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IN THE TREATMENT OF

PULMONARY TUBERCULOSIS

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RATIONAL IMMUNISATION

IN THE TREATMENT OF

PULMONARY TUBERCULOSIS

AND

OTHER DISEASES

Comprising Paper read before the Royal Society of Medicine, March, 1909

BY

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The Antitryptic Index.

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It is generally considered that production and maintenance of immunity to infection are questions only of protection against bacteria and their products.

I submit, in the light of increasing knowledge of the phenomena of cellular pathology :—

(1) That this interpretation ignores such additional factors in the sum-total of infection as autolysis and other anomalies of cell-metabolism, as well as the toxic products of such anomalies, and is therefore far too restricted.

(2) That its acceptance accounts for the limited success that has so far attended all hetero-inoculative methods of fighting infective disease.

(3) That until this be realised no great advance is possible in the specific treatment and prevention, not only of conditions admittedly the result of bacterial invasion, but of many other diseases in no way related thereto.

In order to maintain such propositions as these I shall bring evidence to show :—

(1) That spontaneous auto-inoculation, being a process of natural cure of infection by auto-serum and auto-vaccine therapy, incites the restraint of all the factors concerned, and

(2) That artificial auto-inoculation is on that account immeasurably superior to hetero-inoculation, whenever it can be conveniently applied.

I shall also call attention to a novel method of interpreting temperature charts in terms of immunity curves, and shall refer to the advantages of measuring the antitryptic powers of the blood.

The word "hetero-inoculation" is one that I have coined, on obvious analogies, to denote inoculation of immune serums, and of tuberculin and other vaccins from without.

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(1)

The Relation of Treatment by Inoculation to other Methods of Treatment of Established Infection.

THERE are three known methods of treatment of established infective disease: the general, the specific, and the surgical.

(1) Surgical treatment in its strictest sense aims at direct removal or destruction of the infective agent, or where this is not possible, at rendering such agent inoperative. There are two methods available—the mechanical and the chemical. The mechanical method is to remove the source of infection by incision and subsequent evacuation. The purely chemical method lies in the use of artificial antiseptics, whereby the infective agent is destroyed, or its action inhibited. The uses, abuses, and limitations of both methods need no notice here, though in passing it may be observed that a patient's own serum is often a better antiseptic than any the chemist can provide.

(2) General treatment of established infection aims, in common parlance, at building up the powers of reaction. In technical language its goal is efficient exhibition by the economy of effective response to natural or artificial stimulus; in other words, it strives to render specific treatment more effective than it otherwise could possibly be. Whatever methods, or combination of methods, of general treatment are adopted, climate, open-air *régime*, sanatorium supervision, diet, drugs, &c., are accessories only to specific treatment. They are, however, accessories that can never be dispensed with, whatever the advances made in specific treatment, because the latter is worse than useless unless the impaired power of reaction, which is the ultimate cause of successful infection, is capable of reinforcement by intelligently applied general treatment.

(3) Specific treatment of established infection may be defined as a direct biochemical attempt to repair the breakdown in the mechanism

of immunity which has rendered the continuance of infection possible. Such attempt may be a natural effort on the part of the economy, or may be the outcome of artificial measures deliberately applied.

Natural specific efforts at immunity restoration are themselves the result of a natural process of spontaneous auto-inoculation which may come into action immediately infection has become established, or from inflammation, or from the operation of various natural functions which no amount of rest can control.

So long as free communication between the lymph-stream and the focus of infection is maintained, spontaneous auto-inoculation is followed by simultaneously acting processes of active and passive immunisation.

Passive immunisation appears to be a process of automatic neutralisation of infective material by such antagonising substances as exist performed in a patient's own lymph and tissue cells. Such process is, however, strictly limited; for not only in a given infection has the natural supply of preformed protective bodies already been drawn upon to allow of infection, but the balance has been gradually shrinking under the stress of its continuance. Hence, unless some provision be made for replenishing the original deposit, such balance sooner or later must become exhausted. This provision the economy ensures by a process of active immunisation.

Active immunisation may be defined as a process of stimulation of a patient's own powers of defence by and against his own tissue-cells and their products, and such bacteria and their products as are for the time being his pathogenic guests. The expression of achievement is the manufacture of a larger supply of protective bodies, endowed with tropic functions, than before infection existed. The infective agent is in fact induced to forge an instrument for its own destruction from material supplied by the responsiveness of its host.

The process of active immunisation that immediately follows spontaneous auto-inoculation must not be confused with the natural, but not spontaneous, process that follows auto-inoculation induced by inflammatory hyperæmia. Further, it must be distinguished from the natural process of immunisation following intermittent auto-inoculation occurring in chronic diseases in which the focus of infection is from time to time insulated from the general lymph-stream. In the early stages of any infection, so long as free communication is maintained, the immediate operation of active and passive immunisation may be sufficient to bring the infection to an end, provided that the economy is able to provide material for such immunisation.

Inflammatory Hyperæmia.—Where, however, free communication is limited, or where, even with free communication the preformed supply of antagonising substances is insufficient, or where, as a result of inadequate stimulus, response is weak, some further impetus to immunisation efforts is needed. This need the economy attempts to meet by inducing the form of hyperæmia known as inflammation. Inflammation we now know to be, within certain limits, a protective mechanism, one of the chief virtues of which lies in its increased determination of fertilising and restraining lymph to an infected area. In this determination a fresh supply of preformed bodies is provided, as well as fresh opportunity for the formation of new ones; in other words, fresh processes of active and passive immunisation are set in motion. Inflammation *quâ* bacterial invasion is, therefore, actually a process of auto-serum and auto-vaccine therapy, especially provided by Nature to enable the economy to deal with an infection that has succeeded in gaining a footing. Inflammation is, in fact, the predominant factor in the economy's fight against infective disease.

Non-inflammatory Hyperæmia.—In many cases, as, for instance, in apyrexial cases of chronic pulmonary tuberculosis and in many cutaneous and other lesions, free communication between the focus of disease and the general lymph-stream is interrupted. In such event the local supply of preformed antagonising bodies may be seriously curtailed. As a further result of this condition of relative insulation, itself often the result of inflammation, the stimulus necessary for the production of new anti-bodies is wanting. In order to meet this want, a condition of hyperæmia is intermittently induced by various natural agents, of which, for instance, the act of coughing is an excellent example. Cough is up to a certain point undoubtedly, in apyrexial cases, a conservative function, though liable to serious natural abuse. The condition of pulmonary hyperæmia that it produces is eminently favourable to the induction of processes of active and passive immunisation by means of natural auto-inoculations. There can be no doubt that such operation is frequently demonstrable, and it affords a good example of attempts made by Nature to overcome an infection that resisted its earlier and simpler methods. This consideration is in no way affected by the harmful effects of hyper-auto-inoculation so frequently observed after excessive cough or other quasi-involuntary movement, especially in cases accompanied by fever.

Artificial Methods of Immunity Restoration.—The chief value of a study of natural methods of treatment of established infections lies in the

clear idea that may be gained therefrom of the rationale of artificial measures. The chief of these are :—

(1) Artificial auto-inoculation.

(2) Hetero-inoculation of immune serums as serums.

(3) Hetero-inoculation of vaccins.

(4) Local use of normal serums.

In all of these methods the same principles that guide natural methods of treatment are involved, excepting, however, as will be seen, that these principles are in the case of artificial treatment infinitely more restricted in their application.

In the case of artificial auto-inoculation processes of active and passive immunisation are employed, viâ the various channels of artificial hyperæmia.

In inoculation of immune serums as serums a process of passive immunisation is alone employed, dependent, however, for its value on active incitation of immune body production in the animal employed.

Inoculation of immune serums as vaccins is said [1] to be often unwittingly employed, though never, presumably, with deliberate intent. The possibility of unconscious employment of immune serum as vaccin is supposed, though on insufficient grounds, to explain the excellent results obtained by the use of Professor Chantemesse's serum in enteric fever. There is, no doubt, much to be said for such a view, though a simpler and more satisfactory explanation is more probable.

Inoculation by vaccins is primarily a process of active immunisation, though once a definite increase of newly formed substances has been obtained, a process of passive immunisation must, provided intercommunication be free, also come into action.

The local use of normal serums is mainly a question of passive transference of preformed bodies to the site of damaged immunity, as I have shown in the treatment of ulcerative conditions of mucous membranes and skin.[2] It is not, of course, the ideal way of treating a local loss of cell-immunity. Its chief value lies in its approximation to the normal method by which the economy locally immunises itself, and is only to be exhibited when such natural methods cannot be conveniently set in motion.

(2)

The Present Position of Hetero-inoculation.

The rationale of the practice of inoculation of immune serums and artificial vaccins has, of course, only one basis, involving as it does the exhibition of anti-bodies in response to very similar stimuli. The stimulus, in fact, is always from vaccins, whatever the source of such.

With regard to antitoxic serums the only one of pre-eminent value in treating infections already established is the diphtheria antitoxic serum. The worth of this serum, however, lies far more in indirectly protecting from toxins cells still undamaged than in direct restoration of integrity to cells already affected.

The value of all the anti-microbic serums, as at present employed, is, with one or two exceptions, admittedly small.

From time to time many suggestions have been advanced to account for this limitation. Some such suggestions are undoubtedly sound, such as exhaustion of complement, the co-existence of other organisms causing a mixed infection, and variations in the strain and virulence of the same organism. To these may be added the unquestionable absence from most of the anti-microbic serums of sufficient quantum of antitoxin. Even, however, when these suggestions have taken practical shape the results have not been strikingly improved.

With regard to artificially prepared bacterial vaccins their possibilities have been widely exploited of late, and are still extensively proclaimed. That bacterial vaccine therapy has achieved a great deal, and will undoubtedly achieve more, it would be idle to deny. For many brilliant successes, mainly, however, in chronic and relatively unimportant conditions, have been recorded, as well as some in more serious diseases. Though the number of failures recorded is small, few will deny that the number of cases in which, even under ideal conditions, no benefit whatever has accrued, is very large. It is, in fact, worth enquiring if the movement is not leading us too far. For instance, to attempt to show, as has been attempted, that bacterial invasion is

responsible for such conditions as diabetes, jaundice, pancreatitis, &c., and that these might therefore prove amenable to bacterial vaccins[4] is surely to lose a proper sense of perspective.

As in immune serum therapy, so in vaccine therapy many suggestions have been advanced to account for the limited success met with, such as the co-existence of mixed infection, variations in the strain of the particular organism concerned, and so forth. But here again the practical results of acting on these suggestions have too often been most disappointing.

If this presentment of the actual achievements of serums and vaccins be accurate, does it not seem as if some vital factor in the sum-total of infection, and of the means that should be adopted to antagonise such, has been overlooked?

That such is actually the case I shall now attempt to show.

The basis of all hetero-inoculative treatment is the familiar sequence of inoculation, intoxication, response. Response is at present only expressed in terms of specific anti-bodies to bacteria and their toxins, and the possibilities of cellulo-tropic response are ignored. It is generally held, in other words, that to protect a cell against parasitic invasion it is only necessary to provide against heterogeneous agencies. Hence a cell is not supposed to be in danger from autogenous factors either as the cause or the result of infection. It may be true that a healthy cell is not primarily in danger *de se*. There can, however, be no question but that disturbances of cell-equilibrium, even when initiated from without, run a truly autogenous course. This being so they must be restrained by equally autogenetic means if integrity is to be directly maintained or restored. Integrity of form and function of a cell is, of course, constantly in jeopardy from the vicissitudes of cell-life. But a cell may be primarily attacked from within as well as from without. Its potential enemies from within are apparently not only its own intracellular enzymes, the very bodies essential to its life, but also the products of the morbid activity of such. Unless these are constantly restrained equilibrium cannot be maintained. It is not the stomach only that can, under suitable conditions, autolyse or digest itself. Every tissue in the body has similar powers. That the body as a whole does not digest itself is apparently due to the inhibitory action of its anti-enzymes. These seem to be incited into being and action by the intracellular enzymes, on the strict analogy of toxin and antitoxin. Between perfect integrity of a cell and the act of autolysis there are many grades of cell-aberration. Fatty degeneration, cloudy change,

and many other processes, including, possibly, even cancer itself, are familiar examples. Between demonstrable auto-intoxication from the products of autolysis and other anomalies of enzymic activity and its earliest stages there must also be an infinite number of grades.

Under the stress of life there could be no escape from one or other of these aberrations unless there were some restraining influence constantly at work to hold a tendency to perverted action in check. This restraining influence may be defined as the protective response called out by cellular enzymes and their products whenever cell-integrity is threatened by anomalies of cell-function. In the evolution of cell-maintenance it is only this power of restraint that enables a cell not only to remain a cell of its own kind, but to remain a cell at all. In other words, natural selection transforms what was in the first instance accidental into protective purpose. To paraphrase Herbert Spencer, cell-life is the equation of cell-reaction. But the conception of reaction must not be confined to reaction against outside forces. It must also embrace a cell's reaction against its own enzymes and against the products of enzymic activity. The very weapons with which a cell can destroy itself incite the restraint necessary to avert such disaster. When, therefore, a cell is damaged by bacteria or their toxins, its powers of restraint of what are then abnormal enzymic metabolic processes are impaired. It can of its own accord only return to a normal state by inciting responsive reaction in the fertilising lymph that supplies it. The sign of restoration is the exhibition of appropriate restraining bodies. Cell-life is, in fact, inconceivable in the absence of such restraint, which is the only intelligible explanation of the horror autotoxicus postulated by Ehrlich.

Hence bacterially infected tissues must, I maintain, defend themselves, not against one factor only, bacteria and their products, but against many. Amongst the remaining factors are their own enzymes, and the products of their own enzyme activity. If attack is plural, defence must be plural. Antitoxin production *quâ* bacteria will do much, only, however, by protecting from harm cells still undamaged. It cannot directly enable cells already damaged to restore the condition of immunity on which effective cell-life depends. Many cells, no doubt, are injured beyond repair, but there must be also hosts of cells not beyond hope of spontaneously or artificially induced recovery. For such as these no antitoxin, bactericidal body, nor opsonin can be of the slightest avail, except by preventing further injury. If this be so, artificial specific treatment, which aims at production of bacterio-tropic bodies only, to

the exclusion of cellulo-tropic, can never meet with full success, so long as tissue damage is extensive. Further, the economy itself can never be relied on to spontaneously effect a cure unless it can consider the cellular element as well as the bacterial. The very fact that more people get well of infection than die of infection is strong proof that auto-cellulo-tropic restraint does actually and naturally occur, and is also the strongest possible argument for artificially inducing such restraint when natural efforts fail.

If the exponents of the hetero-inoculative method had not confined themselves to the use of vaccins of bacterial origin, and of artificial immune serums, dependent for their value on the production of bodies inhibitory to bacteria and their toxins only, there would have been the less excuse for this communication. Inasmuch, however, as the value of artificial vaccins made from emulsions of cells and cell-enzymes, and of immune serums dependent for their value on the production of bodies inhibitory to perverted enzymes and anomalies of cell-metabolism, and to the products of such, has been neglected, the possibilities of such enlargement of the scope of hetero-inoculation are worth exploring. No doubt the inherent difficulties of preparing cell-emulsions and enzymic vaccins are very great. There can, however, be little question that if they could be satisfactorily prepared, the addition of such to the armoury of the hetero-inoculator would enormously enhance the effect of his bacterial vaccins and serums. Even then, however, the combined value of artificial inoculation with cellular and bacterial vaccins would be considerably less than the same weapons when autogenously wielded, as what I have to say on the subject of auto-inoculation is intended to show.

It has, of course, always been laid down that tissue resistance must be reckoned with in the treatment of established infective disease, and that the object of general treatment is to provide for this factor. But hitherto we have only imagined that tissue resistance must be encouraged against extrinsic attack. We have, I maintain, not realised that it must also be encouraged against intrinsic. Obviously by adequate food supply and so forth we can encourage cell-nutrition and so indirectly aid in passive immunisation against extracellular and intracellular forces. But to promote cell-nutrition is not to ensure cell-restraint. No amount of general treatment can ensure active immunisation. All it can do is to make it possible for bacteria and cells to incite bacterio-tropic and cellulo-tropic restraint, or, in other words, to call out specific response to specific stimulus from without and from within. We believe the former

to be the essence of specific treatment *quâ* bacteria, whether such treatment be naturally or artificially induced, and there is much evidence to show that exactly the same principles are applicable to specific restraint of such intracellular agencies as enzymes and their toxin-like products.

If these observations are well founded it is clear that future progress in Immunity research is inseparably bound up with the study of cell-enzymes. Such study must embrace the phenomena of autolysis and other anomalies of cell-metabolism, and their relation to intracellular enzymes. Further, it must concern itself with intoxication from the by-products of morbid enzymic activity, and, above all, with the methods by which restraint of all these phenomena is naturally maintained.

(3)

The Unreliability of the Tuberculo-opsonic Index.[1]

It frequently happens in hospital practice and in private that a reliable method of diagnosing difficult cases of infection is urgently needed. In no disease is this more true than in tuberculosis. For general use, where ordinary methods fail us, the cutaneous methods of von Pirquet, Moro, and Wolff Eisner, including Calmette's modification of these by conjunctival instillation, are not of pre-eminent value. In private practice the dangers and fallacies of Calmette's test effectually bar its universal acceptance. Of Professor Courmont's modification of the serum diagnosis of tuberculosis there are not as yet sufficient data to judge. In this country, and in America, it is widely believed that in the opsonic index we have at last a method which is trustworthy not only for diagnostic purposes, but also for prognosis and in determining treatment. After extensive trial of its merits, mainly in tuberculosis, over a period of three years, I am not able to endorse the view that the index is a safe guide to diagnosis and treatment, even when estimated by acknowledged masters of the opsonic art.

In order to test its value as presented to us to-day, I have from my own private practice taken a series of cases, some of which had been sent for diagnosis, and in whom a trustworthy opinion, apart from physical signs, was therefore of real importance. No sort of selection has been made, and results that favour the opsonic method of estimation have been impartially recorded side by side with the unfavourable ones. In all cases the nature of the test has been explained to the various observers, who have without exception encouraged the inquiry. One observer, indeed, expresses the hope that the tests will be published in order to stimulate further efforts in improving the technical details. Such devotion to the highest traditions of scientific research cannot but

[1] This section is reprinted by the courtesy of the Editors of the *British Medical Journal*.

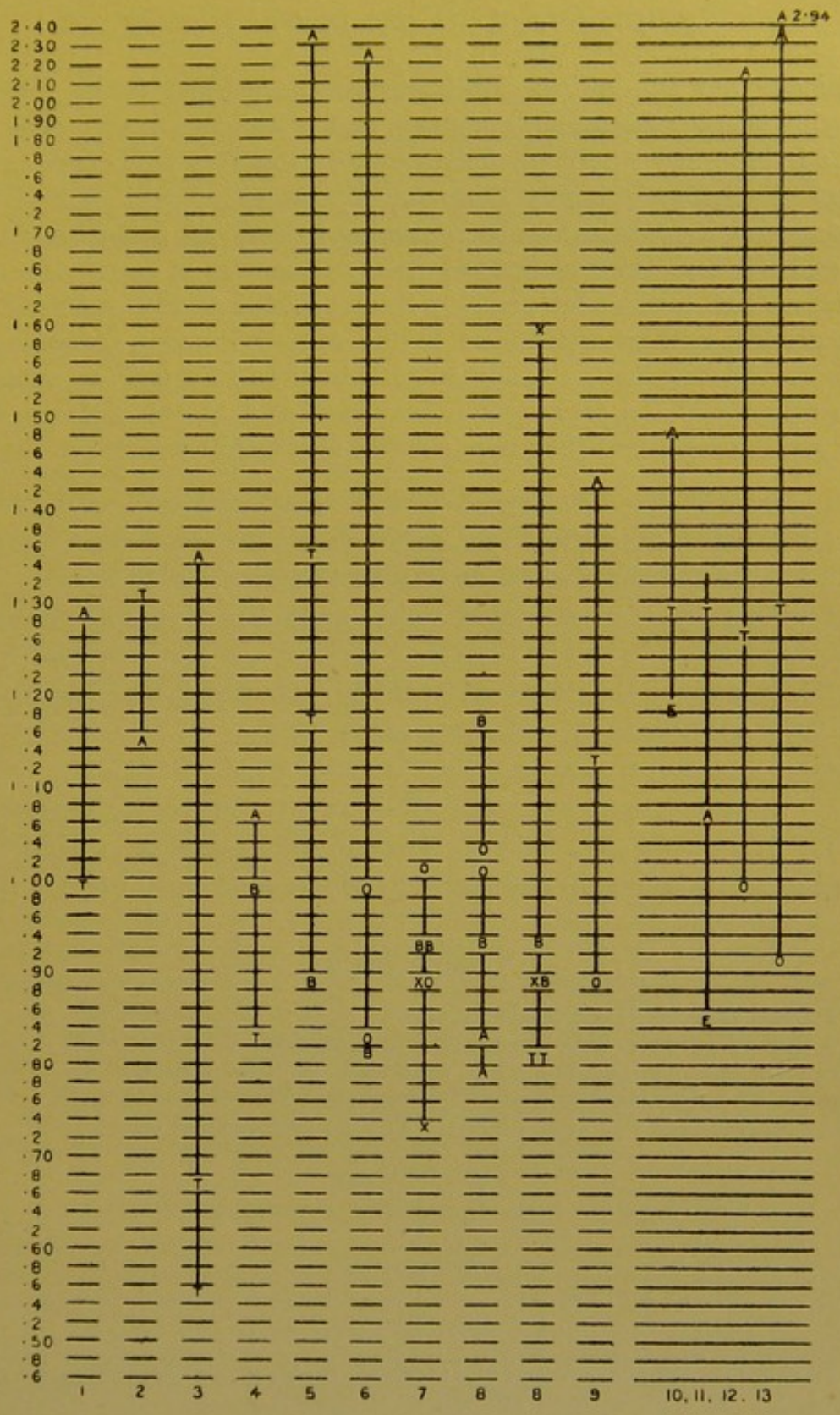

Chart showing Different Opsonic Indices of Identical Serums, as Estimated by Different Observers.

command our admiration. Each observer mentioned in the accompanying chart is the same throughout, and is designated always by the same letter. It is, perhaps, unnecessary to say that only experts with years of practice and only those directly connected with well-known laboratories have been asked to examine the various serums supplied. In each of these twelve cases two or more samples of serum drawn at the same time and under precisely similar conditions have been sent to two or more workers, sometimes in the same laboratory, sometimes in different laboratories. In addition to this, as will be seen, occasionally two samples of the same serum have been sent to one observer, who was not informed that they were samples of identical serums.

In each case the following precautions were taken:—

(1) Whether taken from vein, finger, or ear, the serum was separated from the clot at the end of six hours after puncture of skin or vein.

(2) No serum was estimated unless quite free from contamination from red cells.

(3) In sealing the tubes all possibility of heating the serum was obviated by using tubes with long drawn ends.

(4) All tubes were sealed within five minutes of collection.

(5) All indices were estimated within twenty-four hours of collection.

(5) All samples of each batch of serum were taken from blood provided by one bleeding, in most cases by venu-puncture.

Tests 1 and 2.

Disease suspected: renal tuberculosis.

A dose of $\frac{1}{1000}$ mg. T.R. tuberculin was administered by the mouth, and the indices to tubercle bacillus were estimated by two observers in different laboratories, both before and after inoculation. The interval between the two sets of observations was fifteen hours. The indices returned were:—

Before Inoculation.

Observer A., O.I. to T.B.	...	1·29	Phagocyte count not kept
,, T. ,,	...	0·97	,, ,,

After Inoculation.

Observer A., O.I. to T.B.	...	1·15	Phagocyte count not kept
,, T. ,,	...	1·30	,, ,,

In this case observers A. and T. differed in their estimation of the index after inoculation by 0·15, a small difference. Before inoculation they differed by 0·32, a not inconsiderable difference. Further, whilst A. estimated that inoculation was followed by a fall of index, Observer T. registered a rise. Two indices were within normal limits and two outside it.

Tests 3 and 4.

Disease suspected: tuberculosis, position of focus unknown. In this case there was no direct evidence of any organ being directly the seat of tuberculous infection, but in view of anomalous pyrexia it was necessary to exclude, if possible, such a contingency. Two series of observations were therefore undertaken with a week's interval. In the first test two samples of the same serum were sent to one observer, and a third sample was sent to a second observer in a different laboratory.

The indices returned in the first test were :—

Observer A., O.I. to T.B.	...	1·34	Phagocyte count not kept
,, T. ,,	...	0·67	,, ,,
,, T. ,,	...	0·55	,, ,,

In the second test three tubes of the same sample of serum were sent to three observers in three laboratories a week after the first test.

The indices returned were :—

Observer A., O.I. to T.B.	...	1·06	Phagocyte count not kept
,, B. ,,	...	0·98	,, ,,
,, T. ,,	...	0·82	,, ,,

In the first test the maximum variation was 0·79, the minimum 0·12, and the middle variation 0·67. Observer T. differed from himself by 0·12. In no case was the index within normal limits.

In the second test the maximum variation was 0·24, the next largest 0·16, the minimum 0·8. In no case was the index outside the normal limits.

Test 5.

Disease: pulmonary tuberculosis, with well-marked physical signs, fever, and tubercle bacillus in the sputum.

Four tubes of the same sample of serum were sent to three observers in three different laboratories. To observer T. two tubes of the same serum were sent without his knowledge. The indices returned were :—

Observer B., O.I. to T.B.	...	0·88	Phagocyte count of 100 cells	...	211 : 240
,, T. ,,	...	1·17	,, not kept		
,, T. ,,	...	1·34	,, ,,		
,, A. ,,	...	2·34	,, ,,		

The maximum variation here was 1·46, the next largest 1·17, and the minimum 0·17, the figure by which Observer T. differed from himself. In this case two indices were within normal limits and two above.

Test 6.

Disease suspected: miliary tuberculosis. In this case the patient was extremely ill with high fever, but the physical signs in the lungs were anomalous.

Four tubes of the same serum were sent to three observers in three different laboratories, two tubes of identically the same serum being given to Observer O. without his knowledge. The indices returned were :—

Observer A., O.I. to T.B.	...	2·20	Phagocyte count not kept		
,, O. ,,	...	0·96	,, of 100 cells	...	126 : 130
,, O. ,,	...	0·82	,, ,,	...	107 : 130
,, B. ,,	...	0·82	,, ,,	...	193 : 240

In this case the index returned by B. was practically identical with one of the indices returned by O., who differed from himself by 0·14. The maximum variation between A. and B. was 1·40. In a case almost certainly tuberculous clinically, of four observations only one was outside normal limits.

Test 7.—Serum from Normal Individual.

In this case six samples of the same serum were sent to three observers in three different laboratories, each observer receiving unknown to him two samples of the same serum.

The indices returned were:—

Observer	X.,	O.I. to T.B.	...	0·72	Phagocyte count of 100 cells		...	202 :
,,	O.	,,	...	0·87	,,	,,	,,	... 222 : 268
,,	B.	,,	...	0·92	,,	,,	,,	... 231 : 250
,,	B.	,,	...	0·93	,,	,,	,,	... 232 : 250
,,	X.	,,	...	0·89	,,	,,	,,	... 249 :
,,	O.	,,	...	1·07	,,	,,	,,	... 288 : 268

In this case B.'s observations were practically identical, and were very close to single observations of O. and X. The latter, however, differed from himself by 0·17, and O. differed from himself by 0·20. The maximum variation also was considerable—namely, 0·35. The fact, however, that all observers returned an index within normal limits is striking.

Test 8.

Disease suspected: renal tuberculosis. In this case there was present, in addition to the signs incriminating the left kidney, a large inflamed tuberculous cervical gland undergoing rapid softening. Massage of the kidney was undertaken, and the opsonic indices were estimated before and after massage. In each case six samples of the same serum were sent to six observers in five different laboratories, each observer receiving, unknown to him, two samples of the same serum. Observer B. alone was given tubes before and after massage.

The indices returned were:—

Before Massage.

Observer	A.,	O.I. to T.B.	...	0·78	Phagocyte count of 100 cells		...	—
,,	A.	,,	...	0·83	,,	,,	,,	... —
,,	B.	,,	...	0·93	,,	,,	,,	... 193 : 208
,,	O.	,,	...	1·00	,,	,,	,,	... 228 : 226
,,	O.	,,	...	1·03	,,	,,	,,	... 233 : 226
,,	B.	,,	...	1·17	,,	,,	,,	... 245 : 208

After Massage (twenty hours).

Observer	T.,	O.I. to T.B.	...	0·81	Phagocyte count of 100 cells		...	227 : 281
,,	T.	,,	...	0·82	,,	,,	,,	... 229 : 281
,,	B.	,,	...	0·89	,,	,,	,,	... 220 : 250
,,	B.	,,	...	0·93	,,	,,	,,	... 232 : 250
,,	X.	,,	...	0·89	,,	,,	,,	... 246 : 277
,,	X.	,,	...	1·59	,,	,,	,,	... 443 : 277

In this case some of the results are remarkably consistent. Observer A. differs from himself by only 0·05, Observer O. by only 0·03, Observer T. by only 0.01, and Observer B. returns an identical index before and after massage 0·93. On the other hand, the value of this unanimity is upset by the maximum

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variation before massage, 0·39, and a maximum variation after massage of 0·78. Again, whilst B. returns an identical index before and after massage, his second reading gives a drop after massage of 0·24, the difference between his first two observations. Further, Observer X. is seen to differ from himself by 0·70. In conclusion, it is worth noticing that in a case obviously tuberculous only two indices were returned as being outside the normal limits, one being 0·02 below and the other 0·39 above.

The interval between the two sets of observations was twelve hours.

Test 9.

Disease suspected: pulmonary tuberculosis.

In this case three samples of the same serum were sent to three observers in two laboratories.

The indices returned were:—

Observer A., O.I. to T.B.	... 1·42	Phagocyte count of 100 cells	... 95 : 67
,, T., ,,	... 1·02	,, ,, ,,	... 180 : 176
,, O., ,,	... 0·95	,, ,, ,,	... 178 : 190

Here A. differed from O. by 0·47. The next largest variation was 0·40, and the smallest 0·7. Two indices were well within normal limits, and one much above.

Tests 10, 11, 12, 13.

Disease suspected: pulmonary tuberculosis. Moderate fever.

In this case, on three successive days three samples of identical serums were sent on four different occasions to three different observers.

The indices returned were as follows:—

11.30 a.m. first day:			
Observer A., O.I. to T.B.	... 1·48	Phagocyte count of 100 cells	.. 136 : 92
,, T., ,,	... 1·28	,, ,, ,,	... 230 : 180
,, E., ,,	... 1·18	,, ,, ,,	... 159 : 134
6 p.m. first day:			
Observer A., ,,	... 1·6	,, ,, ,,	.. 147 : 92
,, T., ,,	... 1·28	,, ,, ,,	... 230 : 189
,, E., ,,	... 0·84	,, ,, ,,	... 113 : 134
6 p.m. second day:			
Observer A., ,,	... 2·16	,, ,, ,,	... 145 : 67
,, T., ,,	... 1·26	,, ,, ,,	... 221 : 176
,, O., ,,	... 0·95	,, ,, ,,	... 178 : 185
6 p.m. third day:			
Observer A., ,,	... 2·94	,, ,, ,,	... 197 : 67
,, T., ,,	... 1·28	,, ,, ,,	... —
,, O., ,,	... 0·92	,, ,, ,,	... —

It is of interest to note that the temperatures at the times when the various sets of observations were made were as follows:—

First set	Second set	Third set	Fourth set
99·6° F.	100·6° F.	100·2° F.	99·0° F.

The observations of Observer T. were remarkably consistent, being on all four occasions practically identical. The maximum variations of T. from A. on each occasion were, however, 0·20, 0·32, 0·90, 1·66. The maximum variation in all the observations was 2·02.

That opsonins do exist as factors to be reckoned with appears to have been firmly established by Sir Almroth Wright and his many followers. That they represent more than a fractional part in the highly complex machinery of immunity production we may still be permitted to doubt. Granted, however, for the moment, that opsonins are the important factor in the phenomena of immunisation that many believe them to be, the question of reliability is constantly arising. Technical considerations of standardisation of emulsions, cultural difficulties, agglutination questions, and so forth concern only those experts whose responsibility it is to render such technicalities as free from sources of error as possible. They do not affect the practising physician, whose only concern is with the pertinent questions of reliability and cost. As regards cost, as every one knows, it is high and necessarily so, and a most serious objection to wide use of the method it is. Regarding the question of reliability, it is quite impossible to ignore the fact that countless observations have been reported in which estimations have appeared to be of the highest value, either in diagnosis, or in directing some particular line of treatment. This is by no means, however, a universal experience, even when every effort has been made to secure the services of the high priests of the art. There appears, indeed, to be a growing conviction that, except possibly in the hands of an extremely small band of experts, the method is not of the general utility with which it has been credited.

The results I have quoted seem to support this conviction. If there is a satisfactory answer to these results, no doubt it will be forthcoming.

(4)

Auto-inoculation, Spontaneous and Artificial, its History, Value and Limitations.

I have now to show that the natural method of cure of infection is one of spontaneous auto-inoculation, and that it is therefore the best possible guide to artificial procedures when natural methods fail. I maintain, that is, that it is the best model, mainly because it antagonises all the factors in infection—namely, the tissue elements as well as the bacterial.

The following sketch, therefore, deals with an explanation of what is meant by the term auto-inoculation. The history of the process is touched on, together with methods of induction and inhibition. Clinical estimation of induction and inhibition is then referred to, with illustrative charts. A few general considerations receive attention, and finally a comparison is made of the relative advantages of hetero- and auto-inoculation. Discussion of the best practical methods of artificially inducing auto-inoculation both in pyrexial and in apyrexial conditions is reserved for a future occasion, as also are clinical and hæmatological estimations of infective conditions in which fever is absent. Most of the charts referred to are from cases of pulmonary tuberculosis with fever. This disease has been chosen not only because it admirably illustrates the principles I desire to enunciate, but also because its frequency makes it particularly suitable for investigation.

Definition.—There seems to be some ambiguity as to what is meant by the term auto-inoculation. The word hetero-inoculation, with its familiar sequence of inoculation from an outside source, intoxication and response, is intelligible enough. The meaning of auto-inoculation is, of course, precisely similar if we allow for the prefix. The real ambiguity, therefore, is not as to what the word means, but as to how inoculation can be initiated from within. The difficulty at once disappears if we recognise that auto-inoculation can be produced spontaneously or artificially. Provided that there is free communication between an active focus of infection and the blood of lymph-stream, natural or

spontaneous auto-inoculation can clearly always be potentially in operation. Where, however, a focus is absolutely or relatively insulated, artificial means must be employed to induce hyperæmia, or, in other words, temporarily to destroy insulation. In the case of generalised infection, where, although intercommunication is free, response may be sluggish on account of stimulus being weak, artificial increase of stimulus has also to be employed. The effects produced by auto-inoculation are processes of active and passive immunisation.

History.—The history of the evolution of auto-inoculation as a therapeutic measure to be deliberately applied is intimately associated with that of hyperæmia, whether such hyperæmia be a natural phenomenon, as in inflammation and spontaneous inoculations, or artificially induced, as in any of Bier's methods. Inflammation, as we know, so long as it is neither inadequate nor excessive, is largely a protective and curative mechanism. The protection afforded thereby is partly due to transference of preformed tropic substances to a damaged area, and partly to the restraining response called out by stimuli from tissue-cells and bacteria. In other words, to spontaneous auto-inoculations employed by Nature from the beginning of time, though unrecognized by us.

Artificial auto-inoculation has been unconsciously applied from time immemorial. Whenever fomentations, poultices, stupes, setons, blisters, and the like have been applied in the treatment of established infections of joints, skin, serous sacs, sense organs, abdominal or thoracic viscera, &c., our forefathers have unwittingly employed processes of active and passive immunisation by inducing a form of artificial hyperæmia. Such hyperæmia may be directly induced, or indirectly by the agency of neurons. This is also true of other methods of inducing artificial hyperæmia, whether arterial or venous. When, for instance, Ambroise Paré treated fractures with obstructive bands, or when early Egyptian physicians employed light and heat baths, artificial auto-inoculations were in use. In 1894 the possibilities of active and passive hyperæmia were insisted on by Bier, whose methods have since invaded every domain of medicine and surgery. The conception did not, as is often supposed, originate with Bier.[43] As pointed out by Adami,[44] Bier's methods were based on the observations of Farre, Travers, Louis and Frerichs. Even to-day, however, Bier does not seem to have fully realised on what a sound basis his work stands. He makes no mention of auto-inoculation, and yet it is to this factor, as much as to any other, that his happiest results are due. As an instance in point may be given the use of the mask in inducing hyperæmia in the treatment of

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apyrexial cases of pulmonary tuberculosis, a method which clearly foreshadowed the modern adoption of graduated labour in the treatment of that affection. The conscious and deliberate employment of the principles of auto-inoculation in the treatment of apyrexial cases of pulmonary tuberculosis will always be associated with the names of Freeman, Meakin,[45] Wheeler, Paterson,[46] and Inman.[47] The remarkable results obtained by Paterson, and elucidated by Inman,[48] in the use of graduated labour, are well known, though these authors have unnecessarily restricted their field to the treatment of apyrexial cases, as I shall presently show. The history of spontaneous auto-inoculation is of much greater antiquity, dating back as it does to the first invasion of man by infective disease. Whenever in man such disease has obtained a footing, and has run a chronic course extending into months and years, and whenever the subject of such disease has been cured or has progressed towards cure without the aid of outside specific treatment, spontaneous auto-inoculation has been in operation. Further, even when disaster has finally overtaken him as a result of any given infection, auto-inoculative efforts have at some stage or other in his disease been at work. Evidence in support of these statements will be produced later. In the meanwhile, the following is worth consideration. It used to be said, on fairly sufficient grounds, that one-seventh of the human race died of tuberculosis in some shape or form. In 1904 the Registrar-General informs us that 55,000 fatal cases of this disease were recorded in this country by him.

It was not long ago estimated in France that in that country one in three of the total population living to the age of 30 either had had, had then, or would have some form of tuberculous infection. In more recent days Hamburger, of Vienna, Ehrlich, von Behring, Naegeli and others have estimated that by the time puberty is reached practically every European has received tuberculous infection demonstrable before or after death.

In this connection it may be said that the theory of universal infection is not, as at first sight appears, necessarily bound up with the doctrine of latent persistence of infection.

The proofs of statements as to fatality percentages are, of course, only approximately reliable. The more important proofs of statements as to the total incidence of a disease like tuberculosis must be largely inferential, though considerable evidence is available from post-mortem records of unexpectedly discovered tuberculous lesions.

The ratio of mortality to incidence in tuberculosis is of the highest

importance, because, if the theory of universal incidence be well founded, the wonder is not that in this country 55,000 die of the disease, but that such a huge majority get well. Since only a very small number of those that recover, or at least do not die of their infection, receive specific treatment by hetero-inoculation with tuberculin, it is clear that some other factor must have been at work to protect them. We have seen that no amount of general treatment is, in the absence of specific treatment (spontaneous or artificial), of the slightest avail in the treatment of a chronic disease like tuberculosis; hence such specific treatment can only have been supplied by unrecognized auto-inoculations.

If we turn to other infective diseases we find, for instance in 1904, that the ratio of deaths to notifications in London and the 256 towns was 63,052 : 9,887 in the following affections: smallpox, scarlet fever, typhus, erysipelas, enteric, continued relapsing fever, puerperal infection and diphtheria. The highest mortality was from diphtheria, 3,726 with 27,748 notifications. The lowest, excluding typhus and relapsing fever, was small-pox, 329 with 5,945 notifications. The other ratios of notifications to deaths were: enteric, 11,210 : 1,978; erysipelas, 17,100 : 727; typhus, 133 : 34; scarlet fever, 79,398 : 2,414; relapsing fever, 184 : 21; and puerperal fever, 1,324 : 658. Taken as a whole, the ratio of notified incidence to notified mortality was approximately in these diseases 10 : 1.

We know of no really efficient means of artificial specific treatment of any of these diseases except diphtheria. Hence the truth of the statement that in tuberculosis a much larger number of people recover from infection than die of infection is well supported by the analogy of the other infective diseases quoted.

The various methods of inducing and inhibiting auto-inoculation may be thus tabulated:—

INDUCTION OF AUTO-INOCULATION.

(*A*) *Spontaneous.*

(*a*) The occurrence of infection, given free communication.
(*b*) Inflammation.
(*c*) Involuntary movements—*e.g.*, of heart, lungs, stomach, &c.
(*d*) All voluntary movements.

(*B*) *Artificial.*

All methods for inducing artificial hyperæmia, active and passive, such as

(*a*) Counter-irritation.
(*b*) All of Bier's appliances.
(*c*) Active and passive movements.
(*d*) Light and heat.
(*e*) Respiratory exercises.
(*f*) Radium and X-rays.
(*g*) High altitudes.

INHIBITION OF AUTO-INOCULATION (NATURAL AND ARTIFICIAL).

(*a*) Response called out by auto-inoculation in so far as it is expended on inhibiting activity of focus of infection.
(*b*) Removal or destruction of infective focus.
(*c*) Arrest of inflammation by cold, &c.
(*d*) Rest.
(*e*) Drugs: opium, belladonna, &c.

In this table the only points that can be noticed here are the inductive action of radium and X-rays, and the inhibitory action of rest and drugs.

As regards radium and X-rays, Neuberg[49] and Willcock[50] maintain that they have no restraining action on autolytic enzymes, though they are credited with inhibitory action on most other enzymes. Hence, according to Neuberg, cancer tissue exposed to radium undergoes autolysis much faster than cancer tissue not so exposed. Heile regards their action as due to liberation of leucocytic enzymes as a result of autolysis. The effect of both forms of emanation appears to be, in short, in the direction of direct or of indirect stimulation of action of autolytic enzymes. If this be so it becomes easily intelligible that radium should be a powerful weapon for producing auto-inoculation. For by undue activity of autolytic enzymes thereby incited not only will self-destruction of abnormal tissues be set up, but the stimulus afforded by abnormally acting enzymes may well be in itself a process of auto-induction leading to active immunisation against the aberration exhibited by cancerous cells. Experimental work in this direction is much wanted.

ARTIFICIAL INHIBITION OF AUTO-INOCULATION.

The value of rest in inhibiting auto-inoculation is unquestionable. Rest, however, can never be absolute, on account of the impossibility of controlling ordinary vital functions. At times, as shown by Dr. Arthur Latham,[51] the immediate effect of complete rest on pyrexia, a failure of the temperature to rise sometimes indicating absence of auto-inoculative stimulus, is very striking. In other cases the effect is absolutely *nil* in this direction.

The number of drugs capable of controlling auto-inoculative processes is unfortunately limited. The only two drugs of general utility appear

to be opium and belladonna. The effect of the administration of calcium salts in this direction is alleged to be due to their reputed power of retarding coagulation time *in vivo*. It is, in fact, widely believed that when given by the mouth calcium salts lead to increase of the calcium content in the blood, this to induction of acceleration of coagulation time of the blood, and this to inhibition of inoculation. Such accelerating action of coagulation time, however, has now been shown to be legendary, both by Dr. Golla[29] and T. Addis.[52] The latter observer has shown from a long series of experiments that coagulation time is, in fact, unaffected by the oral administration of soluble calcium salts, and, be it noted, of citric acid. In order to test clinically whether calcium salts had any effect or not in inhibiting auto-inoculation, I undertook a series of experiments by administering by the mouth calcium lactate in half-drachm doses to cases of pulmonary tuberculosis with fever. The clinical test was to be an appreciable fall in a rising temperature after the exhibition of the drug. Reference to Chart T will show that in none of the eight observations was the administration of the drug followed by any fall in temperature. In twenty-two other observations not charted, a fall of temperature within six hours of administration of the drug took place only twice. Obviously, therefore, the drug can neither be relied on to accelerate coagulation time *in vivo*, nor in any way to produce the definite clinical effects with which it has been credited.

Spontaneous inhibition of auto-inoculation is effected by all those natural methods which the economy employs in order to arrest the disease.

Methods of Estimating Induction and Inhibition of Auto-Inoculation.

(*a*) *Clinical Methods of Estimating Induction.*

In cases of infection accompanied by fever, it seems as if we have at hand a ready way of demonstrating not only the presence or absence of auto-inoculation, but also of presence or absence of response to such. The truth of the statement that a temperature chart can reveal the existence of intoxication and response is to some extent associated with the view that fever is a protective mechanism.

In the early days of medicine fever was undoubtedly held to be a conservative process. Subsequently the indiscriminate use of coal-tar products indicated the prevalence of an opposite teaching.

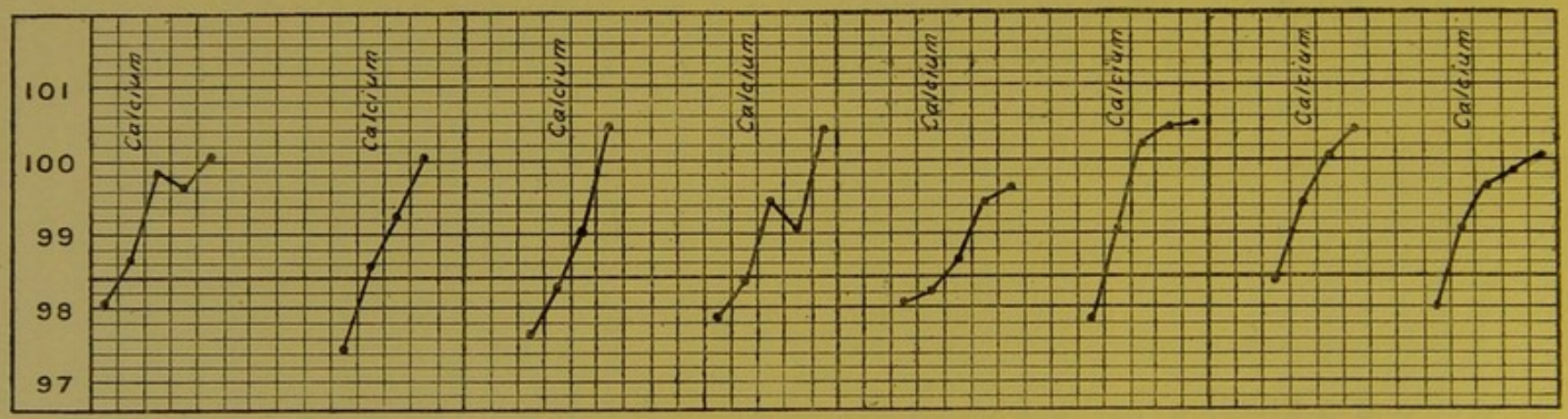

CHART T.—FOUR-HOUR CHART SHOWING NON-EFFECT ON TEMPERATURE OF 30-GRAIN DOSES OF CALCIUM LACTATE.

This has been again succeeded by the more rational view that within certain limits fever is essentially protective, and, in the case of infection of obvious source, actually an expression of effective neutralisation of such infection. In support of this view the following considerations are, amongst others, generally urged :—

(1) Experimentally a high temperature enables animals to resist infection more readily than does a low, as shown by Richter after puncture of the corpus striatum.

(2) An animal like the fowl, normally resistant to anthrax, shows no such resistance if the temperature is artificially lowered, as was shown by Pasteur.

(3) In lobar pneumonia in man, apart from hyperpyrexia, the prognosis largely depends on the height of the temperature, as has been shown by Hale White and others.

(4) In broncho-pneumonia the same holds good, as was shown by Holt.

(5) It was shown in 1887, by Dr. C. J. B. Williams and Dr. C. T. Williams, that in pulmonary tuberculosis :—

(*a*) In the so-called first stage 80 per cent. of cases either maintained or gained weight, in spite of, or, as I should prefer to say, perhaps even because of, fever. The number of cases was twenty-five.

(*b*) In the so-called second stage 5 per cent. gained weight. The number of cases was nine.

(*c*) In the so-called third stage 27 per cent. maintained or gained weight, whilst 72 per cent. lost weight. The number of cases was thirty-three.

So that of ninety-one cases, all febrile, in all stages, of whom more than one-third were in the "third" stage, and therefore far less able to efficiently immunise themselves than cases in earlier stages, no less than 56 per cent. maintained or gained weight.

(6) High temperatures are fatal to many micro-organisms.

If it be true that reaction against infection can be expressed in terms of the increased work done by tissue-cells, then we should expect to find a direct relation, within common-sense limits, between the amount of pyrexia and the degree of immunity production.

The possibility that temperature charts might prove to be of great service in estimating immunity response in bacterial infections was demonstrated by Dr. Arthur Latham[53] in 1908 in a most valuable contribution to the study of immunity delivered before this Society. His observations were to some extent associated with the inverse ratio

that he found to exist in many cases between the temperature and the opsonic index. If it be held that estimations of the latter, especially in tuberculosis, are, even if consistent, not a trustworthy gauge of immunity response as a whole, some other controlling standard must be substituted. This does not, however, in any degree detract from the value of his contention that in many cases it is possible more or less accurately to read an immunity curve in terms of a temperature chart. This contention, in spite of the fact that it is still unproven from blood examinations *quâ* opsonins or other immunising bodies, is, I submit, true, though, as I shall show, much more information can be gained from a study of temperature charts than has hitherto been elicited. Before proceeding with the evidence it is worth noticing the somewhat fallacious answer recently given to the suggestion that reliable information could be gleaned from clinical charts as to immunity production. In dealing with the subject, Sir Almroth Wright [54] maintains that the temperature curve is a measure of intoxication but not of immunisation, and that there is no direct and constant relation between such curve and the production of anti-bacterial bodies. This statement is surely a confusion of terms. It has been well said by Pembrey that fever is not an entity, but a convenient clinical term for a group of phenomena with a more or less definite sequence and origin.

If this be so, a fever chart, if it means anything at all, ought to reflect such origin and sequence.

The factors in immunisation are stimulus, plus, where such be possible, response. In other words, the combination of stimulus and reply to stimulus represents what we call the act of immunisation, since active immunisation is obviously impossible without the impetus of intoxication. Hence if the temperature curve is also an immunity curve it must be a measure of intoxication and response. If there is no response, the temperature curve in a pyrexial case shows its absence as well as its presence, and is therefore a measure of absence of immunisation. Hence, there may be, I maintain, a most direct and constant relation between a temperature curve and the production of protective bodies. That such relation actually does exist in many cases is suggested, though by no means proved, by a study of the ensuing charts.

Charts 1—4 are of cases of pulmonary tuberculosis from various sources who did well under general treatment. No one of them received artificial specific treatment of any kind. The charts are not, as they appear to be, ordinary charts showing diurnal variations of

temperature. In each case they represent the evening temperatures joined by a continuous line. The reason for this procedure is the great difficulty of getting a correct idea of the general course of intoxication and of response from a series of sheets recording diurnal variations. It is, in fact, impossible for the eye to receive an exact impression of a chart as a whole, if in a disease such as tuberculosis, with wide excursions between morning and evening, the ordinary charts are studied. The abbreviated method has the additional advantage of reducing to small compass the readings of many weeks. Each chart given below is capable of registering the observations of four months. In order to make clear the object of recording in a graphic manner what I conceive to be effective response to spontaneous auto-inoculation, the broken curve of declining indices has marked on it at intervals the letter X. Whenever, therefore, this letter appears, it is intended to indicate the crest of an effective auto-inoculative wave. It will be noticed that each crest is, as a rule, lower than preceding crests, higher than succeeding crests, and is separated from its fellows by intervals of from one to fourteen days. The smaller waves noticeable in the charts are not lettered.

Chart 1 is from a case of pulmonary tuberculosis with well-marked signs in both lungs. The sputum contained tubercle bacilli. The total gain in weight during treatment was 19 lb. Improvement was progressive. The case is of interest because not only does it show to perfection the broken curve of declining indices, but it also shows the absence of this curve in the first month of treatment before there was any sign of clinical improvement.

Chart 2 is from a case of pulmonary tuberculosis under treatment for five weeks only. The broken curve of declining indices coincided with well-marked clinical improvement.

Chart 3 is from a case of pulmonary tuberculosis published by Dr. F. W. Burton-Fanning, and treated by him in 1896, under the open-air *régime*. Tubercle bacilli were present. Fever declined, he said, after four months' treatment, and in a further seven months all physical signs and symptoms, as well as tubercle bacilli, had disappeared. The total gain in weight was almost 14 lb. He was well and at work twelve months after discharge. The case is interesting on account of the favourable course with many weeks' high fever. The chart shows very well, not only the broken curve of declining indices, but also the sharp elevations at X1 and X2, which seem to have been followed by great improvement.

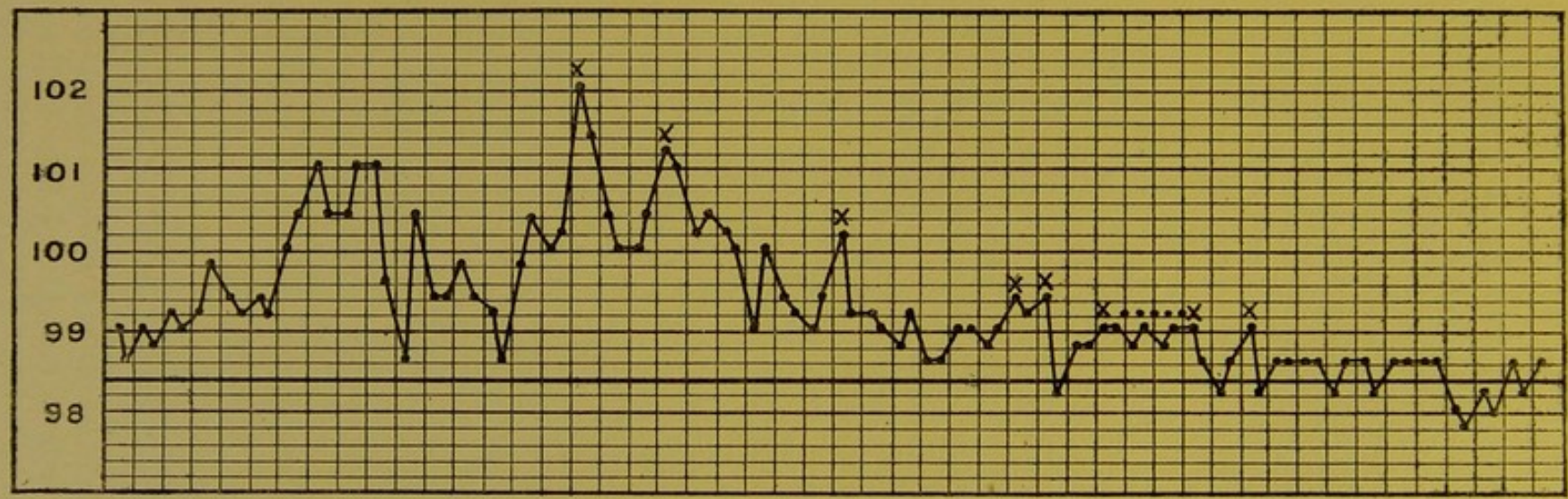

Chart 1.—Continuous Evening Chart.

Chart 4 is also one of pulmonary tuberculosis published by Dr. Burton-Fanning. There was, he says, a large cavity in one lung and a softening deposit in the other. The duration of treatment was four

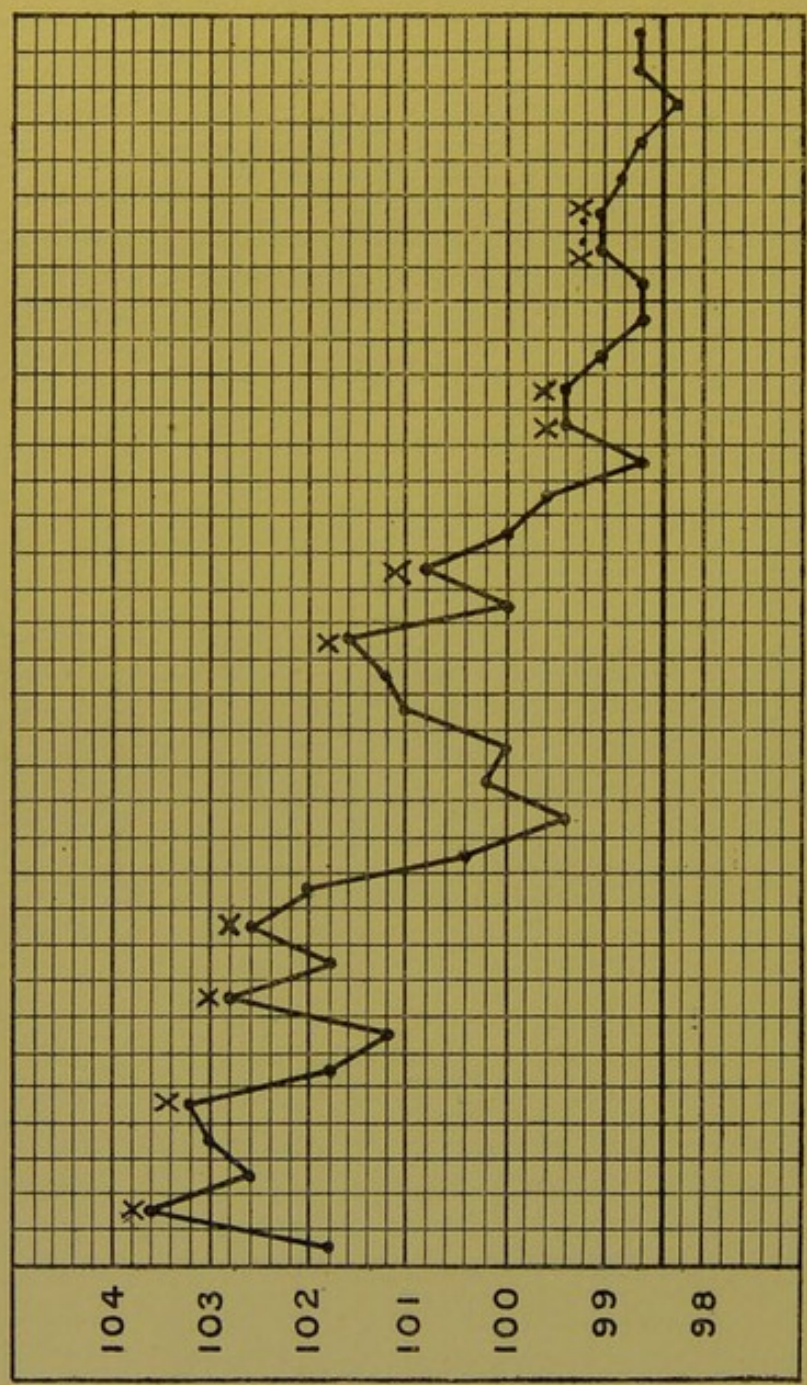

CHART 2.—CONTINUOUS EVENING CHART.

months, and the gain in weight 16 lb. Result—arrest and great improvement. The gap in the chart denotes the patient's temporary absence. On return she evinced a fresh rise from a spontaneous auto-

PULMONARY TUBERCULOSIS.

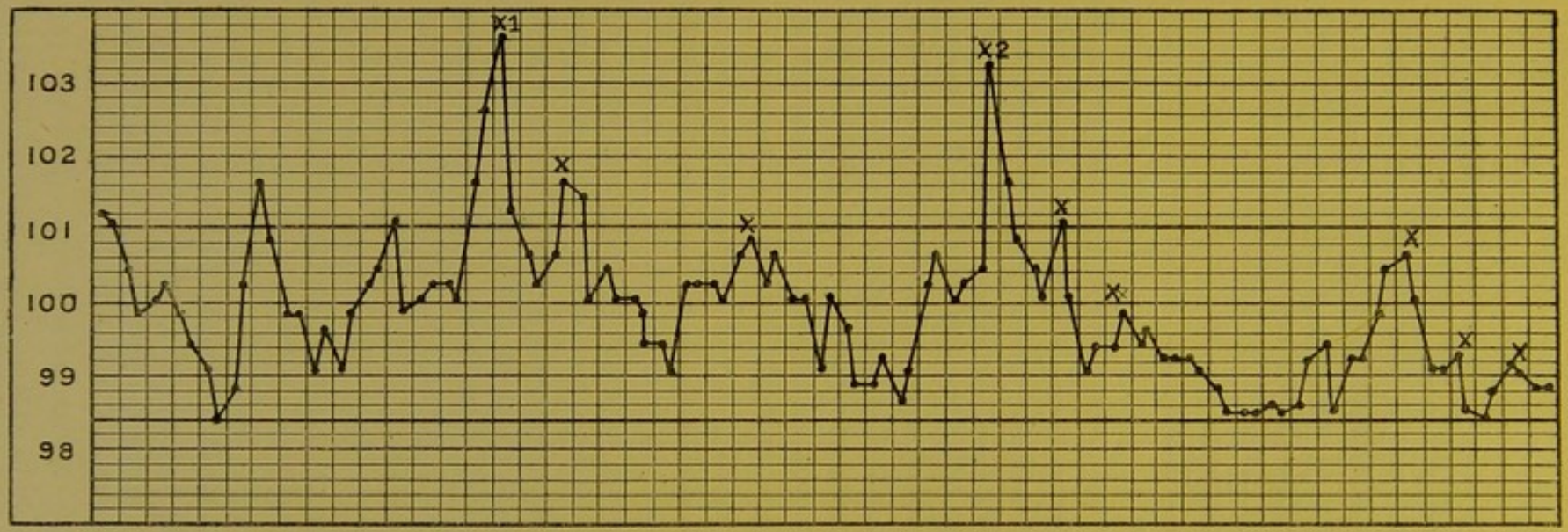

Chart 3.—Continuous Evening Chart.

inoculation which was again followed by a further declining curve and final descent to nearly normal.

Chart 5 is from a case in whom no attempt at inoculative treatment was made. He went steadily from bad to worse, and the chart shows almost total absence of attempts at effective response to spontaneous auto-inoculation. This chart is reproduced in order to demonstrate the reverse picture to that shown in Charts 1—4.

Charts 6—10 represent broken curves of declining indices in cases of enteric, scarlatina, influenza, and non-tuberculous broncho-pneumonia. They are reproduced to show that the picture of spontaneous and effective auto-inoculation is not confined to tuberculosis. The two enteric charts are continuous evening temperatures, the morning temperatures being again omitted as obscuring the point at issue. The influenza chart is a four-hourly one. In acute infections running a short course, such as scarlatina, influenza and measles, the insertion of morning temperatures is essential to correct interpretation. Since the remittency is slight there is no difficulty in reading.

Chart 11 represents an exactly opposite type to that shown in Charts 6—10. Effective response to auto-inoculative stimulus is, as a rule, conspicuously absent in cases in which death finally occurs.

This is a convenient place to notice that in some cases ultimately ending in death a broken curve of descending indices is occasionally shown almost up to the time of death. In such cases, however, it appears that, although response to auto-inoculation may be fair, the economy is unequal to the strain, and the ship goes down, literally with all flags flying. This is well seen in Chart 5, from A to B.

In order to represent more graphically still the contention that a temperature chart may often indicate with great accuracy presence or absence of effective response to auto-inoculation, the following auto-inoculation curves are reproduced.

Chart 12 is moulded from temperature Chart 2, and will be found to represent with sufficient accuracy for practical purposes the rise and fall of intoxication and response, leaving out of account minor variations.

Chart 13 is moulded on Chart 1. While Chart 12 represents undisturbed response to effective auto-inoculations, Chart 13 represents an early stage of nearly four weeks' duration in which response to such was in abeyance, and in which the patient was actually losing ground.

Chart 14 represents in the first half a partial absence of response to acute inoculation which was completely overpowered and eventually, in the second half, ended in death. The picture of Chart 14 is the inverse therefore of 12 and 13.

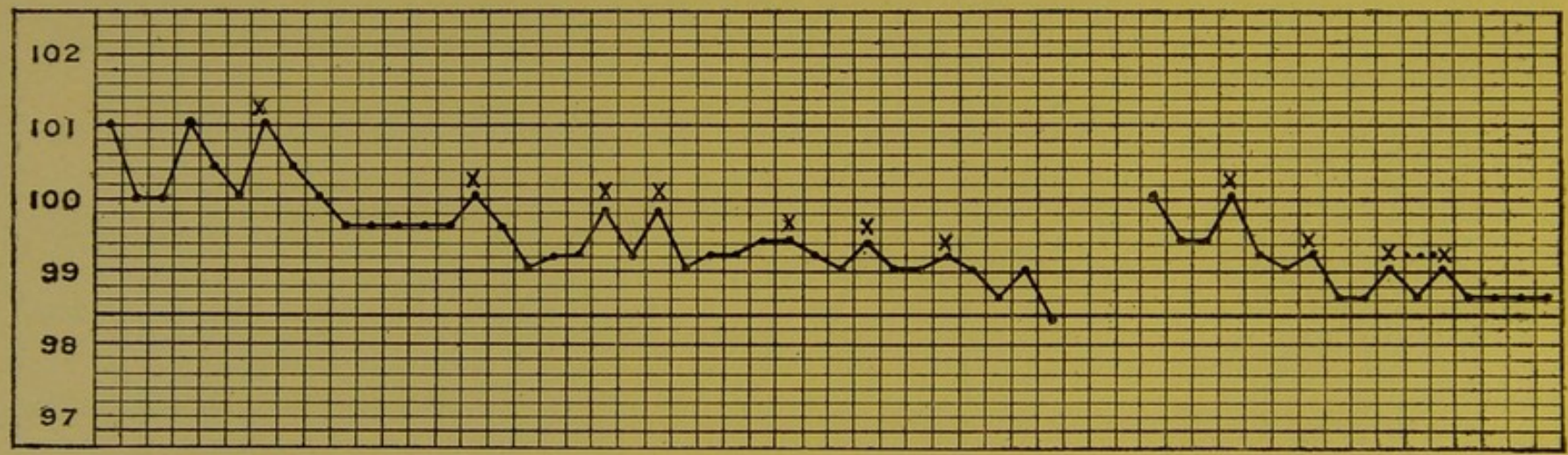

Chart 4.—Continuous Evening Chart.

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PULMONARY TUBERCULOSIS.

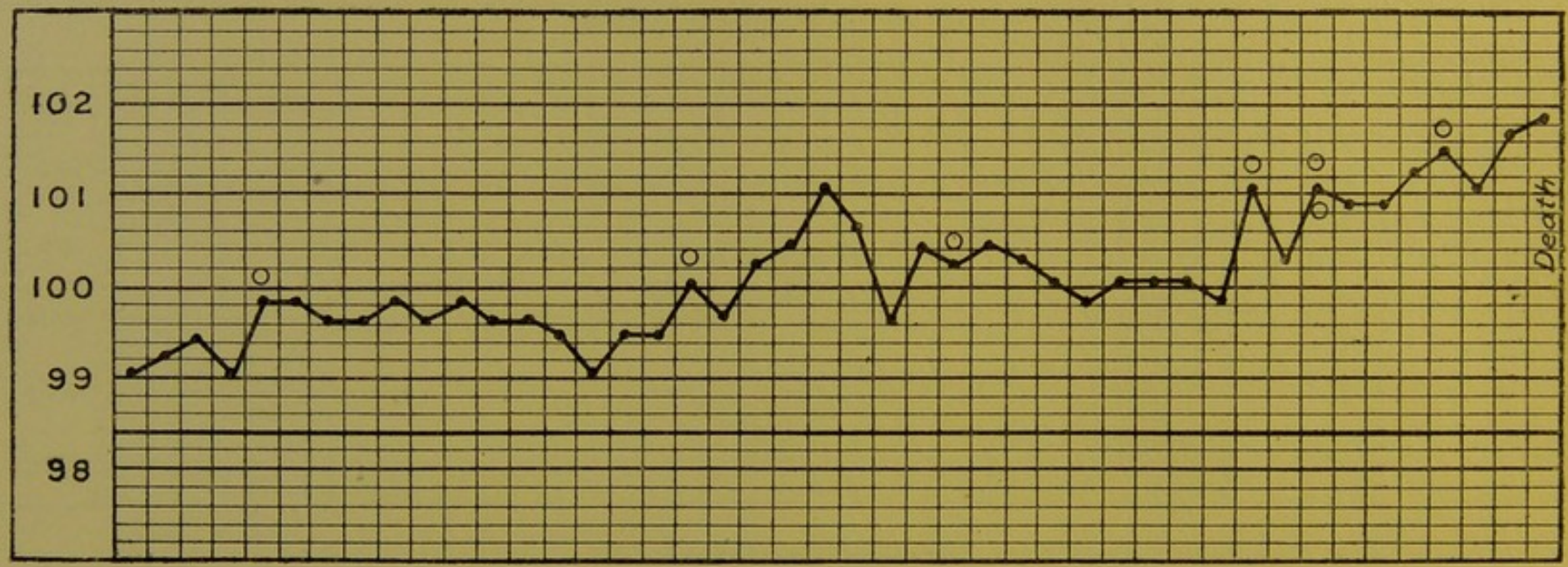

CHART 5.—CONTINUOUS EVENING CHART.

ENTERIC FEVER—RECOVERY.

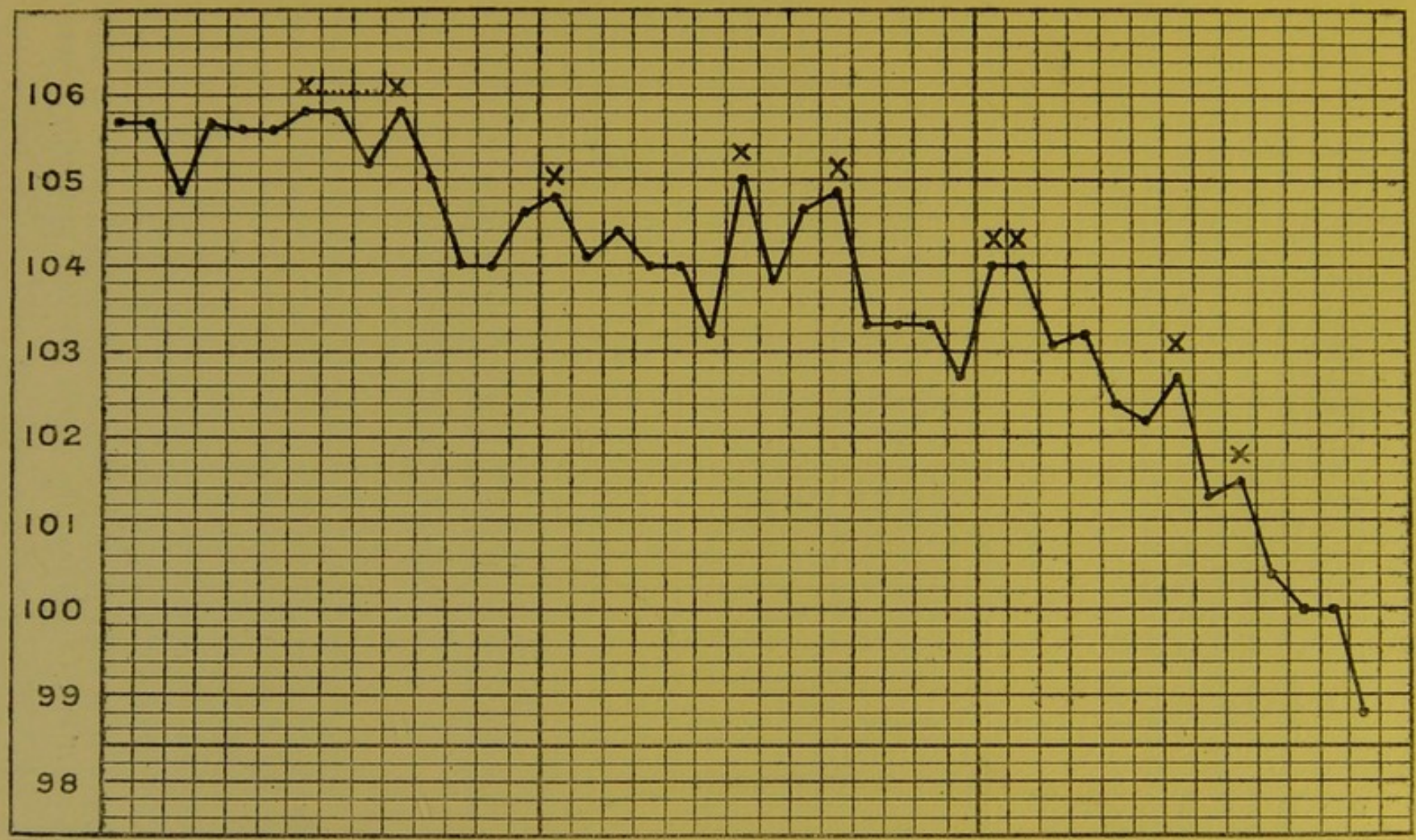

Chart 6.—Continuous Evening Chart.

Chart 15 represents a case of pulmonary tuberculosis which, clinically, was not markedly going downhill, but in which no material improvement was taking place. Towards the end of the chart, however, a slight increase in the extent of lung involved is reflected in the chart.

Chart 16 represents the spontaneous inoculation curve moulded on Chart 15. It will be found to represent a striking contrast to Chart 13, in which the patient did very well, and to occupy an intermediate position between 13 and 14, Chart 14 being that of a case ending in death.

SCARLET FEVER—RECOVERY.

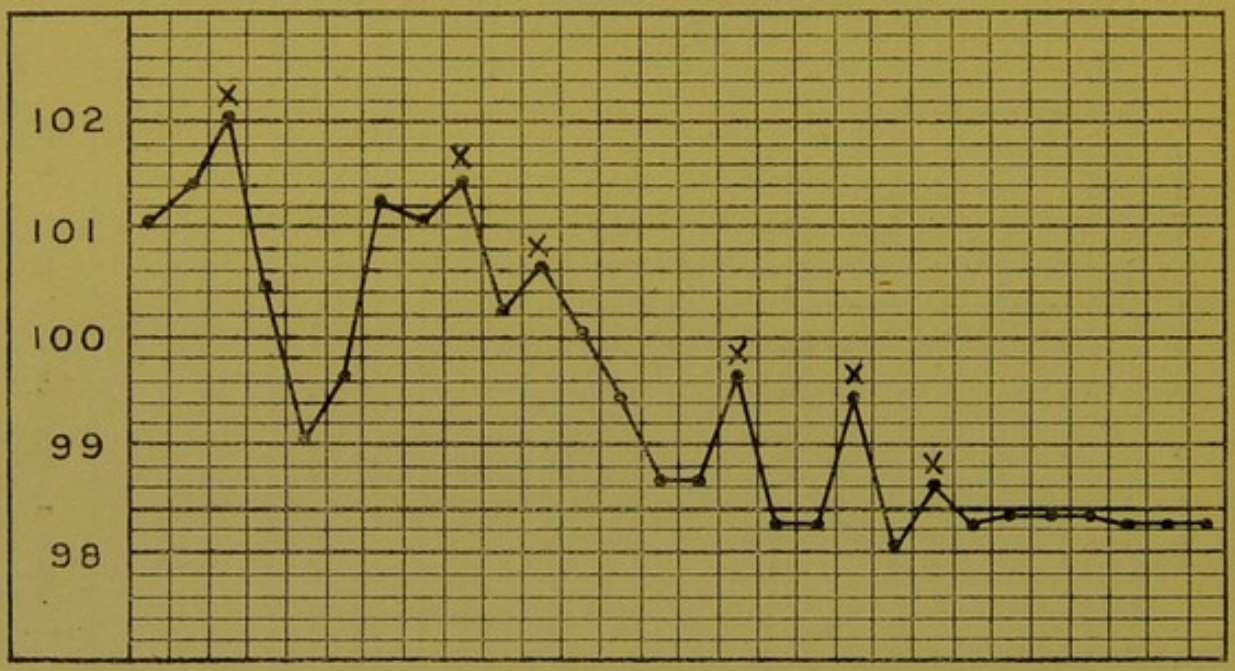

CHART 7.—CONTINUOUS EVENING CHART.

Having thus sketched the course taken in certain cases of pulmonary tuberculosis by the temperature charts and by what appear to be their intoxication-response curves where they were—

(*a*) Progressing towards cure;

(*b*) Rapidly going downhill;

(*c*) Doing neither well nor ill;

it remains to study the charts and auto-inoculation curves of cases in classes B and C in whom the course has been artificially altered by artificial means.

INFLUENZA—RECOVERY.

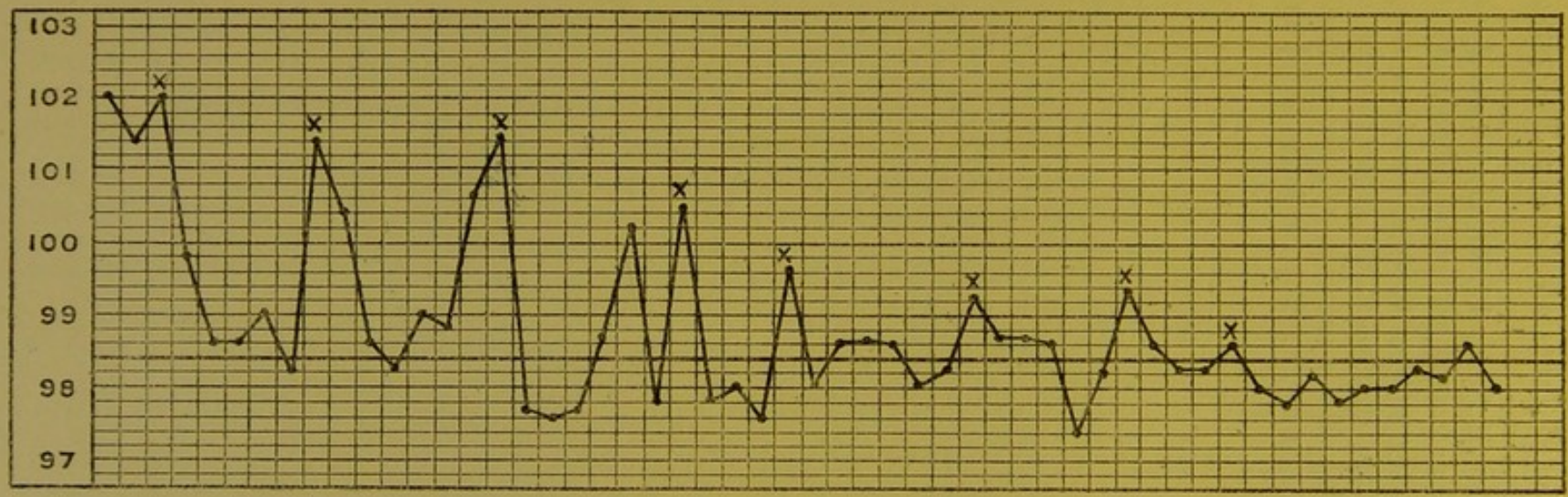

CHART 8.—FOUR-HOURLY.

Charts 17—23.—Of these, 17, 20, 21, 22 and 23 are reproduced to demonstrate how far cases of pulmonary tuberculosis that are not doing well can be artificially induced to approximate to cases that are doing well. The procedure adopted in all cases was one of artificial auto-inoculation, modelled on the information gleaned from Charts 1—17 of natural auto-inoculation. The material is not large, but it affords suffi-

BRONCHO-PNEUMONIA—RECOVERY.

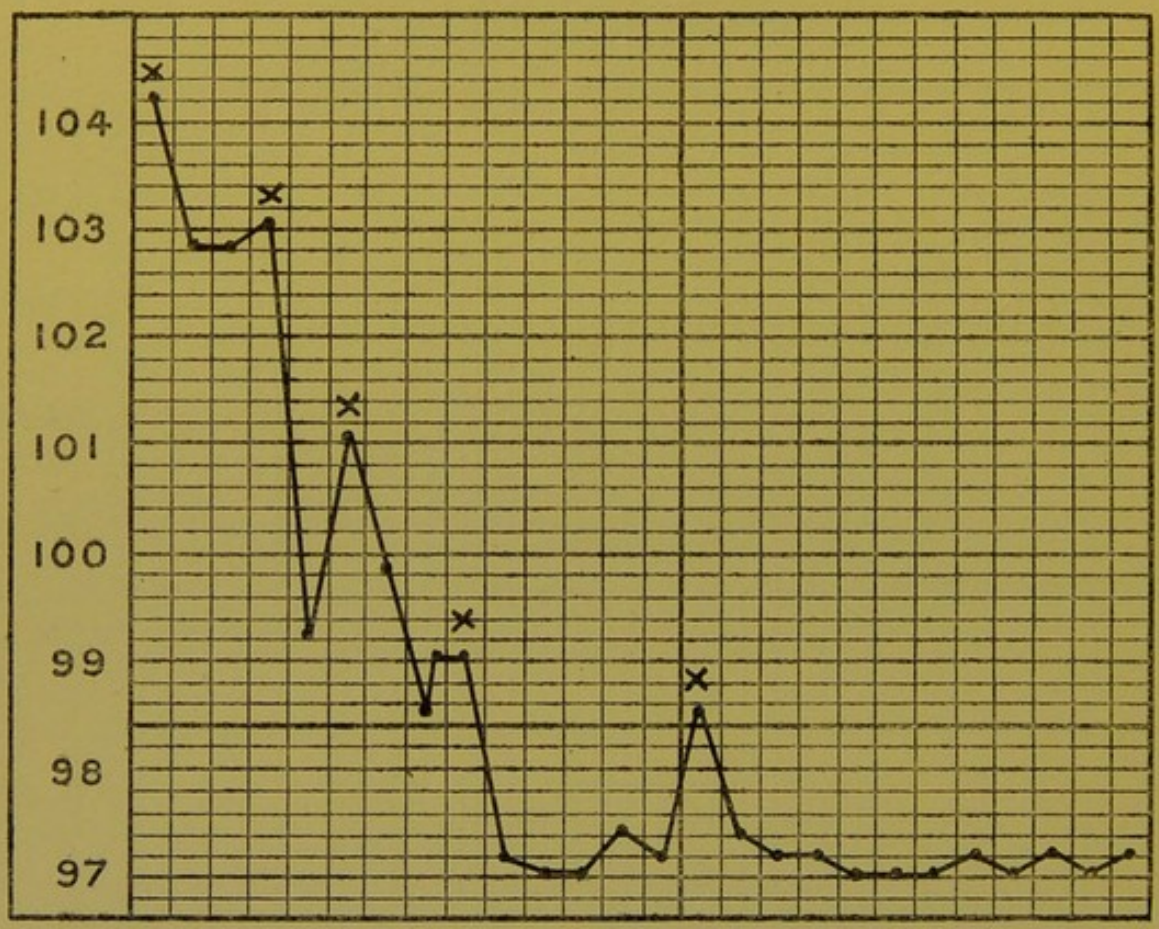

CHART 9.—CONTINUOUS EVENING CHART.

cient justification for extended trial of the method. In other cases not here reported in which tuberculin has been employed, the results obtained bear no comparison with the results obtained with artificial auto-inoculation although the guiding principles were identically the same.

ENTERIC FEVER—RECOVERY.

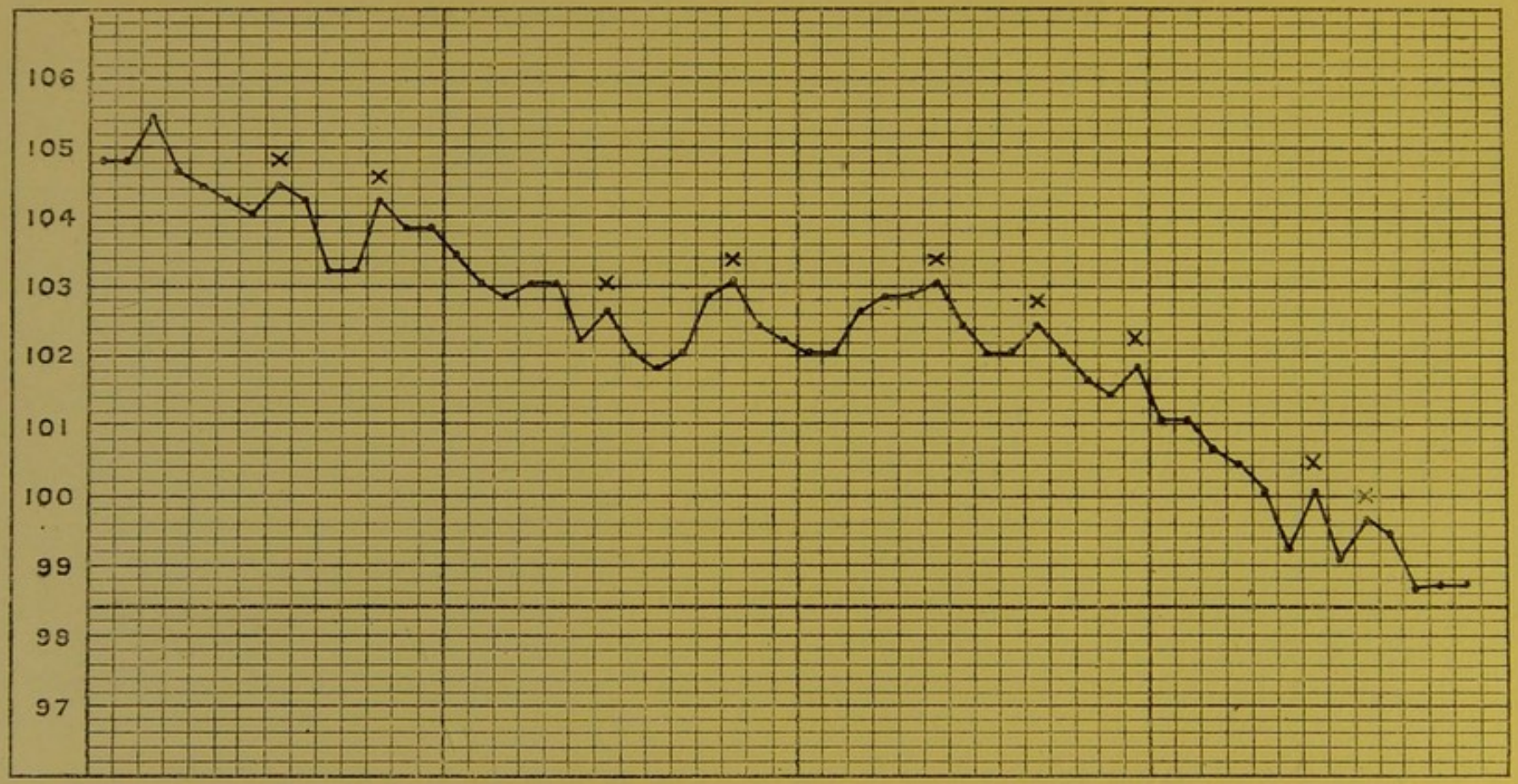

Chart 10.—Continuous Evening Chart.

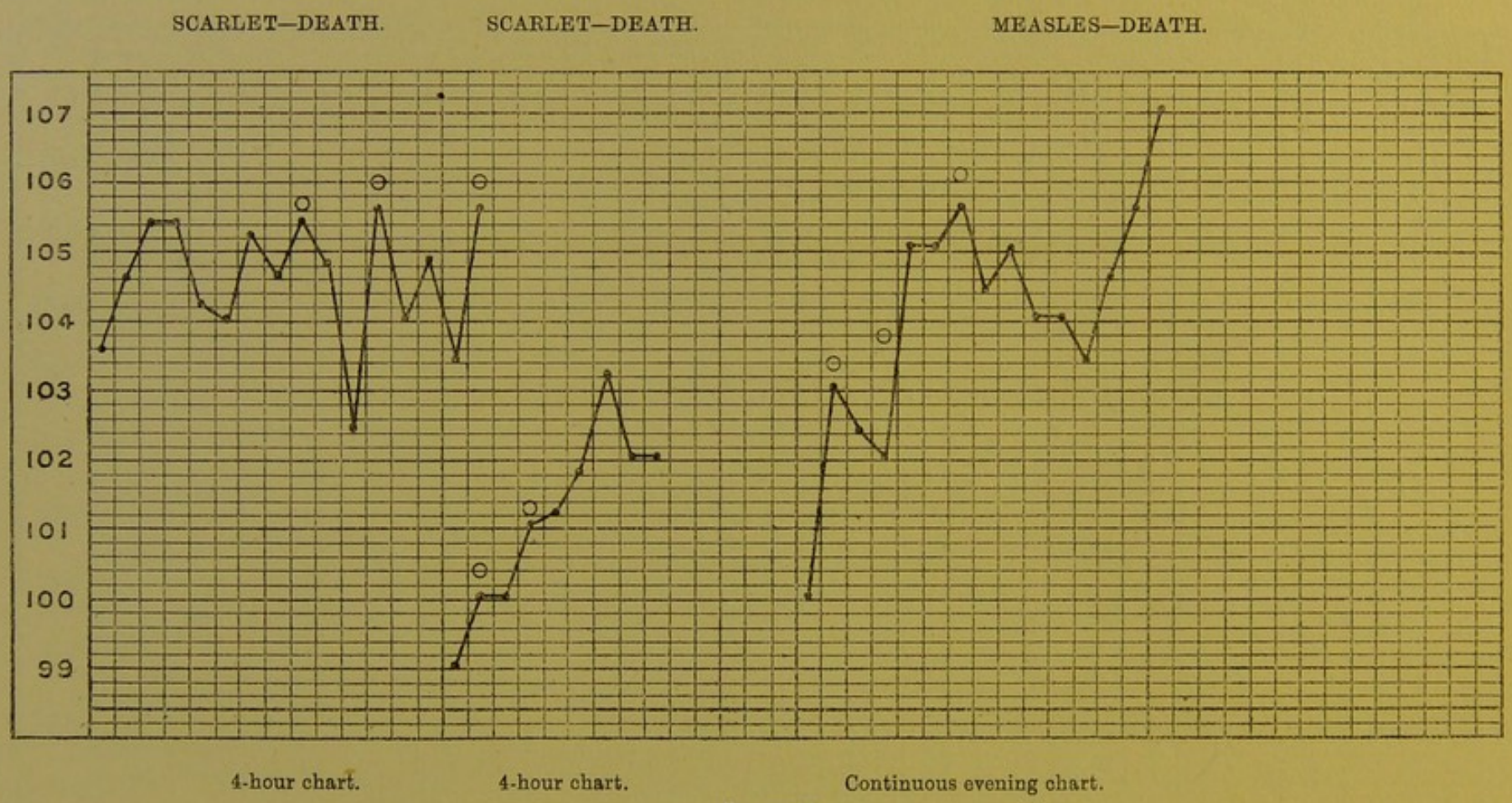
SCARLET—DEATH.
SCARLET—DEATH.
MEASLES—DEATH.
107
106
105
104
103
102
101
100
99
4-hour chart.
4-hour chart.
Continuous evening chart.

CHART 11.

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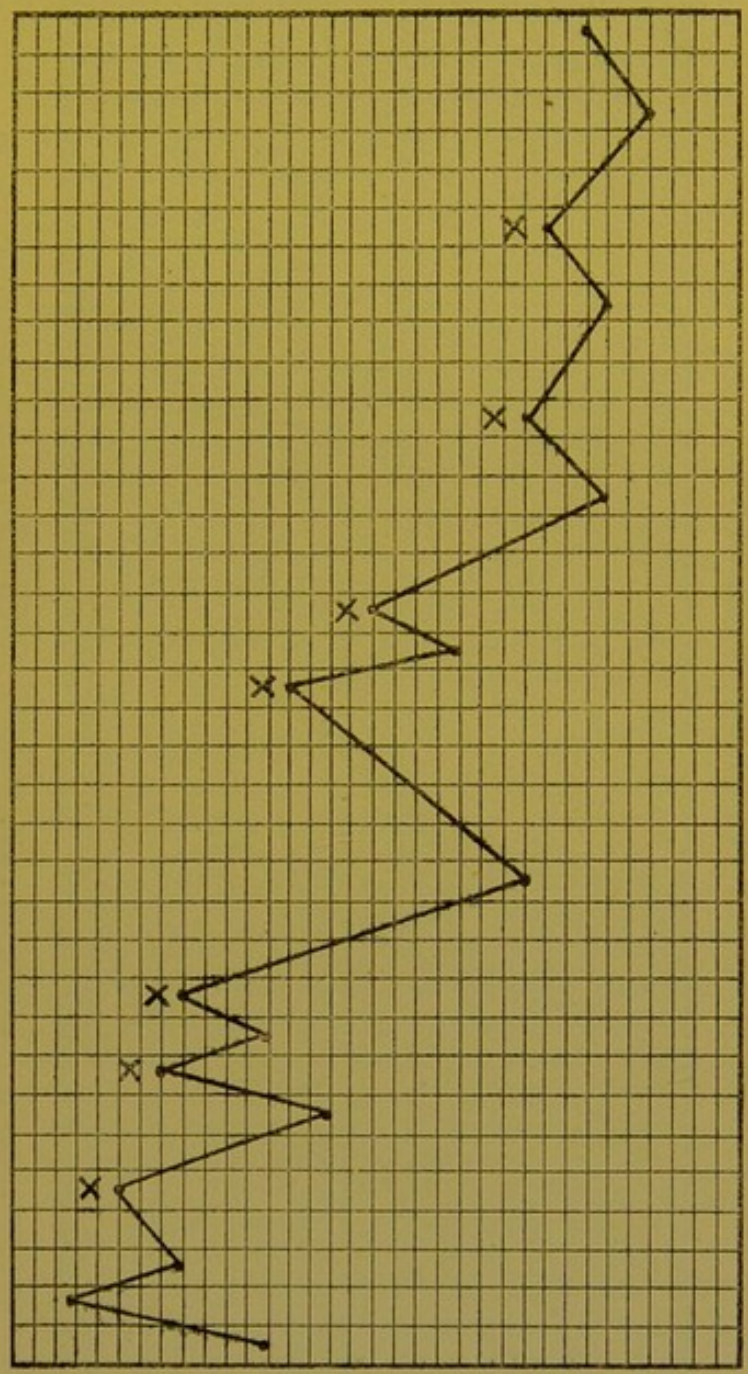


CHART 12.—INTOXICATION-RESPONSE CURVE OF CASE DOING CONSISTENTLY WELL.

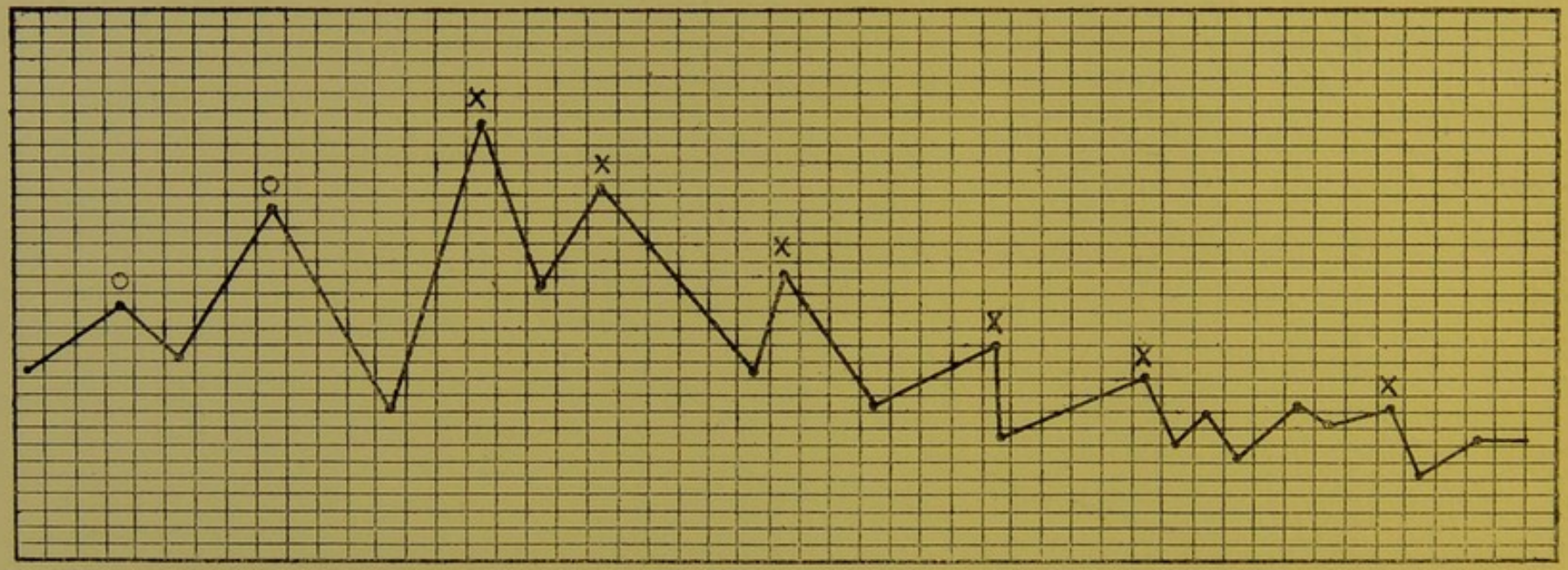


CHART 13.—INTOXICATION-RESPONSE CURVE OF CASE DOING AT FIRST BADLY, THEN WELL.

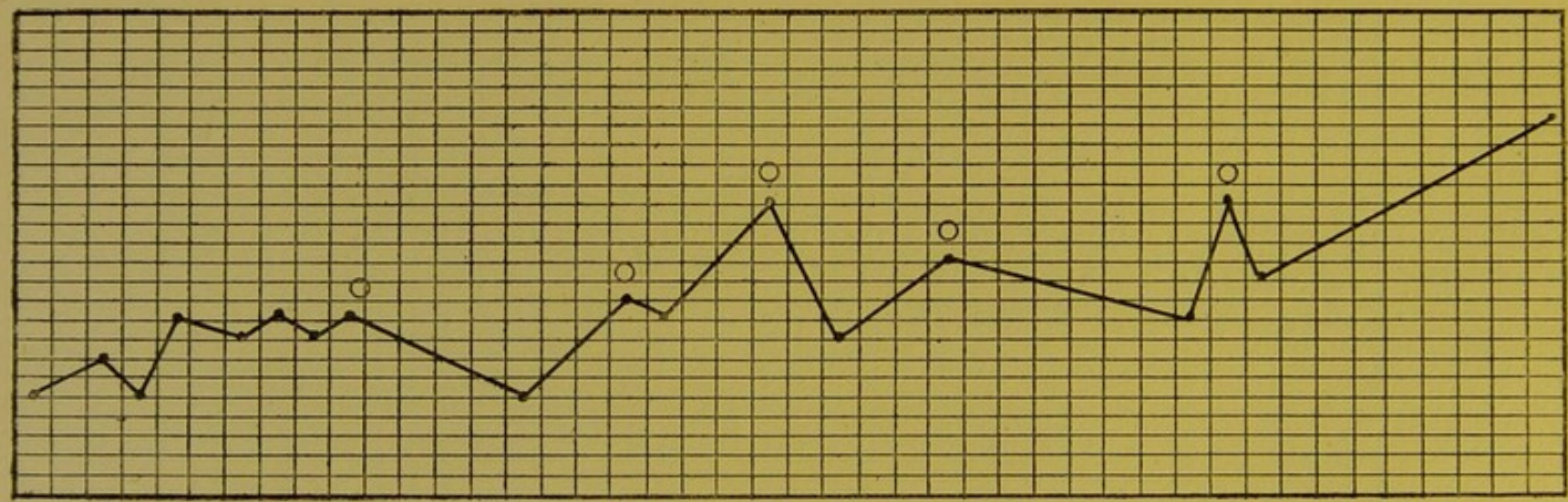
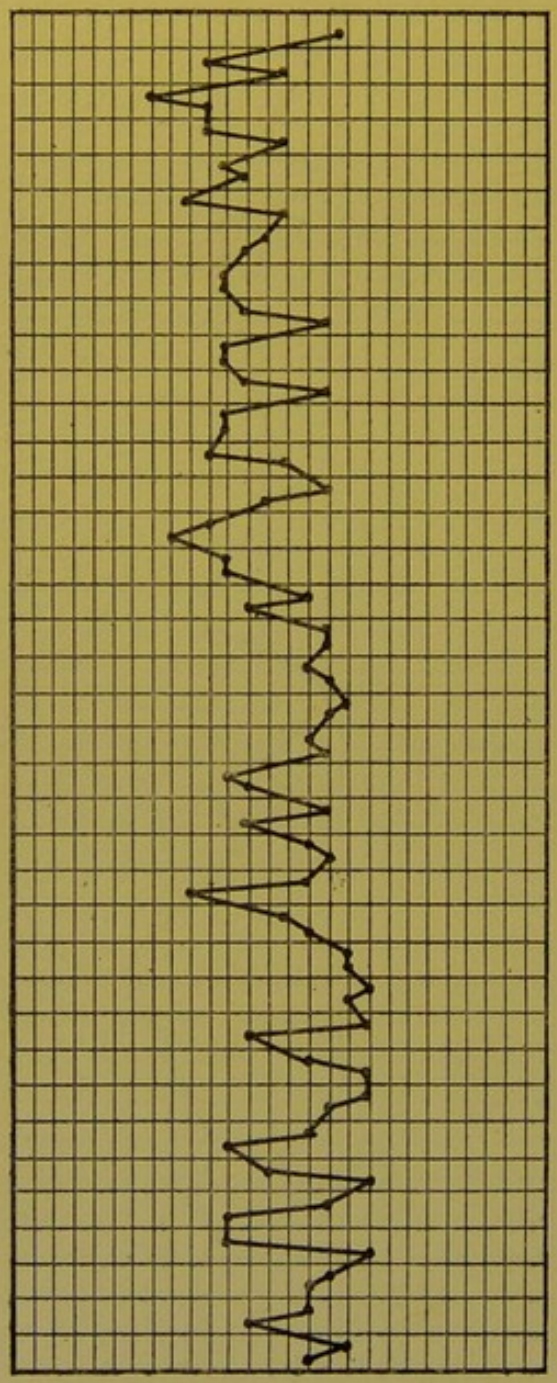
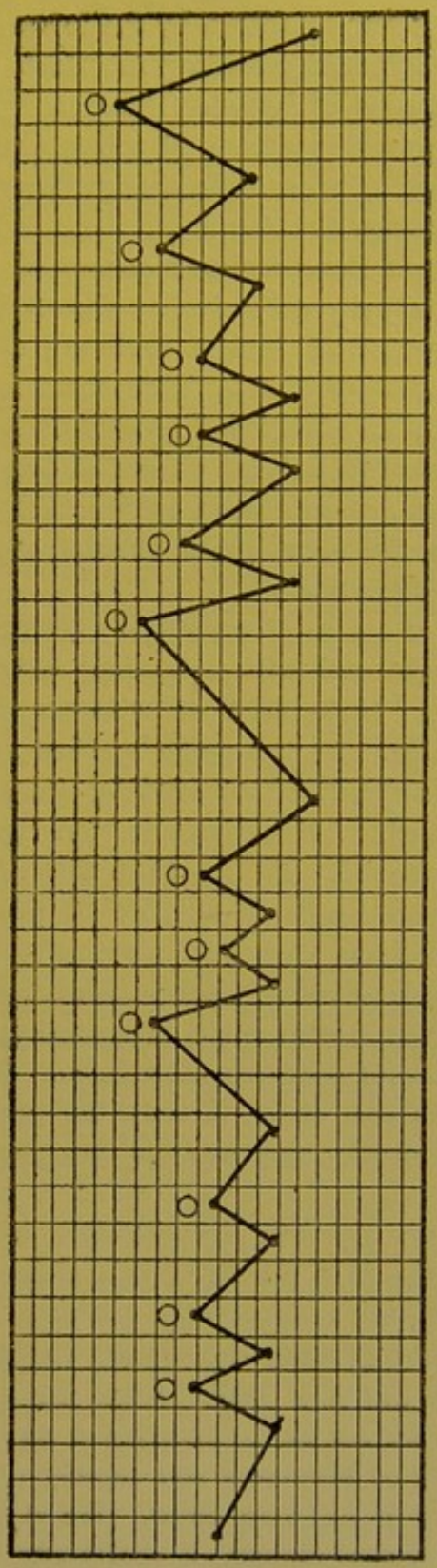


CHART 14.—INTOXICATION-RESPONSE CURVE OF CASE DOING BADLY. DEATH.



PULMONARY TUBERCULOSIS.

CHART 15.—CONTINUOUS EVENING CHART.



PULMONARY TUBERCULOSIS.

CHART 16.—INTOXICATION-RESPONSE CURVE OF CASE DOING NEITHER WELL NOR ILL.

Chart 17 represents four isolated phases where a correct auto-inoculative dose was given, as shown by the lower range of temperature following the apex of response preceding it. Such curves are apt to be misinterpreted as instances of hyper-inoculation. That such interpretation is erroneous, however, is shown by the coincidence of clinical improvement with the broken curve of declining indices. This consideration also applies to the injection or other administration of tuberculin.

Chart 18 represents three isolated phases of three different cases where the dose was actually excessive, as shown by declining physical improvement and absence of broken declining curve. It is therefore labelled a hyper-inoculation chart. This chart is a true intoxication record, with practically no evidence of response.

Chart 19 represents two isolated phases of two different cases where the dose was too small, as evidenced by practically no result following inoculation, either in the chart or in clinical signs. It is therefore labelled a hypo-inoculation chart.

Chart 20 is that of a case of pulmonary tuberculosis with moderate fever, but losing weight and with extending physical signs. Tubercle bacilli in the sputum. Until artificial auto-inoculation was begun no improvement took place. At the point marked on the chart a higher rise of temperature was produced by artificial auto-inoculation than had previously been recorded. At intervals further inoculations were given, and steady progress ensued. By the time this chart comes to an end the patient had lost all cough as well as all physical signs of active disease, and returned home with half a stone to her credit. For the time being the disease is arrested. Auto-inoculations are still being kept up. The absence of the broken curve of declining indices before interference is as marked as its presence afterwards. A continuous morning curve is introduced in this chart, to show the gradual lessening of the excursion between morning and evening temperatures as the patient improved.

Chart 21 is that of a boy with physical signs in both lungs and bacilli in the sputum. In the first month of this chart he had been treated with tuberculin T.R., with apparently nothing but harm. For two months he rapidly lost ground, the disease extending to an alarming extent, especially in the left lung. After the correct dose of auto-inoculation had been arrived at, he received a series of graduated doses through auto-massage of his lungs and rapidly improved, as the chart and present condition of his lung show. He is still under treatment, and, though still a source of anxiety, is continuing to do well.

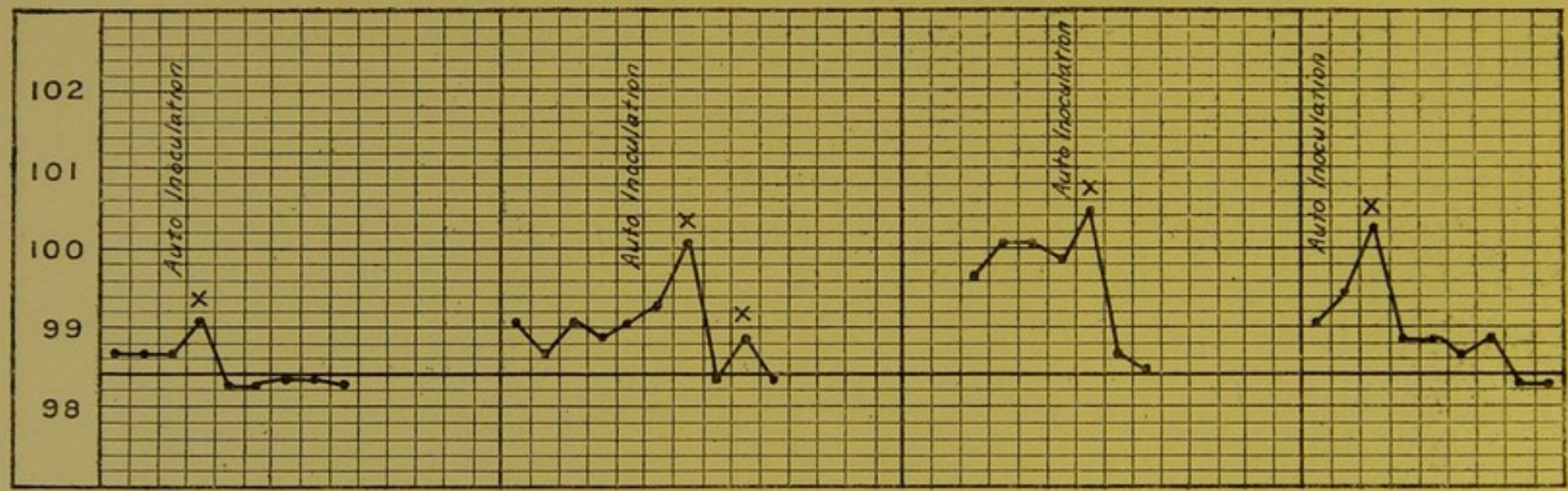


CHART 17.—AUTO-INOCULATIONS. CORRECT DOSE.

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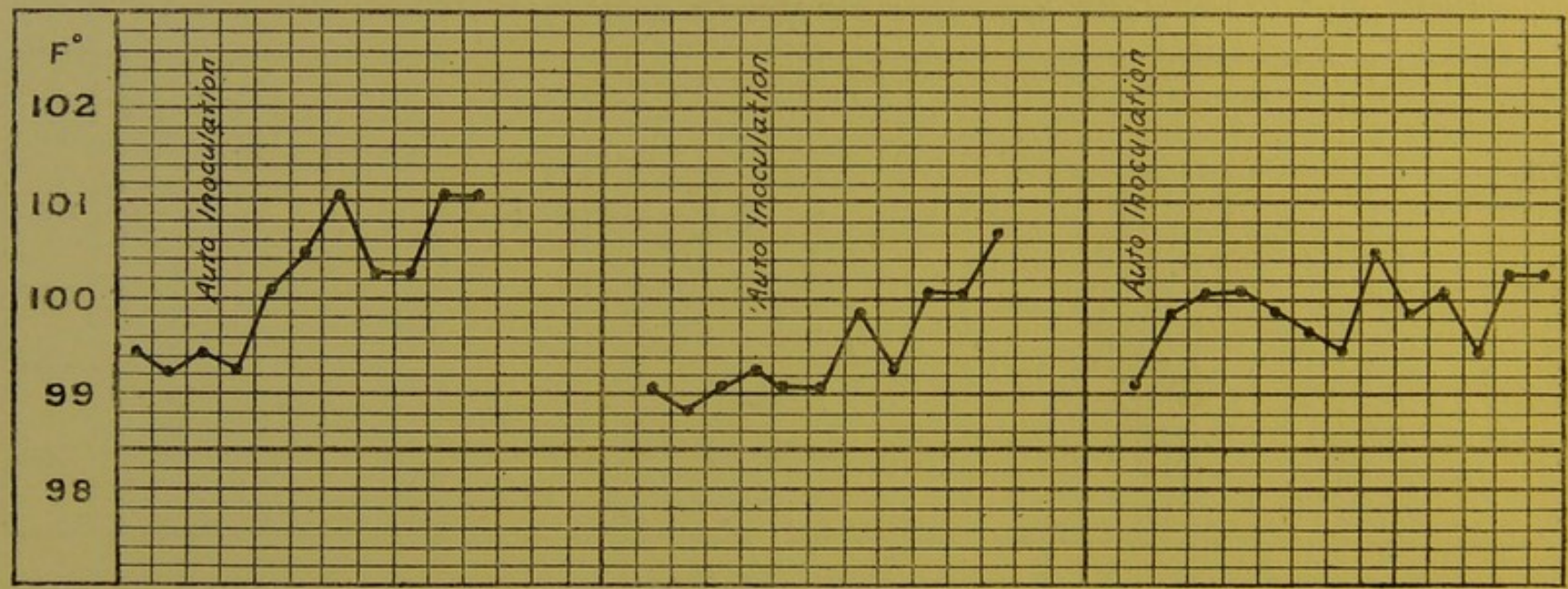


CHART 18.—HYPER-INOCULATION. INCORRECT DOSE

Chart 22 is that of a severe case of pulmonary tuberculosis. For two months the patient and her temperature chart were carefully watched without any form of specific treatment being given. During these two months she steadily lost ground in spite of absolute rest in bed. At the point marked in the chart auto-inoculation was at last carefully begun. Improvement had been as marked as before it was absent. The patient is still under treatment and there is good hope of eventual arrest. For three weeks after this chart was completed the temperature has improved still further. On two occasions she has in these three weeks been inoculated under the skin with $\frac{1}{500}$ mgr. tuberculin T.R. In both cases the injection has been absolutely ignored so far as clinical manifestations,

PULMONARY TUBERCULOSIS.

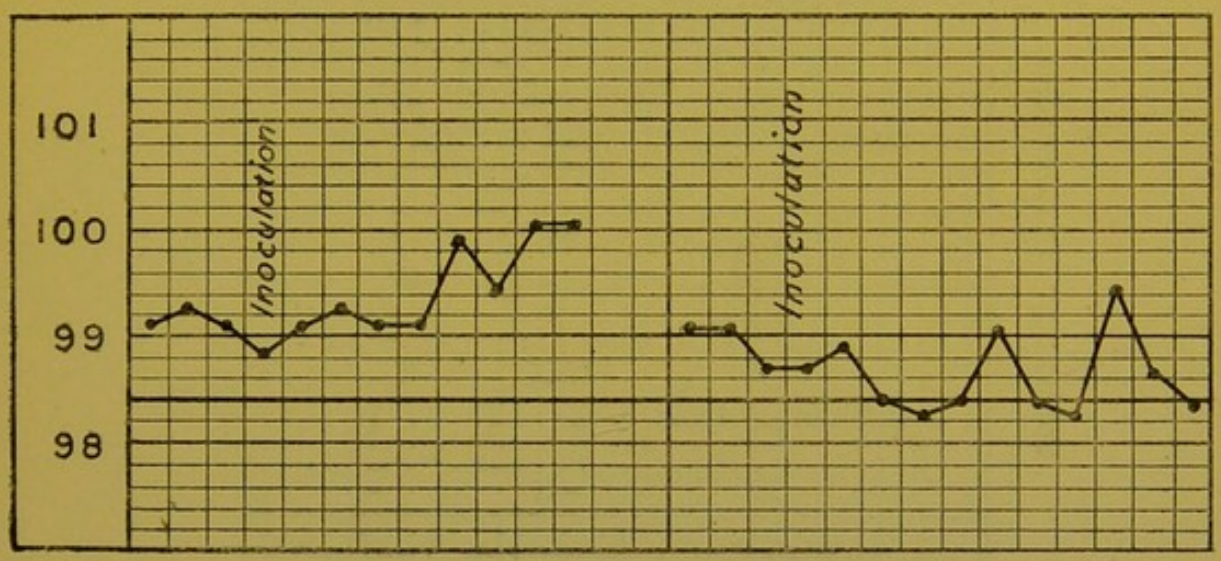
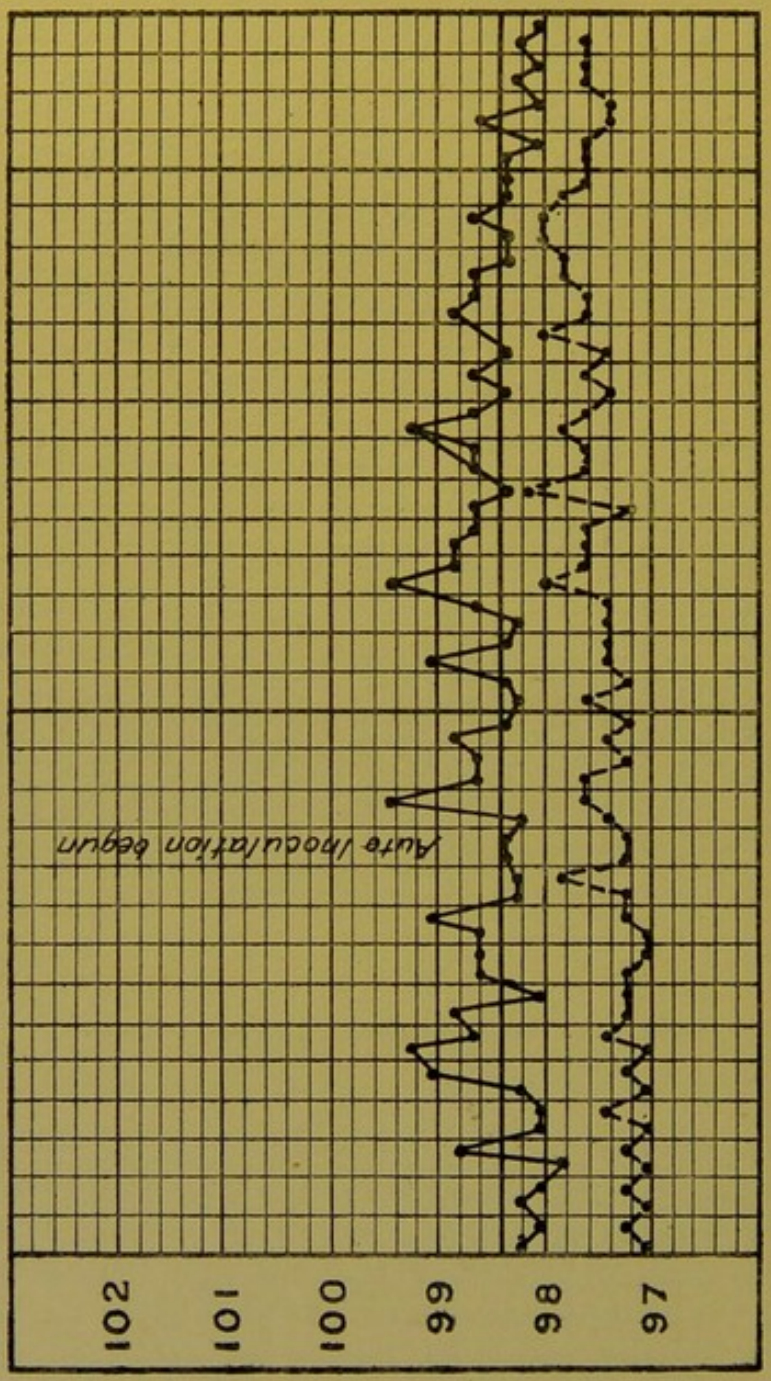


CHART 19.—HYPO-INOCULATION. INCORRECT DOSE.

including temperature, go, as I have frequently observed to happen where the temperature is at or near normal in cases approaching quiescence.

Chart 23 is worth showing to illustrate the effect of artificial auto-inoculation in a case of influenza complicated by a touch of pneumonia. At the time the artificial auto-inoculations were given the temperature was on each occasion rising. A further rise occurred, apparently as a result of the inoculation, followed in each case by fall. The curve of declining indices after the second inoculation is well shown. The physical signs in the lung rapidly cleared, and though convalescence was slow the ultimate result was good.



PULMONARY TUBERCULOSIS.

CHART 20.

PULMONARY TUBERCULOSIS.

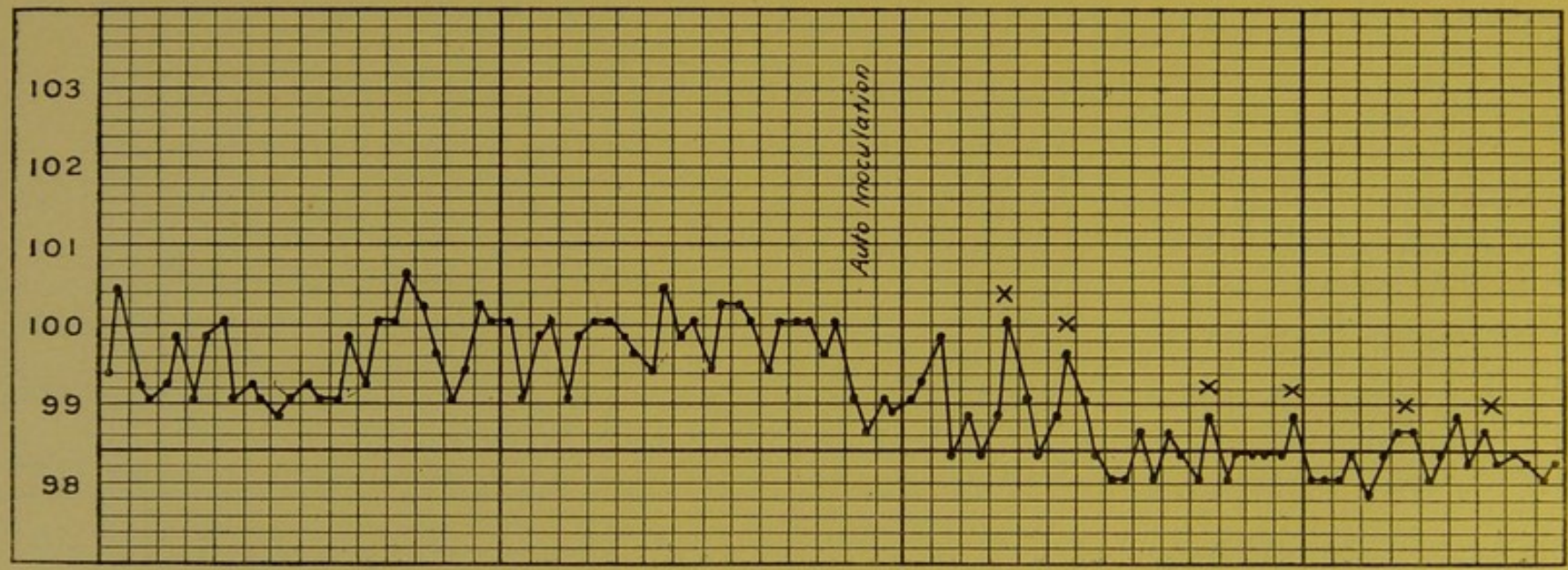


CHART 21.

PULMONARY TUBERCULOSIS.

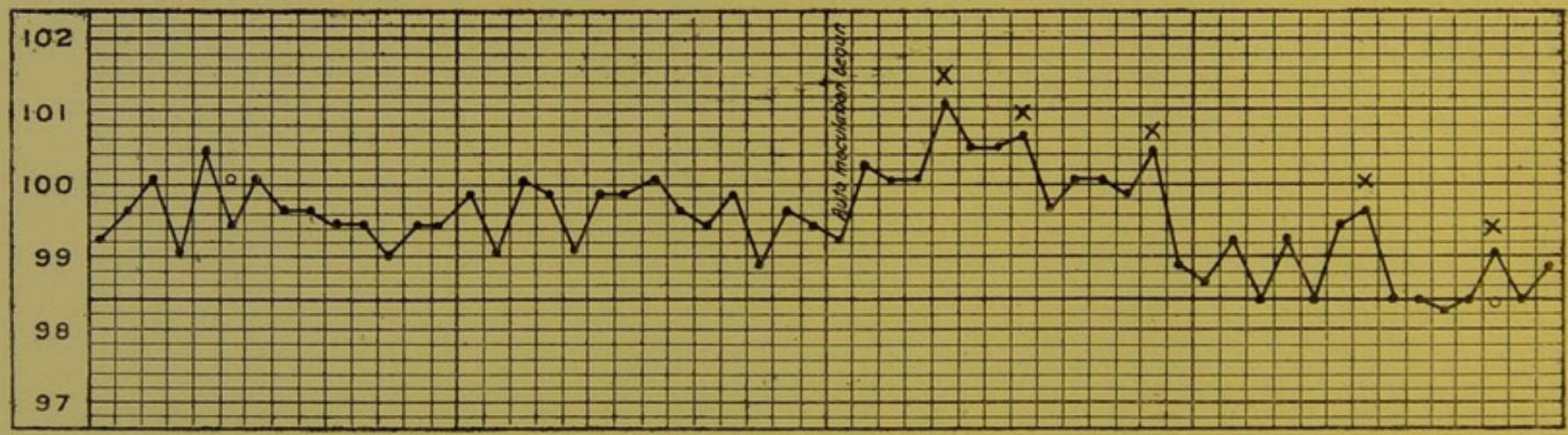


CHART 22.

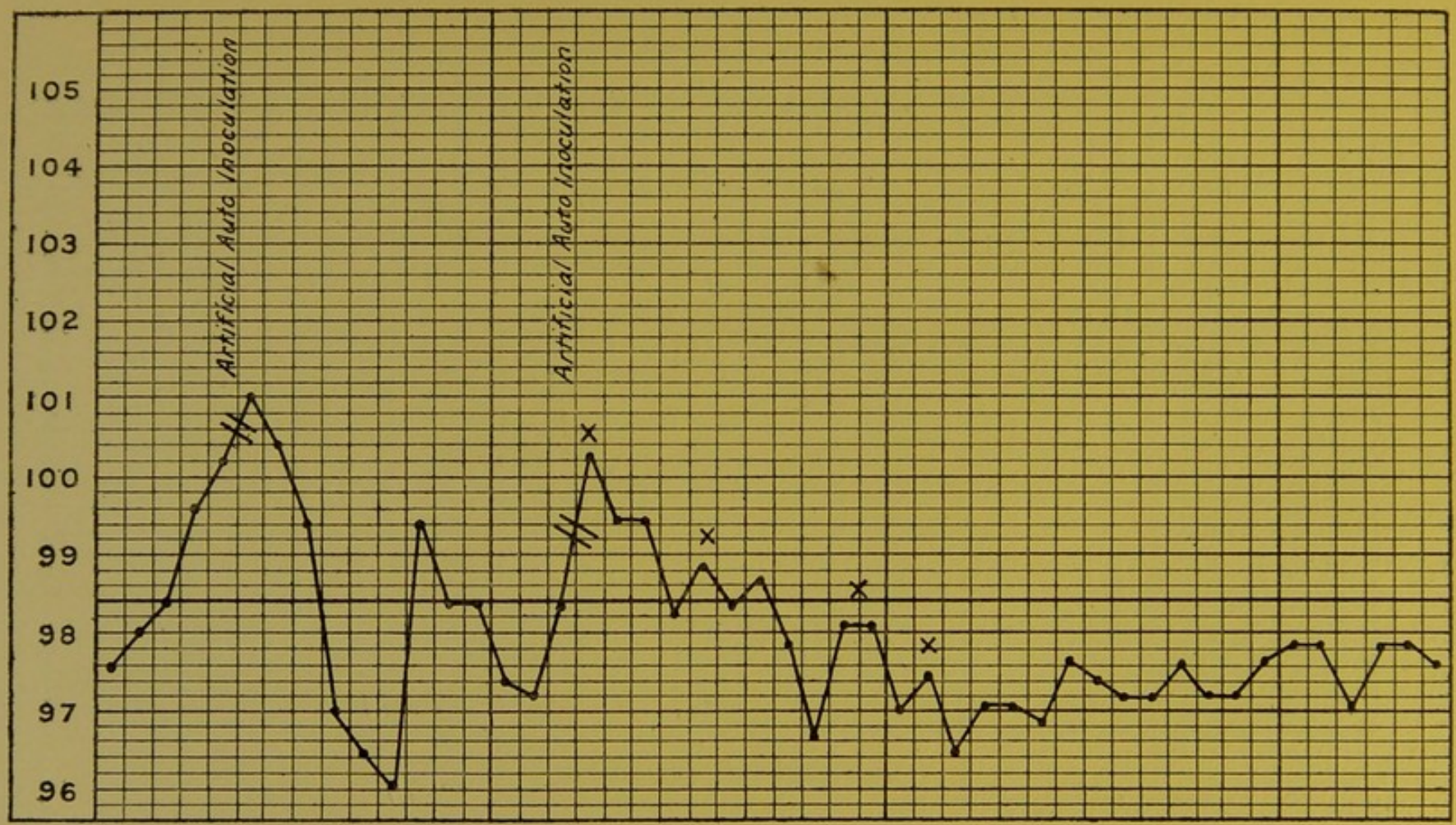


Chart 23.—Three-hourly Chart.

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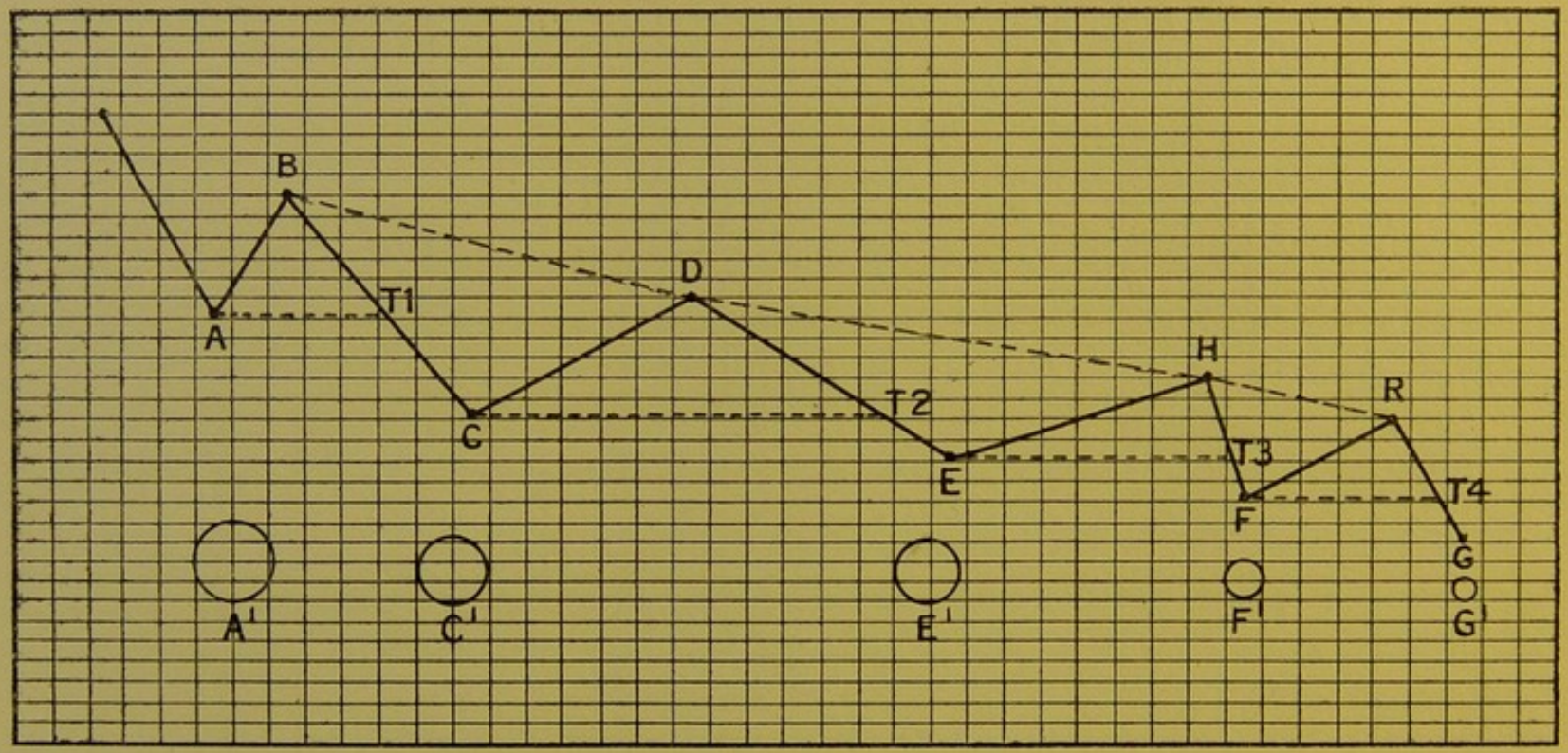

Chart 24.—Intoxication—Response Curve from Continuous Evening Chart.

At this point I wish to summarise the remarks so far made by showing three curves, one of a patient doing well, a second of a patient barely holding his own, and a third of a patient getting progressively worse.

Chart 24 represents a curve moulded from the continuous evening temperature chart of a case of pulmonary tuberculosis that did extremely well without artificial specific aid. In this chart we note that at the point A there has occurred an intoxication followed by a rise of temperature. The intoxication is followed by an increase of anti-body production. This has effectively neutralised the examination and a fall of temperature results, as seen in B—C. But the increased protective content called out by the intoxication has done more than merely

PULMONARY TUBERCULOSIS.

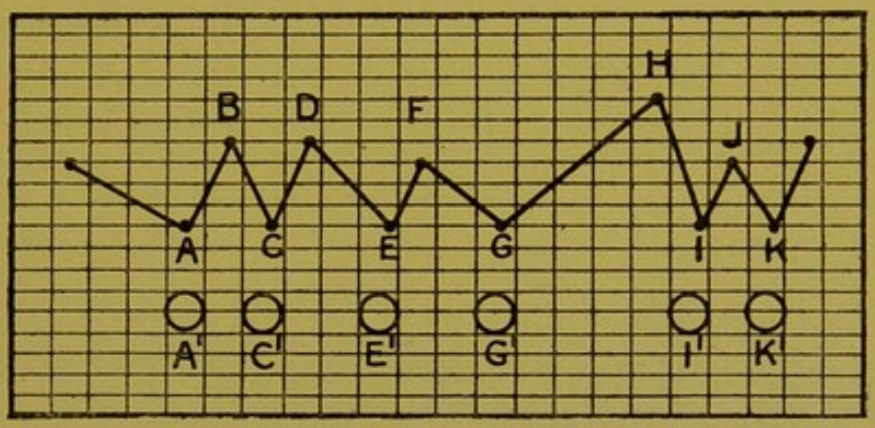

CHART 25.—INTOXICATION-RESPONSE CURVE FROM CONTINUOUS EVENING CHART.

neutralise it. It has also neutralised or diminished the activity of the area of the focus of the disease which I represent diagrammatically by the large circle A1. When, therefore, the excess production of anti-body elicited by the intoxication has worn off the influence of the toxic activity of the infective focus again reasserts itself, but it now proceeds from a smaller and less active focus. The result, therefore, is that the succeeding intoxication beginning at C produces a less rise of temperature than that beginning at A. The same phenomenon is repeated throughout the curve.

Chart 25 represents a similarly moulded curve from a case of pulmonary tuberculosis in which for many weeks no improvement took

place in general condition or in physical signs. The disease, on the other hand, was not markedly advancing. In this chart we find no increase of anti-body production sufficient, as in Chart 24, sensibly to affect the focus of disease. The only effect of the intoxication is to cause the temperature to rise at A, and when the influence of the anti-body production thereby elicited has worn off the temperature returns to its own level. But, as we have seen, there is an insufficient amount of anti-body sensibly to reduce the focus of infection. Hence this remains constant, and the temperature again rises to the same height as before. The patient, in fact, is at this stage at a standstill, and unless we can devise some method of eliciting a larger immunity response we cannot look for cure.

Chart 26 represents a curve from a case rapidly going from bad to worse. Here the immunity response has been less than in the two preceding cases. That is, the temperature has not been sensibly reduced in response to the intoxication at A. The focus of disease therefore proceeds to develop unchecked, which is graphically represented in the widening circles drawn. When, therefore, the slight excess of anti-body production has worn off, the temperature rises higher than ever from unchecked activity of the disease focus expressed in acuter intoxication.

This patient died with a pre-mortem fall of temperature, whilst the patient to whom Chart 24 belongs recovered.

In these charts this extension, diminution, or constancy of area of disease is of course purely diagrammatic.

It is not claimed for Charts 24, 25, and 26, that they are anything more than three main types, or that such perfect curves as these will be generally found, if temperature charts are treated in the manner suggested. There are, of course, infinite gradations between the types, and in any one curve there may be from time to time one or more phases of one or other type. I suggest, however, that by careful study of a temperature chart treated in this way, not only in tuberculosis, but also in many other diseases, a predominant tendency to any one type may be of the utmost value in determining both prognosis and treatment.

Charts similar to Charts 1 to 26 may be found in the wards of any hospital, or in the office of any hospital registrar. Perfect examples of the broken curve of declining indices, such as shown, will, of course, only be found as a rule in cases that have been cured, or considerably improved, or at the time of examination are undergoing improvement. The exceptions have already been referred to. Neither, of course, will

they be found in cases in which the focus of disease is neither increasing nor proceeding towards arrest, nor in those cases going downhill. Each of these classes have their own peculiar curves. Though the

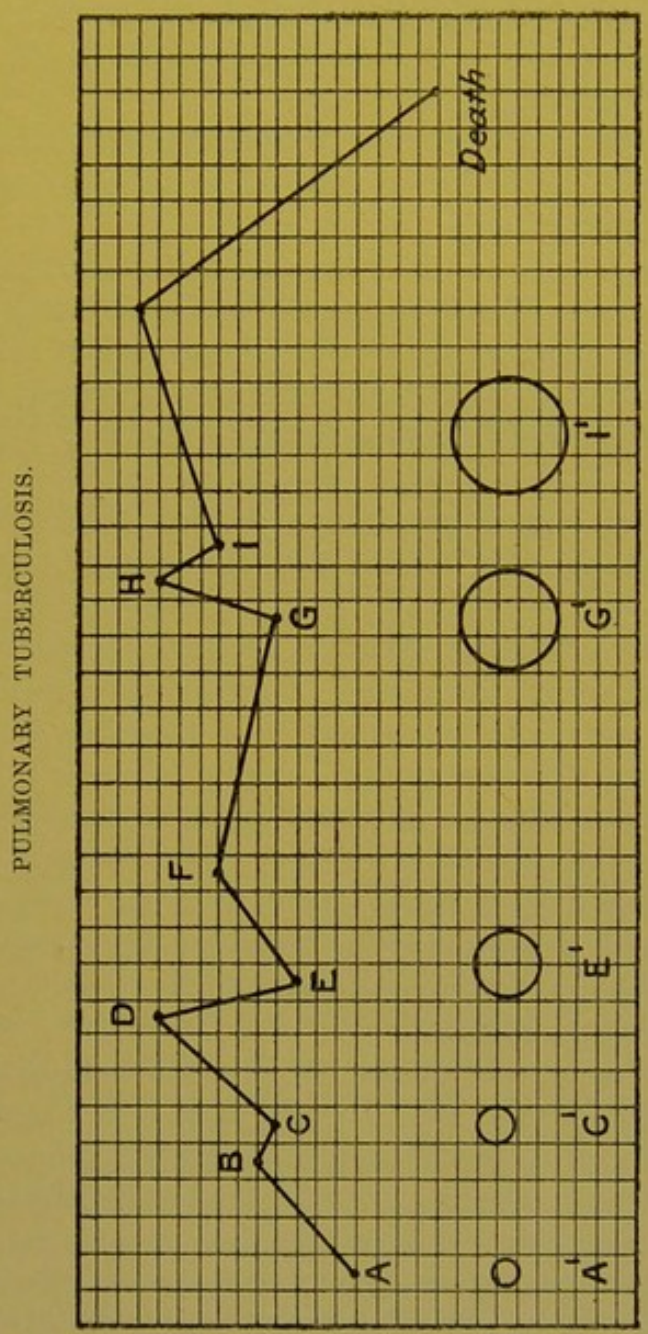

CHART 26.—INTOXICATION-RESPONSE CURVE FROM CONTINUOUS EVENING CHART.

best examples are to be found in chronic tuberculosis, typical charts may often be seen in broncho-pneumonia, measles, small-pox, and many other infections. The very prevalence of the type argues strongly in

favour of the interpretation suggested. In the acute infections it is necessary to examine three or four hourly charts, or otherwise, in a short infection, the characteristic features may be missed. When the experiments which are being conducted by Professor Gamgee to perfect his method of continuous registration of temperatures are completed, invaluable aid in reading a thermometric immunity curve may be expected to be forthcoming.

If it be true that examination of temperature charts in the manner described can give reliable information as to presence or absence of response to inoculative stimuli it will be clear.

(1) That when taken as a whole the auto-inoculative stimuli, though apparently a succession of isolated inoculations, are in reality potentially continuous. If it were not so the restraining influence of the anti-bodies, called out by intoxication, would be overcome at some point other than it actually is. In other words, the temperature would at such point rise instead of fall.

(2) That pyrexial cases progressing towards cure afford in many instances an inimitable model for directing our treatment in cases not so progressing.

(3) That cases exhibiting effective response to spontaneous auto-inoculation are not necessarily in need of extraneous specific treatment, whether by tuberculin or by auto-inoculation. Further, that such interference may result in the utmost harm.

(4) That in cases that are obviously going downhill the danger of extraneous artificial treatment is infinitely great, and may only precipitate disaster. In such cases, if the exhibition of trial doses of tuberculin or of auto-inoculation does not rapidly transform the dangerous type of curve into the type of declining indices, further specific interference ought to be absolutely prohibited.

(5) That cases doing neither well nor ill are pre-eminently the ones that call for artificial specific aid. In such cases it is a matter of great difficulty to know at what point to insert an inoculative dose. Examination of isolated phases is useless. Even if the results of blood examinations were to be absolutely relied on they can, in pyrexial cases, be of little value in determining at what point to inoculate unless a curve be plotted out of observations extending over several weeks in such a chronic disease as pulmonary tuberculosis. The possibilities of a thermometric immunity chart may be gauged by the following curve, which is moulded on the temperature chart of a man who had been under observation for many weeks. As Chart 27 shows, he had barely held his own from

A to B. Clinically, this was fully borne out in every respect. It was obvious that he could not go on indefinitely in the same way. He was bound to get either better or worse. At the points T^1, T^2, therefore, I

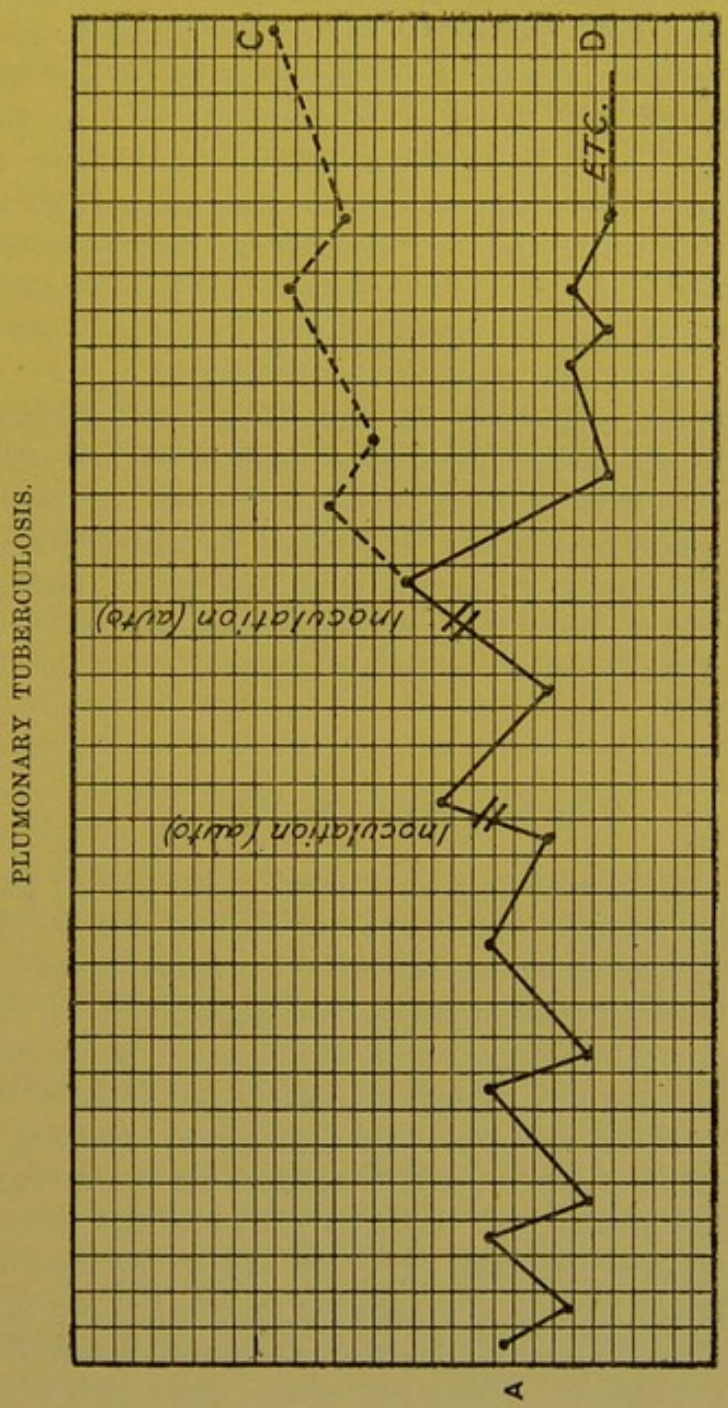

CHART 27.

inserted two artificial auto-inoculations by inducing, as in other cases referred to, artificial hyperæmia of the lungs by making him expire for

fifteen minutes through a special form of spirometer adapted for the purpose. The result is admirably reflected in the curve and in the great improvement that ensued. It has since been maintained. The point, however, on which special stress should be laid is this: If the auto-inoculation had not been inserted at the correct phase he might well have been precipitated into the curve represented by the dotted line B—C. The main object of this chart is, therefore, to show that if the inoculative stimuli T^1, T^2, had not been followed by the curve B—D, to continue with inoculations at any other point than the one selected would have most probably been useless or disastrous. It appears, in fact, if these curves can be taken as a guide, that to insert a stimulus in the response-phase can do no good, though as to this there is not sufficient evidence as yet to make such an assertion definite.

(6) That in a case, as in Chart 24, that exhibits the declining curve of broken indices and is, therefore, as a result of effective spontaneous auto-inoculation, apparently doing well, such terms as negative and positive phases cannot be applied. The reason for this is that according to such curves each response is an actual positive phase, and each succeeding intoxication a potentially positive phase, as may be seen from its achievement, and therefore only relatively negative.

General Considerations.

What applies in the preceding and following remarks to auto-inoculation applies also *mutatis mutanda* to hetero-inoculation. To get a correct idea of the amount of response called out by any given inoculative measure, examination of isolated phases in a temperature or inoculation chart is of no value. Interpretation of any phase is only possible in the light of many previous and subsequent phases. It is most important that a naturally broken curve of declining indices denoting effective response to spontaneous auto-inoculations should not be mistaken for the results of artificial inoculation. What is often regarded as an instance of correct inoculation is frequently in reality one of hypo-inoculation or no inoculation at all. What is sometimes regarded as an instance of hyper-inoculation may actually be one of correct inoculation. The appearance after inoculation of transient clinical signs, such as headache, malaise, &c., is not necessarily indicative of an excessive dose. When such occur in conjunction with fever, they may be merely the necessary accompaniments of an intoxication essential to effective response. The

absence of fever does not argue the inverse. A patient may very well be inoculating himself to good purpose, especially in apyrexial cases, without any change being observable, either clinically or by blood examination. The absence of response as reflected in the blood-stream is said by the opsonists to denote absence of inoculative stimuli. This dictum must be taken with reserve, especially if there is amongst opsonists wide divergence of opinion as to what the opsonic reading of any given serum actually is. In cases of pulmonary tuberculosis doing so well as to justify the view that the focus of disease is relatively quiescent, it can obviously not be possible to exclude the continuance of spontaneous inoculations if improvement in what physical signs remain is observed. In such cases, in fact, there must be auto-inoculations going on, in spite of the absence of demonstrable blood-change. It is frequently stated that a rise to 99° F. after manual labour or other exercise indicates hyper-auto-inoculation, particularly if the rise be maintained for an hour or more. This statement must be received with caution, as it may mean nothing of the kind. On the contrary, some of the cases of pulmonary tuberculosis which do best are those which for weeks have had high but gradually declining fever as a result of their own auto-inoculations. This point is well shown in Charts 1—5. The benefits of artificial auto-inoculation are, in fact, deliberately confined by some observers to those patients whose temperature is practically normal or even subnormal. In other words, to many of those who are effectively inoculating themselves without artificial specific aid. Many such cases require no artificial inoculative treatment. The majority of cases of pulmonary tuberculosis without fever do well. There is no difficulty in detecting the minority. Not every rise above 99° F. represents an auto-inoculation. Many intoxications produce a fall in temperature.

It is said that cases of pulmonary tuberculosis in which arrest has occurred are more liable to relapse if they are not then treated with tuberculin than if they are so treated. This may be true, but it is not therefore necessary to submit such cases to treatment with artificial tuberculin. Those whose fortunate experience it has been to watch many patients partially immunise themselves without artificial specific aid, and after return to active life apparently completely immunise themselves against relapse or reinfection by the sole use of their own tuberculin and cell-contents, will agree that hetero-inoculation is in such cases an uncalled-for procedure. The argument advanced in favour of the use of artificial tuberculin in such cases is based on a fallacy. The argument

is that in a focus nearly or relatively quiescent auto-inoculations are no longer incitable, and that response must be elicited, therefore, by artificial tuberculin. The fallacy is that, if a lesion be so insulated that auto-inoculation is no longer possible, response to tuberculin administration cannot possibly be conveyed, without further procedures, to such lesion. The truth appears to be that until a focus is absolutely insulated, and therefore quiescent, auto-inoculations may still be induced. So long as further progress towards arrest is feasible, as evinced in improvement of physical signs, so long is response not only possible but probable. There comes a time, of course, in which ordinary auto-inoculations cannot be induced, though unusual effort may incite demonstrable stimulus and response. As Paterson has well pointed out, the ideal of attainment is the point at which no reasonable labour will provoke inoculation.

Advantages of Artificial Auto-Inoculation.

The merits of artificial auto-inoculation in the treatment of established infection may be thus summarised :—

(1) It is based on a natural model of spontaneous auto-inoculation which appears to be responsible for the cure of the vast majority of all cases of infection.

(2) It incites the production of cellulo-tropic bodies, as well as of bacterio-tropic.

(3) It incites the production of antagonising bodies to the toxic products of morbid cell-changes.

(4) It incites the production of bodies specific to the particular strain of organism responsible for any given case of infection. For instance, in the case of pulmonary tuberculosis there may be many strains of Koch's bacillus, and therefore a standardised emulsion of new tuberculin or other preparation is not necessarily the correct form to use.

(5) It incites the production of bodies specific to the particular form of cell-enzyme concerned in any given case of infection. Inasmuch as the difficulties of isolation of enzymes and cells for preparation of cellular vaccine are extreme, all such difficulties are obviated by the use of natural vaccins.

(6) If there be a real distinction between bovine and human sources of tuberculosis, the use of artificial auto-inoculation removes both the necessity for establishing the distinction and for meeting the increased difficulties of treatment.

(7) Whenever mixed infections are present it allows for the opportunity of the exhibition of specific antagonising bodies to each and all of the various organisms concerned.

(8) It is free from the danger of adding fresh toxins to those already existing.

(9) It involves no danger of accidental sepsis as with inoculation with artificial vaccins.

(10) It entirely meets the natural and often strong aversion exhibited by the public to artificial inoculative procedures.

(11) It is simple because it obviates the necessity of determining all the organisms concerned in any infection.

It is cheap, because the costly manufacture of often multiple vaccins is avoided.

(12) In co-ordinates all the vast mass of work that has been done in the field of serum and vaccine therapy, and its guiding principle is the same as in methods that have received the sanction of extended trial, though its rationale has not been fully appreciated. Since the practice of hetero-inoculation has become extensive, approved methods of general treatment are in some danger of being deliberately discarded. Auto-inoculation reveals the value of them all, mainly by reason of the attention it calls to the supreme importance of general methods of improving cell-nutrition and cell-restraint.

(13) It renders the difficult problem of dosage incomparably easier than when such agents are laboratory products.

This last statement might be regarded as a paradox, which is, however, more apparent than real. Exponents of the method of inoculation with dead bacilli maintain that by inserting a measured dose of so many million organisms it is possible to get a correct idea of response. Up to a certain point this is no doubt true in infections that are strictly localised and insulated. But whenever artificial vaccins are injected into pyrexial cases, whatever the infection, the case is very different. For in these there is a continuous or intermittent stream of tropins from the infecting bacteria and the cells they have damaged. To add a measured dose of bacteria to an unmeasured dose of bacteria and toxin and an unmeasured dose of cellular toxin, and then expect to get back even a rough response to the whole triad of infection, is surely to place expectation high. If, however, it be true, as I submit it may be true, that in pyrexial cases inoculation can be more or less accurately measured by a temperature chart, the measurement of response observed records the sum-total of anti-tropin incited both by damaged cells and their products, and by bacteria.

(5)

Autolysis, Autolytic Toxæmia, Anti-autolytic Defence; the Antitryptic Index.

For a complete survey of work already done on such subjects reference must be made to publications by Opie, Cathcart, Wiener, Müller, Koltschmann, von Dungern, Levene, Wells, Stookey, Hill, Schryver, and many others. Here only the most salient points can be touched on with the object of showing the nature of autolysis and of anti-autolytic defence. A study of these will incidentally throw light on their relation to the protective measures employed by the economy to antagonise other forms of cell-aberration.

(1) *Autolysis.*—All the known work on autolysis is based on observations made in 1871 when Hoppe-Seyler indicated the resemblance that we now know to exist between the action of the digestive ferments and non-putrefactive solution of dead tissue *in vivo.*

In 1890, Salkowsky[5] showed that this liquefaction was due to the digestive action of intracellular enzymes with by-production of leucine and tyrosine. In 1900, Jacoby[6] gave the name of autolysis to the process of self-digestion by intracellular enzymes noticed by Salkowsky. As is well known, this observer's fundamental experiment was to pound a specimen of liver and to add toluol or some similar antiseptic. In twenty days digestive changes were demonstrated, the control, of course, being heated to destroy its enzymes. The rate and extent of autolysis were then determined by estimating the nitrogen content of the coagulable and non-coagulable residue. Autolysis seems in general to be effected by the combined action of lytic enzymes liberated from the tissues themselves and of hetero-autolytic enzymes liberated from other cells, particularly leucocytes. Since 1900 a host of observers have shown that there is no body cell or tissue which cannot digest itself under appropriate conditions, either *in vitro* or *in vivo.* The rate and extent of autolysis varies in different tissues. Liver-cells autolyse

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apparently quicker than any other, while vascular endothelium is the slowest. The intracellular enzymes responsible for autolysis are endowed with the power of lysis not only of proteins but also of glycogen, lecithin, fats, sugar, &c. The autolytic enzymes of each kind of cell appear to be more or less specific, with the exception of enzymes from leucocytes, which seem, as is generally recognised, to be capable of almost universal proteolysis. For a time autolytic enzymes were supposed to have only lytic functions. Soon, however, it became clear that it was not possible to exclude the probability of their having synthetic properties as well as lytic, and so they were called proteases, lipases, &c.

(2) *Toxicity of Enzymes.*—In 1890, Hildebrandt[7] published his observations on the toxicity of certain secreted enzymes such as pepsin, diastase, rennin, &c., when injected into animals. In the following year it was shown by Achalme that the toxic effects produced were not due to bacterial infection; for by injecting only enzymes that had been sterilised (*sic*) by filtration through porcelain, he obtained the same symptoms of toxæmia.

In connection with the discovery of the toxic effects of enzymes there are many striking points of resemblance between non-bacterial enzymes and toxins. Enzymes are not destroyed by low temperatures, not even by liquid air, nor are toxins. Both are most active between 35° C. and 45° C. There is a further apparent similarity in their behaviour in that they may both be accused of possessing a haptophore group and a toxophore, the former combining before the latter can become active. Again, immunity to their action may be produced by receptors capable of combining their haptophore groups, thus giving rise to anti-ferments. Horschan claims that he has produced an anti-rennin, also a fermentoid. On the other hand enzymes are more heat-labile than bacterial toxins, and do not produce their effect according to the law of definite proportion. Both are very difficult to isolate in anything approaching a pure condition; neither will stand boiling, both resist dry heat of over 100° C., and both on standing lose something of their toxicity.

(3) *Specific Anti-enzymes.*—The basis of all subsequent work on anti-enzyme production is, of course, Calmette's and Sir T. Fraser's well-known work in 1893 and 1894, when they first immunised animals against the salivary enzymes of poisonous snakes. Shortly after this it was shown by Hildebrandt[30] that animals could be immunised against emulsion, and that their serum when so treated restrained the action of diastase. It is of interest to note that it was Hildebrandt who

first succeeded in producing immunity by the method of rectal injection of the enzyme which he wished to immunise against. The first to immunise against rennin was apparently Morgenroth,[31] whose success it was that induced Professor Dean to immunise against trypsin. Since 1900 a considerable amount of work has been done in immunising against other enzymes, such as pepsin, lactase, urease, tyrosinase and fibrin ferment. Injection of these bodies into animals appears in fact to lead to the production of antagonistic bodies exactly in the same way as in immunisation against bacterial toxins or foreign proteids. Von Dungern[32] has also shown that specific anti-bodies to bacterial enzymes could be demonstrated, especially to staphylococcal enzymes. In 1898 this observer demonstrated that the serum of a patient with osteo-myelitis was more than twenty times more inhibitory of the proteolytic enzymes of the organisms found in the diseased area than was normal serum.

(4) *Toxic Products of Autolysis.*—The by-products of anomalies of cell-metabolism, however induced, may be themselves highly auto-intoxicative. This, of course, can only be if the normal protective mechanism against such toxic products be at fault. Of such auto-intoxicative products of morbid tissue activity the toxic bodies of fatigue, acute yellow atrophy, hepatic cirrhosis, abnormally active thyroids, phosphorus and chloroform poisoning, the leukæmias, pernicious anæmias, possibly diabetes, marasmus, extensive ulceration, absorption of exudates, traumatic changes induced by burns, and even of autolysing cancers, are all possible examples. If this be true of cellular disturbances not induced by bacteria, it may equally be true of cellular disturbances the direct result of bacterial invasion. A case in point is diphtheria. In this disease, as Sidney Martin points out,[35] the toxæmic effects are probably as much due to secondary conversion of tissue proteids into poisonous albumoses by the diphtheritic poison as to direct intoxication by such.

Some of the products of self-digestion initiated by enzymes (non-bacterial) are unquestionably toxic, such as albumoses, peptones, &c. Experimentally the chief toxic effects of injection of proteoses seem to be retardation of coagulation time of the blood, arterial pressure fall, fever, and possibly lymphagogue action (Heidenhain).[36] The appearance in the urine of proteoses when extensive tissue destruction is going on is suggestive. The same remark applies to albumosuria when any tissue or fluid is undergoing extensive autolysis: witness that condition occurring in acute yellow atrophy, phosphorus poisoning, resolving lobar

pneumonia, breaking-down carcinomata, rapid lung destruction, absorption of inflammatory exudates, &c. Simon's work[37] on the injection of tuberculin is also highly suggestive. This observer found that by substituting injections of proteoses for tuberculin emulsions he was able to produce the rise of temperature characteristic of tuberculin reaction. It is not improbable that the products of autolysis set in motion by bacterial infection are partly responsible in other diseases besides diphtheria for phenomena generally ascribed directly to the bacterial factor only. If albumoses and peptones are toxic, the other cleavage products may well be so. Inasmuch as fever can follow aseptic suppuration, it is not unlikely that clinical signs such as rigors, fevers, &c., are frequently as much due to autolytic by-product absorption as bacterial. In autolysis of nerve-tissue, the toxic derivatives of lecithin were suggested in 1904 by Halliburton[38] as a cause of intoxication. Mott's work[40] on liberation of cholin from lecithin is also contributory to the same point. Another instance is the occurrence of systemic infection from breaking-down tumours. As a rule, constitutional signs in carcinomatous disease do not manifest themselves till breaking down is well marked—*i.e.*, till autolysis is well established. The process of autolysis and of absorption of by-products of autolysis continues just the same even if bacterial contamination of a breaking-down surface carcinoma be eliminated. The degree of cachexia, indeed, is often quite proportionate to the amount of autolysis. If autolytic and other intracellular enzymes can, as appears to be the case, induce certain anomalies of their own cell-metabolism when the normal restraint keeping these in check is impaired, such aberration is not always necessarily due to bacterial invasion, even in diseases ostensibly bacterial. On the contrary, such disturbance, when autogenously produced, may well pave the way for bacterial infection. In other words, cellular anomalies may precede infection, as well as succeed. In this consideration may lie the key to the difficult problems of cryptogenic infection and latent persistency of infection. Autogenous morbid activity of cell-enzymes would then explain conversion of non-pathogenic bacteria into acutely pathogenic. Again, the products of such morbid activity may be not only auto-intoxicative but also actually infective.

This has, in fact, been suggested by Professor Benjamin Moore[41] in the case of the exanthemata, where laborious search has failed to demonstrate a causal bacterial origin. In such a case the virus would certainly be ultra-microscopic, but by no means necessarily ultra-biochemical. Such questions can only be solved by extending research

along the lines of toxicity and infectivity of cellular products, which is, in fact, much needed. Professor Moore's arguments as regards the exanthemata are worth citing, because of their close bearing on the points I have raised :—

(I) The incubation period would be that required for the production of the auto-catalyst in sufficient quantity to cause a general reaction with the tissue-cells.

(II) The auto-catalyst, acting as the toxin of the disease, would increase up to the point of concentration of maximum effect. The cells at the same time would react as to ordinary toxin and produce the antitoxin, the efficient production of which would limit the disease.

(III) Variation in incubation periods of the same disease would be no argument against such a view, because the length of incubation would depend on the reaction of the cells affected. This consideration is much strengthened by the fact that in many cases of intoxication of purely bacterial origin the appearance of symptoms depends in no way upon any cycle of development of the parasites, but only on the reaction period of the cells.

(IV) Variation in the immune body content of an individual would therefore depend—

(*a*) Upon the presence or absence in the blood of anti-body capable of inhibiting at the outset the trace of auto-catalyst bearing the infection, and

(*b*) Upon the reactive power of the tissue-cells to the auto-catalyst or toxin.

(5) *Normal Restraint of Autolysis.*—Since apparently every tissue in the body can under appropriate conditions digest itself, the old vexed problem of how the living stomach protects itself against self-digestion becomes applicable to all organs and tissues. The suggestion that the reason why living tissue does not digest itself is because it is alive and not dead is only a restatement of the original difficulty. There are, however, certain other suggestions which deserve mention. For instance, it has been expressly urged that intracellular enzymes do not digest the cells they belong to because they only exist there in pre-enzymic form—that is as zymogens. The apparent objection to this view, that if they do only exist as zymogens it is difficult to see how they carry out their normal metabolic functions, is disposed of by Wells.[9] He suggests that they are only activated as need arrives, to be again inhibited when the need is temporarily past. Such suggestion

involves, as he points out, a rhythmicality of function not unknown in metabolism. Wiener,[10] on the other hand, has shown that an organ does not begin to autolyse until sufficient acid is produced by moribund cells to antagonise its alkalinity. Opie[11] has pointed out that two forms of autolytic ferments may be recognized in leucocytes—a peptic ferment acting only in acid media and a tryptic form only active in alkaline media. The tryptic ferment predominates in the polymorphonuclear leucocytes and the peptic in the lymphocytes. The presence or absence of the peptic as distinguished from the tryptic ferment furnishes a distinction between the lymphocytic pus of a tuberculous lesion and the polymorphonuclear pus of most pyogenic lesions. Another possible explanation of the absence of autolysis *in vivo* is that cell-equilibrium is maintained during life in virtue of its food supply. Once this is interfered with equilibrium is disturbed and uncompensated autolysis begins. That this is an important contributory factor to intracellular restraint of autolysis there can be little doubt. Demonstration of bacterial autolysis when the organisms of typhoid and cholera are placed in distilled water or salt solution, the controls being planted in the ordinary media, is a case in point.[12] In 1903,[13] Jacoby found that up to a certain point the autolytic enzymes of one organ are not autolytic to another—that is, he established a specificity.

The Antitryptic Index.—Quite early in the work on tissue enzymes note was taken of what is now a well-established fact. The blood-serum of man, monkeys, sheep, horses, and other animals was found to exhibit in marked degree a varying resistance to the action of autolytic enzymes. This resistance was found to disappear on heating, prolonged standing, and on the addition of dilute acids. The rate of autolysis *in vitro* was found to be markedly lessened if the autolysing organ was placed in fresh unheated horse-serum. The inhibitory body on which this resistant and protective body depends is effective against trypsin, and was therefore called antitrypsin. Inasmuch, however, as it is also effective against pepsin and other secreted enzymes, and also against all tissue enzymes, except against an acid solution of HCl pepsin, which destroys it, a better name would be antilysin, to denote its generic action. According to von Eisler[14] it is not specific in the sense of being more specific to auto-enzymes than to hetero-enzymes. Apparently it is less so. It seems to act not by destroying enzymes, but by inhibiting or paralysing their action. Weinland's observation of the protective power of antitrypsin secreted by certain intestinal worms, as demonstrated by the absence

of their digestion in active secretion, is familiar. Delezenne[15] holds that the antitryptic action of normal serum is due to antikinase, a view contended by Bayliss and Starling,[16] who maintain the direction action of antitrypsin on the activated body. Cathcart[17] declares that the antitrypsin of normal serum is attached to the albumin-fraction of the serum, from which it cannot be detached even by prolonged washing, and not to the globulins. The antitryptic content of normal serum can, as I have elsewhere shown, be clinically demonstrated. If normal horse-serum, for example, be added to wounds or ulcers bathed in the strongly tryptic fluid of their own infected secretions, the tryptic action of the fluid is inhibited to such an extent that a wound treated in this way rapidly cleans.[18] In favourable cases this is followed by rapid healing. By stripping one sample of normal serum of its globulins and adding to it the serum albumin content of another sample, it was found possible so to raise its total antitrypsin content that the rise could be demonstrated both hæmatologically and clinically. This, in fact, is the basis of the preparation of the so-called antilytic serum* which is now being extensively used in the treatment of gastric and duodenal ulcers.[19]

In connection with the antitryptic content of normal serum, the following observations are of interest. Fluctuation, and therefore the site of the most advanced softening in an abscess, is found in the centre of an abscess only—*i.e.*, furthest away from the restraining influence of the antitryptic lymph-stream. The antitryptic content of lymph from a recent healthy wound is high; that of lymph from a wound showing no tendency to heal is, even in the absence of infection, low. An infarct undergoes central autolytic softening sooner than a peripheral, no doubt for the same reason. The antitryptic power of infected pus is *nil.* In old exudates it is also less than in recent ones, and hence autolysis of the former proceeds more rapidly than does that of the latter. In lobar pneumonia is seen an excellent example of unrestrained autolysis. The contents of the alveoli, being removed from the inhibitory action of the lymph-stream, undergo rapid autolysis, whilst the cells of the alveoli, being constantly bathed in lymph with a high antitryptic content, escape.

The first observers to clearly demonstrate the antitryptic action of normal serum appear to have been Camus and Gley[20] in the year 1900. The first serious attempt to measure this action was made by Professor George Dean,[21] who in 1901 published his paper on "Immunity in Relation to the Pancreas and its Ferments." The

* This serum is prepared for me by Messrs. Allen and Hanbury, and I have good reason to be satisfied with the results of its use.

subject was extensively followed up in 1902 and 1904 by Glaessner, Cathcart, Levene,[33] Stookey,[33] Opie,[34] and others.[22] Professor Dean's method was to estimate the rate of digestion by trypsin of measured quantities of albumin, and the degree of inhibition of digestion by normal serum. He then adopted a method suggested by Fermi of estimating the inhibitory power of normal serum of digestion by trypsin of measured columns of gelatin. This method, with substitution of egg albumin for gelatin, now known as the method of Mette, was, as may be seen by reference to Dean's paper, independently elaborately by the latter. Methods of estimating the inhibition of tryptic digestion of albumin and gelatin in this manner are, however, of little practical value.

Various attempts were then made to estimate the antitryptic power of the blood-serum in disease, though until 1908 without any considerable measure of success.

Most of the work previous to that date had been done by the method of Müller and Jochman,[23] which consists in the addition of varying quantities of serum, measured in loops of platinum wire, to a drop of pus in a Löffler plate. The appearance or non-appearance of pitting after incubation was taken as a sign that the amount of inhibitory serum added had been insufficient to neutralise the pus ferment present. Such a method of estimation is obviously far too coarse to afford even an approximately accurate criterion of the antitryptic content of normal serum, and the earlier work of Hedin[24] had already shown that complete neutralisation could never be obtained. The contradictory results of the work of the authors of this method, and their followers, have in fact shown that it cannot be accorded serious consideration. The evaluation of ferment activity and, reciprocally, of the inhibitory power of serum can only be determined by some method which allows the velocity reaction of the ferment to be measured. Hence the results obtained by the serum-plate method, or by the end-point methods of Cross, Bergmann and Meyer[25] are both contradictory and inaccurate. Estimation of the incoagulable nitrogen formed at different points in a tryptic digestion, and through this of the antitryptic content of an inhibiting serum, is impracticable because of the amount of serum required. For these reasons, as Dr. Golla[26] has just shown, this observer has adopted the method of electro-conductivity of Henri,[27] which has been recently elaborated by Bayliss. By this method Dr. Golla[28] states that he is able to gauge the relative antitryptic power of the blood with great accuracy, and in the course of his investigations he has discovered :—

(1) That a rise of this antitryptic activity frequently takes place in tuberculosis.

(2) That such rise is often associated with a bad prognosis.

(3) That hetero-inoculation with tuberculin induces a rise of antitryptic activity in tuberculous subjects.

(4) That accurate determination of such rise affords a reliable guide to the efficacy of tuberculin injection, and that by this method it is possible to determine the point at which a dose of tuberculin should be exhibited.

Some of these observations I am able to confirm from my own clinique.

In twenty cases of tuberculosis a rise of the antitryptic index was found in all but one. The majority of these were pulmonary; the remainder, six in all, were renal, glandular and peritoneal.

Of these twenty cases the only two that died had persistently high indices. Six, when injected with tuberculin, showed a further rise in an index already raised. In one of the cases referred to active disease was associated with a normal index. He subsequently did very well. To these observations I am able to add the following:—

In cases where the guide afforded by a temperature chart, on the lines I have referred to, is absent, either from too small a variation of temperature or entire absence of such, it appears:—

(*a*) That tuberculous patients with a high index react little, if at all, to artificial inoculation.

(*b*) That tuberculous patients with a low index show marked rise after similar stimulus.

A high index such as occurs in some cases with high fever, conforming to the type shown in Chart 26, is often associated with a bad prognosis. An index which was high when the temperature was raised in two cases approached, under artificial auto-inoculation, the normal when marked clinical improvement set in, and became actually normal when the temperature remained undisturbed and when the disease was judged to be arrested. In one case the index did not again rise after tuberculin injection. In another case, with low index, response to inoculation was marked, and as the patient improved the response tended to diminish. In a third, who got progressively worse, the index was very high and tended to rise, whilst the response to inoculation was only comparatively slight, as evidenced by further rise of the index.

These observations, though at present incomplete, tend in some measure to confirm some of the views I have propounded, based on the

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variations in temperature that I have shown to follow auto-inoculation. In particular they support the contention that artificial inoculation of all kinds is contra-indicated in cases where intoxication without adequate response is great.

Apart from tuberculosis there is evidence, as the appended table shows, that variation can be demonstrated in such diverse conditions as carcinoma of breast, tongue, mouth, and cervix, rodent ulcer, acute septicæmia, leprosy and suppurative nephritis. In this table variation in the antitryptic content of the serum was found in twenty cases of tuberculosis of various organs, in four cases of syphilis, in two cases of rodent ulcer, in seven cases of carcinoma, in one case of acute septicæmia, in one case of suppurative nephritis, and in one severe case of leprosy. These serums were from cases in my own clinique or from such hospital cases as members of various hospitals were good enough to place at my disposal. The majority of the serum examinations were kindly undertaken for me by Dr. Golla.

It is also claimed by Brieger and Trebing[42] that they have been able to demonstrate variations in the index in cases of carcinoma, pernicious anæmia and nephritis. Variation in the antitryptic content of the serum in a case of lobar pneumonia was also demonstrated in 1903 by Ascoli and Bezzola.[43]

In view of these facts it appears that marked variation from the normal may be as much a response to cellular changes in no way associated with bacterial invasion as to changes directly connected with such, as well as to bacterial infection without extensive cell-change. That such aberrations of tissue metabolism as the index appears to indicate can be reflected in the blood-stream so as to be capable of ready measurement must be of profound significance.

As regards the interpretation to be placed on variation in the Antitryptic Index in disease little at present can be said.

For the purposes of this paper I am content for the moment to submit that its estimation cannot but have the highest value as a gauge of immunity response, because it appears to reflect, as I have shown, presence or absence of such response not only to bacteria and their products, but also to the factors of morbid enzymic activity and the toxic products of perverted cell-change. The significance of such reflection in diseases such as carcinoma deserves serious study.

If such submission be sound blood examinations exclusively directed to measurement of phagocytic activity and bacterial engulfment, however induced, can clearly, even if reliable, afford only a relatively insignificant gauge of immunity response as a whole.

Table showing presence or absence of variation from the normal of the Antitryptic Index of various Serums.

	Source of Case.	Nature of Case.	No. of Observations.
		ABSENCE OF VARIATION.	
1.	Private...	Healthy male	1
2.	Lock Hospital (*a*)	Healthy male	1
3.	Private...	Healthy female	1
4.	Private...	Hydrocele of cord. (Otherwise healthy) ...	1
5.	Private...	Furunculosis. Male. (Otherwise healthy) ...	1
6.	Private...	Acne. Female. (Otherwise healthy)	1
7.	Private...	Varicose ulcer. Female. (Otherwise healthy)...	1
8.	Private...	Floating kidney. Female. (Otherwise healthy)	1
9.	Private...	Cough, no physical signs	1
10.	Private...	Slight cough, no physical signs	1
		PRESENCE OF VARIATION.	
11.	Private...	Pulmonary tuberculosis. Female	4
12.	Private...	Pulmonary tuberculosis. Female	5
13.	Private...	Pulmonary tuberculosis. Male	4
14.	Private...	Pulmonary tuberculosis. Male	6
15.	Private...	Pulmonary tuberculosis. Male.	3
16.	Victoria Park Hospital (*b*) ...	Pulmonary tuberculosis. Female	1
17.	Victoria Park Hospital (*b*) ...	Pulmonary tuberculosis. Female	1
18.	Victoria Park Hospital (*b*) ...	Pulmonary tuberculosis. Male	1
19.	Victoria Park Hospital (*b*) ...	Pulmonary tuberculosis. Male	1
20.	Victoria Park Hospital (*b*) ...	Pulmonary tuberculosis	1
21.	Victoria Park Hospital (*b*) ...	Pulmonary tuberculosis	1
22.	Victoria Park Hospital (*b*) ...	Pulmonary tuberculosis	1
23.	Victoria Park Hospital (*b*) ...	Pulmonary tuberculosis	2
24.	Victoria Park Hospital (*b*) ...	Pulmonary tuberculosis	2
25.	Private...	Renal tuberculosis. Female	1
26.	Private...	Tuberculosis of cervical glands. Female ...	2
27.	Private...	Probable tuberculosis, site unknown	4
28.	Lincoln Hospital (*c*)... ...	Tuberculous peritonitis. Female	2
29.	Private...	Tuberculous peritonitis. Child	2
30.	Private...	Tuberculous peritonitis. Child	2
31.	Private (*d*)	? Suppurative nephritis. Male	2
32.	Private (*e*)	Acute Septicæmia from ruptured ovarian cyst ...	2
33.	Seamen's Hospital (*f*) ...	Leprosy	3
34.	Lock Hospital (*a*)	Syphilis	1
35.	Lock Hospital (*a*)	Syphilis	1
36.	Lock Hospital (*a*)	Syphilis	1
37.	Lock Hospital (*a*)	Syphilis	1
38.	Cancer Hospital (*g*)	Rodent ulcer	1
39.	Cancer Hospital (*g*)	Rodent ulcer	1
40.	Cancer Hospital (*g*)	Carcinoma cervicis	1
41.	Cancer Hospital (*g*)	Carcinoma mammæ	2
42.	Cancer Hospital (*g*)	Carcinoma of throat	2
43.	Cancer Hospital (*g*)	Carcinoma of scrotum	1
44.	Cancer Hospital (*g*)	Carcinoma of tongue	2
45.	Cancer Hospital (*g*)	Abdominal carcinoma	1
46.	Cancer Hospital (*g*)	Carcinoma of mouth	1

(*a*) By the kindness of Mr. J. E. LANE.
(*b*) ,, ,, ,, Sir HUGH BEEVOR.
(*c*) ,, ,, ,, Dr. DAMAN, of Lincoln.
(*d*) By the kindness of Dr. F. A. HORT, of Nice.
(*e*) ,, ,, ,, Mr. LENTHAL CHEATLE.
(*f*) ,, ,, ,, Sir MALCOLM MORRIS.
(*g*) By the kindness of Mr. CECIL H. LEAF.

To conclude as I began, I submit :—

1. That when Nature cures infection she converts tissues and bacteria into auto-inoculating agents, and thereby incites both cellular and bacterial restraint.

2. That to provoke the last and ignore the first is too often to aim at half and expect the whole.

3. That, whenever practicable, auto-inoculation is the best method to employ when artificial aid is needed, and

4. That in thermometric charts and in measurements of the blood's inhibitory powers we have most useful gauges of presence or absence of many kinds of stimulus and response.

Full conviction I can hardly hope to carry on the slender evidence here produced, but the attempt will not be fruitless if the attention of makers of modern Medicine be for a moment diverted to issues other than the merely bacterial.

I wish to express my thanks to the following gentlemen, whose courtesy has enabled me to collect from their respective hospitals much of the clinical material that forms the groundwork of this paper: Mr. J. E. Lane, at the Lock Hospital; Sir Hugh Beevor, at the Victoria Park Chest Hospital; Mr. C. H. Leaf, at the Cancer Hospital; Sir Malcolm Morris, at the Seamen's Hospital; Mr. Lenthal Cheatle, at King's College Hospital; and Dr. Daman, at the Lincoln Hospital. I also wish to express my indebtedness to Dr. Rolleston and to Mr. Cheatle for their great assistance in preparing this manuscript, and to Dr. Venning for continuous help in collection of the various serums referred to, and in many other ways, and in particular to Dr. Golla, for his unfailing and generous help. Finally, I wish to convey my deep obligation to the anonymous philanthropist whose single-minded devotion to the highest aims of medical research has made this preliminary enquiry possible.

8, Harley Street
March, 1909.

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