of infection (p. 186), with especial inquiries as to milk supply in these cases.

2. Place under the best hygienic conditions—open air; feeding.

3. **Peritonitis.**—Keep recumbent at first, and at later stages of treatment for part of the day. Reduce abdominal distension by regulation of diet and drug treatment when required.

Pleurisy.—Aspirate, or partially aspirate, fluid if in very large quantity, or if no absorption occurs after a reasonable interval.

4. Give tuberculin according to directions on pages 191–203.

5. If no success is achieved after a reasonable interval the effect of a bovine preparation may be tried.

DISEASE OF THE EYE

The conditions under which tuberculin is administered in the case of ocular disease, are rather special ones. On the one hand the diagnosis is likely to be made at a very early stage, as the morbid process is visible and focal reactions can be followed with the greatest ease—it was indeed in the iris that the curative effects of focal hyperaemia were first witnessed; and on the other hand

there appears to be a special type of disorder due rather to toxaemia than to actual tubercular infection of the eye itself.

Type 1. **Lesions due to Circulating Toxin.**—Schöler in a very large experience noted the infrequency of the focal reaction after the injection of tuberculin in cases whose tubercular causation could hardly be doubted, in view of the fact that tuberculin coupled with a certain amount of general reaction subsequently resulted in a cure of the condition. The deduction may be drawn that in these cases of chronic uveitis no definite tubercular lesion was in fact present in the eye, and in one such case in which an autopsy was possible Hayashi was unable to find the slightest evidence of a tubercular lesion in the eye, or indeed anywhere in the body. T. H. Butler records a series of cases of iridocyclitis in which tuberculin effected great improvement, but in only one of which a focal reaction occurred. Rosenhauch stands to the interesting and reasonable hypothesis that phyctenular conjunctivitis is due to circulating tubercular toxin with the addition of a local irritation due in many cases to a staphylococcus infection.

Type 2. **Local Tubercular Lesions.**—It is probably an altogether different type of disease in which actual tubercles develop in the iris, choroid or other parts, and in these cases even a small dose of tuberculin is likely to produce a focal, and probably a severe reaction. It is here that the conjunctival reaction has done harm, whereas in the other type it is unlikely to do so.

Association with other Tubercular Disease.—The

association with other tubercular disease—80 per cent. with regularity in any large series of cases—may have an influence on the method of treatment employed. Of Wolfrum's cases four out of five had phthisis ; Hawes and Floyd found the same proportion, and Derby and Ayer 70 out of 92 collected cases.

Method of Treatment.—v. Hippel's work with **TR** first demonstrated the remarkably favourable effects of tuberculin on ocular lesions. He started with ·2 c.mm. repeated every other day, up to 100 c.mm. which he regarded as always ample. He expressly warns against the careless use of large doses, which may lead to breaking down of corneal infiltrations and to the production of ulcers. Later on he preferred to use **BE**, believing it to have a greater power of preventing relapse.

Other observers have used one or other of these preparations and reported uniformly good results. There is a further consensus of opinion in regard to the extreme sensitiveness to tuberculin ; Hawes and Floyd record a case which had a reaction with ·0001 c.mm. and in one patient they were unable to exceed this dose.

The question of inducing tolerance depends on the presence or absence of associated phthisis. We believe that it will be found safe in practice to begin with ·001 in all cases of type 1, and wherever phthisis is present, using a smaller dose of ·0001 in the rare cases of apparently simple iridic or choroidal tuberculosis. But even when other lesions are present, the dosage must be regulated by the reaction of the eye itself.

Results.—In the first form it appears that recovery may be counted on with certainty. In the second form the disease is the most favourable for recovery of

any local tuberculosis, partly because of the natural vascularity of the uveal tract, and partly because of the nicety with which the visible focal reaction can be graded.

Illustrative Case.—A lady, aged 20, had suffered for 8 months from chronic irido-cyclitis beginning in one eye and affecting the other 2 months later. There was pain in the eye and forehead; interstitial opacities appeared in the cornea and punctate keratitis. Salicylates and mercury were tried with only temporary relief. An injection of T ·25 gave rise to a temperature of 99° (oral) and T ·5 to 100·4° without focal reaction. No sign of tuberculosis could be discovered elsewhere, but the condition began to improve from the time of the diagnostic injection, which was followed up by seven doses of TR ·004 at intervals of 3 weeks. At the end of 5 months of treatment the process was quiescent.

Steps in Treatment.—1. Ascertain the type of disease and whether it is associated or not with phthisis.

2. Where actual intra-ocular tubercular disease is present, begin with a minute dose and increase it to the optimum with extreme care (p. 200).

3. Where the affection is due to a toxaemia, with local irritation determining the incidence in the eye, remove all possible sources of local irritation.

4. Where phthisis is present induce tolerance (p. 87).

KIDNEY AND BLADDER

Kidney.—The evidence as to the value of tuberculin in renal tuberculosis is of a very conflicting character. The opinion of Berlin surgeons is strongly in favour of excision where only one kidney is affected, and they produce some evidence of the failure of specific treatment in kidneys afterwards excised. Krämer, for instance, showed a fresh growth of tubercles in a kidney after seven months' tuberculin treatment, but to this it

might be retorted that the advocates of tuberculin treatment make no claim for a protective action against reinfection. Karo, on the other hand, in three cases that refused operation found great improvement, which he thought would proceed to cure, under treatment with tuberculin. On this account he recommends that tuberculin be tried in cases where there is no urgency. With this advice French clinical teaching appears to be in accord, and Mantoux collected evidence of seventy cases among which one-third were cured and a half much benefited. Teissier records a cure in a case of bilateral disease. The matter in question is considerably complicated by the difficulty of diagnosis; for, to begin with, it is no easy thing to differentiate the tubercle bacillus from other acid-fast bacilli and, moreover, tubercle bacilli may appear in the urine without any recognisable disease of the genito-urinary tract. Bertier found by animal inoculation that tubercle bacilli are demonstrable in the urine of one-third of the subjects of advanced pulmonary tuberculosis. The difficulty of diagnosis generally leads to late detection, and this is apt to delay treatment till the stages where tuberculin might be expected to be of benefit are passed over.

Bladder.—When we turn to vesical tuberculosis we find that here opinion is more unanimous as to the value of tuberculin. Pardoe points out how very unsatisfactory are ordinary surgical methods in dealing with these cases and considers tuberculin the best remedy we have. At the same time he insists that cure can only be effected with ulceration of limited extent, and that much danger of precipitating suppression of urine occurs

if disease of both ureters is present and full doses are given. This fact had been already noted by Hurry Fenwick. Among twenty-one cases treated by Pardoe five were apparently cured, four markedly improved; in six cases there was no improvement, but in some of these the remedy was never given a fair opportunity. Six patients died. These cases were treated with TR after the method of rising dosage, on a five or six basis, and when reaction was once met the dose was no longer increased. In cases of advanced disease Bosanquet and Eyre call attention to the value of tuberculin in relieving symptoms and prolonging life.

Taking the urinary tract as a whole Sanborn states the indications for tuberculin treatment as follows—

1. Where excision is impossible.
2. As an after treatment where it is impossible to excise all the tubercular tissue.
3. In early cases with little softening.
4. In double renal tubercle.

In all but advanced cases, where treatment of symptoms may be called for, the method of immunisation without tolerance is indicated in bladder and kidney cases. Success may be achieved, indeed, by the method of rising dosage but the same immunising response is achieved with less trouble and more accuracy on the small dose system. This is exemplified by the good results achieved by Wright and his followers in cases of this description.

In all cases treatment must be preceded by accurate diagnosis, and for this a cystoscopic examination is required. Focal reactions must be reduced to small dimensions; when overdone they lead to pain and increased

frequency of micturition, to increase of pyuria, and even to haematuria, and these effects must be avoided.

Illustrative Case.—Sir Almroth Wright described at a meeting of the Royal Medical and Chirurgical Society of November 1905 the case of a married woman, aged 43, who suffered with pain on micturition, and frequency, and dragging pains in the loins especially on the left side. The urinary deposit contained pus, epithelial casts, and tubercle bacilli in such numbers that they could be demonstrated in large clumps in every field of the microscope. Examination of the bladder revealed the existence of a large ulcer. The kidneys were enlarged and tender; the left one in particular was affected and suspicious signs were detected in the apex of one lung. Tuberculin treatment was begun in the middle of April 1903. The weight rose from 91 lb. on April 20 to 107¼ lb. on July 13, when she left the hospital. She continued to receive tuberculin as an out-patient, and in September 1903 her weight reached 119 lbs. Treatment was continued up to July 1904. During all this time the tubercle bacilli were gradually becoming less numerous and by May had completely disappeared from the urine. The patient, none the less, still suffered from serious bladder trouble—due as appeared on examination to cicatrisation and great thickening of the bladder walls, and possibly to some superadded ulceration referable to septic invasion by bacillus coli and a gram-staining diplococcus present in millions in her urine throughout. Later the patient returned with a relapse and tubercle bacilli were once more found in her urine. Under the influence of further inoculations of tuberculin these again disappeared and, though she suffered from incontinence, she was free from pain and in good health in October 1905.

Steps in Treatment.—1. Decide suitability for treatment with especial reference to whether cure or improvement are possible under the small dose system, or whether only relief of symptoms by establishment of tolerance can be expected. Exclude, or treat with the greatest caution, cases where both ureters might be involved.

2. Place under good hygienic conditions—Fresh air; good food.

3. Give tuberculin according to the directions on pp. 191–203 or in some advanced cases by the method recommended in Part II.

4. Avoid mixed infections as by passage of catheter, etc., and if necessary, treat mixed infections already present by the preparation and use of a vaccine.

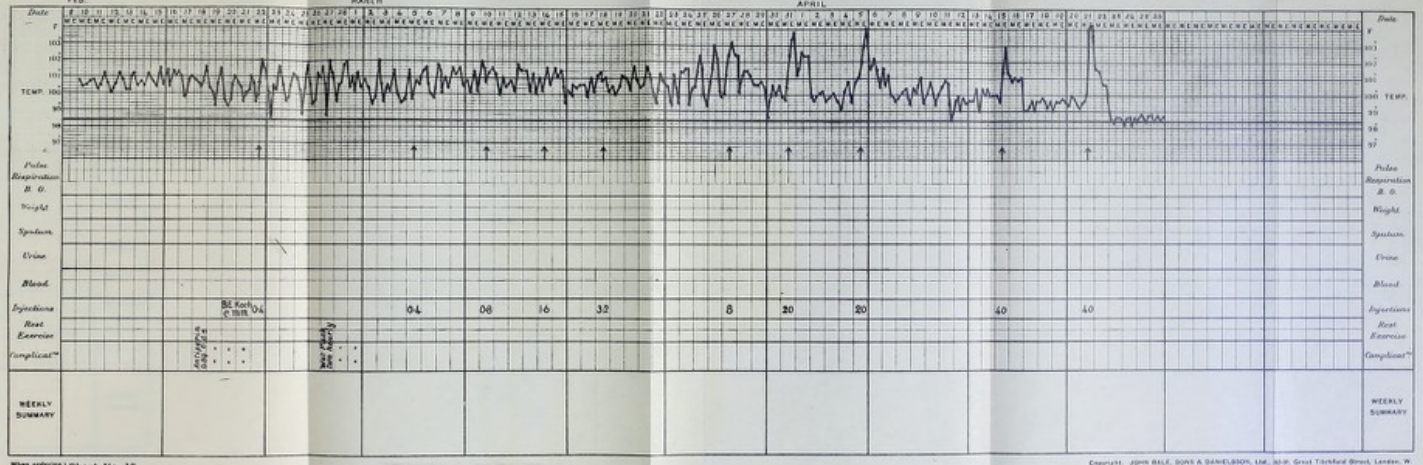


Chart XXVI.—Showing defervescence after febrile reactions (Litzner).

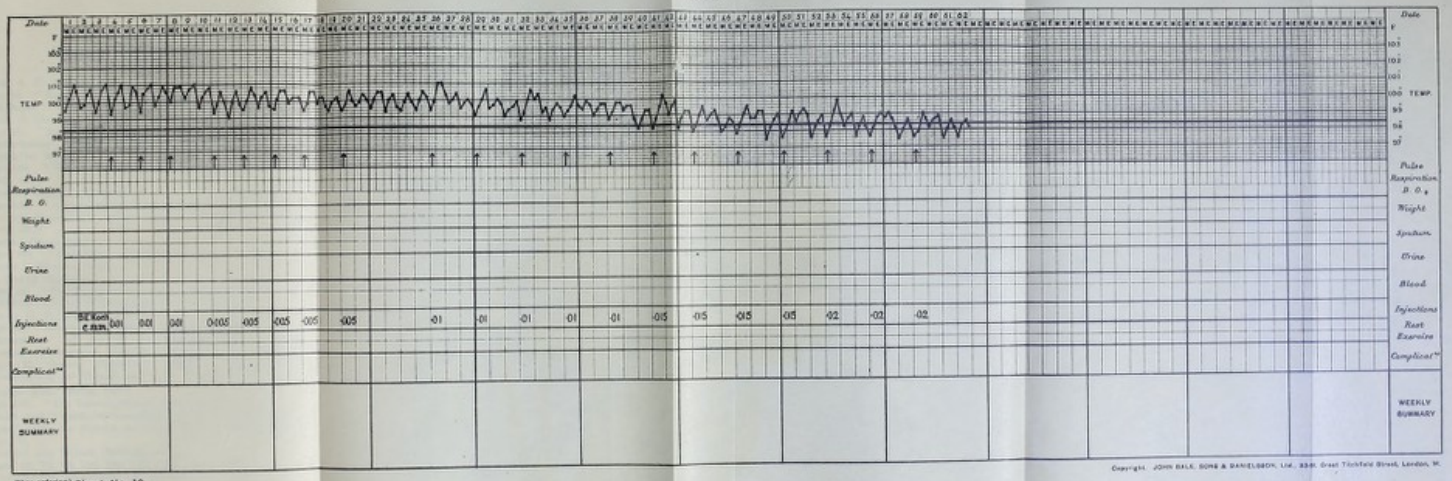
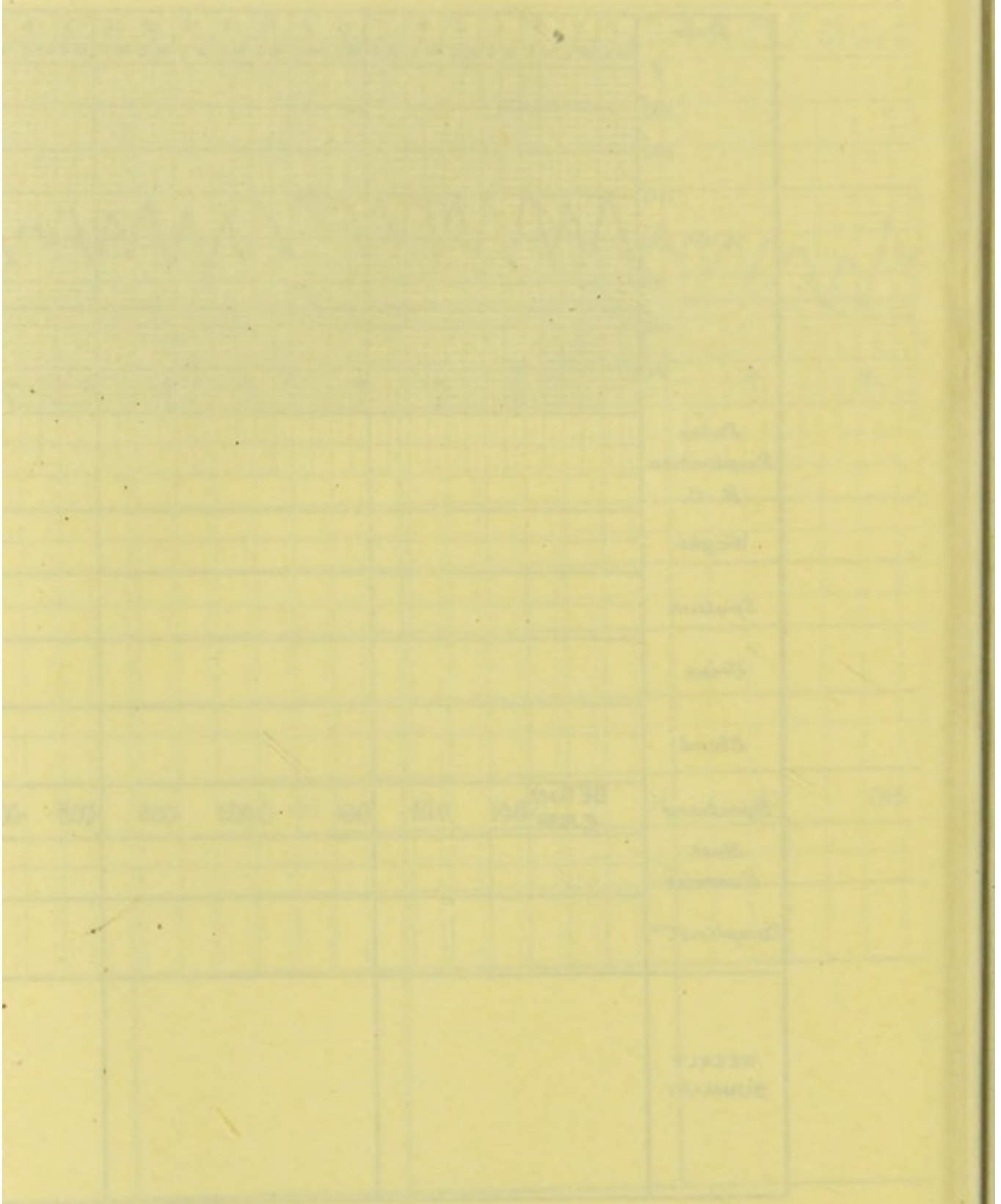


CHART XXVII.—Showing defervescence without febrile reactions (Krause).



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