# COMPLEMENT IN THE TECHNIQUE OF PROTEIN THERAPY.

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THE authors consider that protein or pyretic therapy should have a more scientific basis, and for several years have carried out experimental work on the behaviour of blood complement in patients undergoing this form of treatment.

Observations and serial complement estimates were made on forty patients receiving protein injections, the requisite number of controls being used. Altogether, a thousand complement readings were co-related with the patients' mental and physical condition.

The preliminary results of this investigation are offered with the knowledge that the work is still in the experimental stage.

For many years the work of Bordet, Von Behring, Ehrlich and many others on specificity in therapeutics overshadowed the findings of earlier workers in non-specific therapy. The latter received little consideration, possibly because their opinions were in conflict with orthodox theories of immunity.

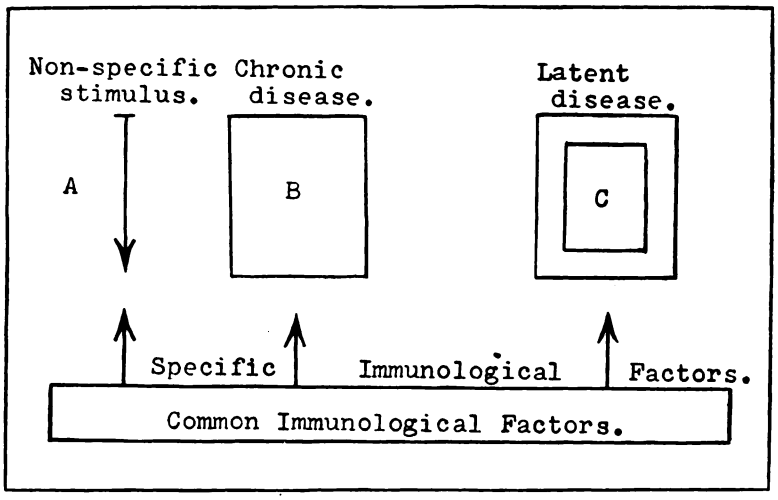
The advances made in the strictest specificity have held firm in many diseases, but not in all; in the latter non-specific methods have given satisfactory results. Many diseases fail to respond to either form of treatment.

An incredible amount of work has been done in investigating the mechanism of immunity, but the biological reactions to disease are so subtle and complicated that even immunologists are hesitant and moderate in their opinions. Nevertheless, much of their work is of value to the therapeutist, even if he must, for practical purposes, accept a somewhat elementary concept of the bodily defences.

The reactions in non-specific therapy suggest that in the mechanism of immunity there are some specific factors, while others are non-specific, and that under certain conditions the specific factors are latent until released or augmented by stimulation of the non-specific mechanism. On this thesis, the natural defences, once stimulated, will attempt, with varying degrees of success, to wall off or drive out all pathological conditions. A mild stimulus may

abort or hasten a simple inflammatory state, while a violent one giving the desired therapeutic result, may also cause an unexpected and undesired reaction at a latent focus of infection, such as a tubercular nodule, which breaks down. This thesis might also explain why some patients are better in health after an illness, while others are worse—the illness in the latter playing the part of a non-specific agent. (See diagram.)

It has also been observed that, in the treatment of some conditions, one non-specific agent is superior to another. In short, the defensive mechanism may respond to agents, specific, para-specific and non-specific.




The immunological mechanism may be stimulated non-specifically by absorption of protein from a raw surface, by the therapeutic use of proteins or active virus and by an attack of acute disease. According to the quality, intensity and duration of the non-specific stimulus (A), a desired result may or may not be obtained in chronic disease (B). A violent and prolonged stimulus at (A) may give a satisfactory result at (B), but may, in addition, give an unexpected and undesired reaction at a latent focus of infection (C), thus activating, e.g., an endocarditis, meningitis, tuberculosis or pneumonia. In short, the patient may be better after treatment, but on the other hand may be worse. Each activated focus in turn becomes a non-specific stimulus.

Even in so-called "passive immunity", e.g., in the use of antidiphtheritic serum, the older preparations, containing a larger amount of the whole serum, and giving, in addition to the specific action, a non-specific reaction, are considered by some authorities superior to the concentrated specific antitoxic sera (12).

The technique, complications and limitations of specific methods are fairly well known, but the position is not quite so clear with regard to non-specific agents.

In chronic illness, unresponsive to specific treatment, one may administer palliatives, or join the radicals who endeavour to obtain results by the injection

of proteins, mixed proteins, split proteins, protein derivatives, colloidal preparations, hetero-vaccines, or finally by the use of living organisms, such as those of relapsing and malarial fevers. The last procedure is not looked upon with favour by many members of the profession.

The object of this paper, however, is not to discuss the merits or demerits of protein therapy, but to suggest, for further investigation, technique involving the use of the more violent forms of protein shock.

It would appear that the method in general use at present is to give the patient a " pyretic shock ", and if nothing happens, to launch a series of more violent shocks. The series of shocks may be interrupted by the physician in his wisdom, and sometimes by the impending collapse of the patient.

In the malaria therapy of general paralysis, 40% of the deaths occur within the first two months after inoculation (13).

It cannot be denied that by this rule-of-thumb method gratifying results have at times been obtained, but the possibility of complications should not be under-estimated. After all, the non-specific agent is used merely to stimulate the body to make another and possibly more successful effort to defend itself.

Since we are dealing with living tissue, a point of maximum stimulation will eventually be reached, after which further attempts at stimulation can only lead to exhaustion and trouble.

## Factors Influencing Shock Reaction.

It is unreasonable to expect all patients to react in exactly the same manner to a non-specific stimulus. The reaction will be modified, aggravated or complicated, by such factors as the substance used, rate of absorption, dose, method of administration, number of injections, previous use of the same agent, disease or diseases from which the patient is suffering, temperature, chronicity, age and general physical condition of the patient, and possibly by a great many biological factors less apparent, but equally important.

The effects immediately following the use of a non-specific agent have been recorded from time to time by experienced investigators, such as Van den Velden, R. Schmidt, Starkenstein, Petersen and Diollken. A short summary of some of the findings is of practical interest. Generally the condition of the patient at first becomes worse, then better. Nervous irritability, pain, delirium, glandular activity (2), nitrogen excreted (3), blood-pressure (4), diuresis (5), permeability of blood-vessels, and tissue cells (6), blood-sugar (7), lymph flow (8), blood-platelets (9) and fibrinogen are increased and then diminished, while temperature, leucocytosis and weight are diminished and then increased. The complement may also be diminished and then increased (10). The findings are conflicting with regard to agglutinins, opsonins, precipitins, antibodies (11) and antibacterial substances. In fact, nearly all these findings have been questioned, and some put in the reverse

order. The point which should be observed is the marked tendency for the reaction to be diphasic in character. Some of the reactions are rapid in onset, superficial and transitory, while others appear to be deeper and more sustained.

It has been suggested that the first or negative phase is irritative and exogenous, while the second or positive phase is endogenous, and is more or less the physiological process of repair (12). Since pyretic treatment is used frequently, especially in mental hospitals, one feels that in some respects a more definite technique is required. The literature on protein therapy is helpful in the selection of proteins beneficial in certain conditions, but information regarding the degree of general reaction necessary and the point at which biological stimulation should cease is not altogether satisfactory.

If the antibody-complement-antigen reaction be accepted, where in simple language the complement is a ferment-like substance which permits the antibody to fix the antigen, the complement might be used as an indicator of the behaviour of the non-specific or common mechanism of immunity. For a considerable number of years the authors have recorded hundreds of complement readings relative to the mental and physical condition of insane patients. The complement estimation was made by recording how much of the patient's serum (containing complement) would permit a known quantity of hæmolytic serum (immune body) to hæmolyse a known quantity of sheep's corpuscles. The figures in the accompanying graphs indicate the smallest amount of patient's serum which (in a water-bath at 37° C. for an hour) permits five doses of immune body to hæmolyse completely 1 c.c. of a 3% suspension of sheep's washed red blood-corpuscles.

When the patient examined appeared well, physically and mentally, the quantity of patient's serum required for this test (and for what at present will be called " normal ") was between 0·06 c.c. and 0·07 c.c. The figures at the side of the graphs indicate from above downwards the amount of patient's serum used for each test. The graphs therefore indicate the rise and fall in the complement titre. (The normal daily (10) variation, according to Cadman, is about 10%.)

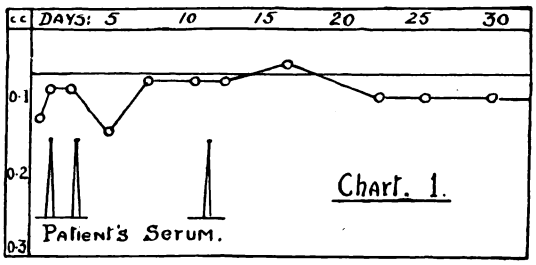
It would appear that the behaviour of serum complement is not so erratic as some of the text-books might suggest. A single complement reading is of much the same value as a single temperature reading—that is, a normal reading is not necessarily an indication of health. A graph, however, is helpful. It sometimes happened that no complement could be found in the patient's serum, and although this condition was compatible with life, it was not so with health.

In the therapeutic use of such different agents as the patient's serum, typhoid-paratyphoid vaccine (T.A.B.) and malaria, the complement titre at a certain point in the proceedings passed into a negative phase. Sometimes the negative phase was preceded by a positive phase, and sometimes by a

repetition of previous readings. Again, during the negative phase it appeared impossible to sustain the complement titre by further use of the same agent. It was also noted that when the complement became highly concentrated (i.e., less than 0·06 c.c. of serum for the test), the patient usually experienced a sense of well-being or euphoria.

The first complement chart extends over a period of thirty days, and indicates the behaviour of complement after the therapeutic use of the patient's own serum.

The case is that of a young female, æt. 20, suffering from " toxic confusion ". She had a raised temperature, and was in a state of extreme terror and excitement. The first two complement readings were low (0·12 and 0·08). Ten c.c. of the patient's serum were given subcutaneously, and in 24 hours the titre



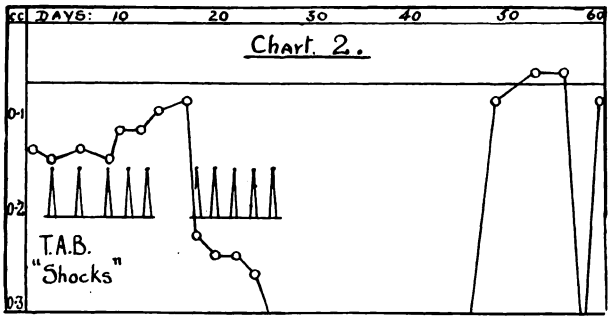

Graph extending over period of 30 days, and indicating the influence of three injections of the patient's serum on the complement titre. The titre passes into a negative phase followed by a rise, then a secondary negative phase. This reaction is frequent even without the third injection.

remained the same (0·08). Another 12 c.c. of serum were administered, and within 48 hours the complement passed into a negative phase (0·17). During this phase the temperature rose, and the delirium and excitement became more intense. Three days later, the complement rose to 0·07 and remained there for three days. A further 15 c.c. of serum were given, and six days later the complement rose above " normal " (0·05). After another six days, the titre had dropped to 0·09 and remained there for the following ten days. While the titre was above " normal " the patient appeared bewildered, but lost her terror and smiled constantly. With the secondary fall the violence of the delirium passed, and although mildly confused, the patient took food, slept well, and looked better physically.

The second and third charts show unsuccessful attempts to raise the complement titre in the negative phase. The cases are those of our colleague, McCully, also working at this hospital. Typhoid-paratyphoid vaccine (T.A.B.) was used in increasing quantities in order to maintain the intensity of the shocks. The average temperature produced was about 103·5°. The shocks were given at intervals of 48 hours.

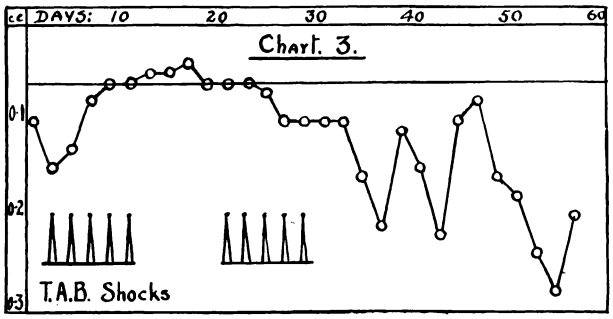
The second chart is that of a male dement, æt. 50, who had developed an

attack of confusion. The first complement reading was low (0·13), but after five shocks the titre gradually rose to 0·08 on the 18th day, then dropped suddenly to 0·22. On the 18th day a second series of five shocks was commenced. The titre continued to fall, and vanished after the fourth shock on




Graph extending over a period of 60 days, and indicating the influence of two series of T.A.B. shocks on the complement titre. The first series caused a slight rise, followed by a negative phase. The second series of shocks not only failed to maintain the titre, but exhausted the patient.

the 24th day. During the next twenty-one days nine tests were made, but no complement was recorded. On the 48th day the complement reappeared at 0·08; four days later it rose above "normal" and remained there for three days (0·05), during which time the patient had a mild euphoria, which vanished




Graph extending over a period of 60 days, and indicating the influence of two series of T.A.B. shocks on the complement titre. The first series gave a short negative phase, then a prolonged rise followed by a secondary negative phase. The second series of shocks not only failed to maintain the titre in the secondary negative phase, but exhausted the patient.

with the complement on the 58th day. On the 60th day the complement reappeared at 0·08. The first series of shocks produced a slight rise, then a sudden negative phase. The second series of shocks failed to maintain the complement titre and exhausted the patient.

The third chart shows an unsuccessful attempt to maintain the titre in

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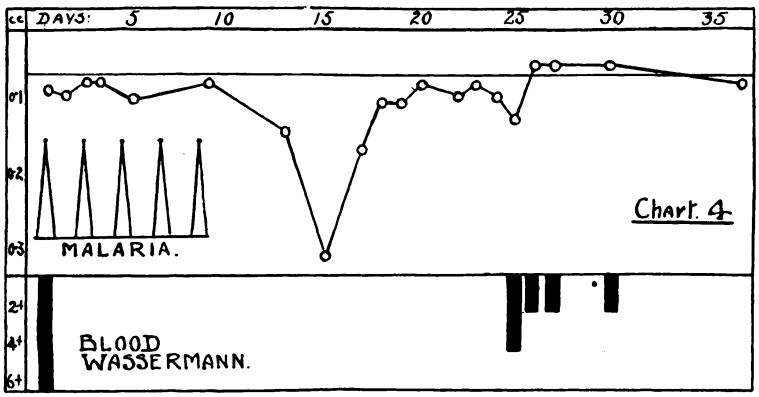
the secondary negative phase. The type of patient was similar to the last. T.A.B. vaccine was used in both series of five shocks. The first series produced a fall from 0·1 to 0 15, then a rise to 0·06 on the 8th day. During the following week the titre was above "normal" (0·04), the patient being euphoric. On the 18th day the titre fell to 0·06, and the second series of shocks was commenced on the 20th day. The titre gradually fell to 0·28 on the 55th day. The second series of shocks failed to maintain the titre, and only exhausted the patient.

The fourth chart is of interest, as it demonstrates the behaviour of the complement when a series of five malarial rigors ceased spontaneously. The blood Wassermann reactions are also indicated.




Graph extending over a period of 30 days, and indicating the influence of malarial rigors on the complement and blood Wassermann titres in a case of G.P.I. The malarial rigors ceased spontaneously and the complement passed into a negative phase, followed by a rise, then a secondary negative phase. Patient withstood the treatment well, and a remission was precipitated.

The patient was an ex-soldier, æt. 50, suffering from a tabetic form of general paralysis. Duration of symptoms about four years. He was tabetic in gait, tremulous in face, hands and speech, and was disintegrated and facile in personality. He had a malarial history, but no attacks for many years. He was infected therapeutically with malarial blood. He had five rigors at intervals of 48 hours and extending over a period of nine days. At the first rigor the blood Wassermann was +6, and the complement fairly high at 0·07. Six complement readings were made during the rigors and the readings remained between 0·07 and 0·08. On the 9th day the patient had the last rigor, after which the complement titre fell, giving the low reading of 0 3 on the 15th day. On the 20th day the titre had risen again to 0 07. On the 24th day it dropped slightly to 0·14, the Wassermann improving to +4. On the 26th day complement rose above "normal" to 0·05 and remained there for the next five days, the Wassermann again improving to +2. The patient during this period was

euphoric. Seven days later, the patient was more subdued and the complement was found to be at 0·07. The patient, however, passed into a state of remission. He improved both mentally and physically, and his speech and gait were almost normal. He said that he had regained the power and control of his limbs. He was discharged from hospital, and five months later two complement and Wassermann readings were made: 0·07, Wassermann +4; 0·07, Wassermann +4, respectively. The patient withstood the treatment quite well, and at no period did he give any cause for anxiety.

The fifth chart demonstrates the behaviour of the complement titre and blood Wassermann in a case of general paralysis, treated with malaria by the rule-of-thumb method. The patient was supposed to get about a dozen shocks.

The graph shows the complement titre, and through it runs the malarial temperature chart. The perpendicular lines below indicate the corresponding blood Wassermann reactions.

In the Wassermann test it should be remembered that what is supposed to be estimated is something in the nature of the patient's "specific antibody" or defence against syphilis; and the article of faith is that the greater the Wassermann reading, the more intense is the patient's infection. This is much the same as estimating a country's enemies by the size of its army—which, of course, may or may not be good reasoning.

In this case, however, tests were made over a period of 66 days, and the greatest possible care was observed in the technique, many of the readings being verified by repetition. Thirty-eight complement estimates and thirty-seven Wassermann end-readings were made.

The patient was a miner, æt. 37, suffering from general paralysis. Duration of symptoms stated to be about four months. He was fat and pale; his cerebration was slow and his speech hesitant and tremulous. He was confined to bed because he was sullen, irritable and resistive.

1st day: During nine days before treatment, five complement and four blood Wassermann tests were made. The first, fourth and fifth complement readings showed no complement, while the second and third gave low readings—0·3, 0·32 respectively. The four Wassermann readings remained at +20.

10th day: On the 10th day patient was infected with malarial blood, 5 c.c. intravenously and 5 c.c. subcutaneously.

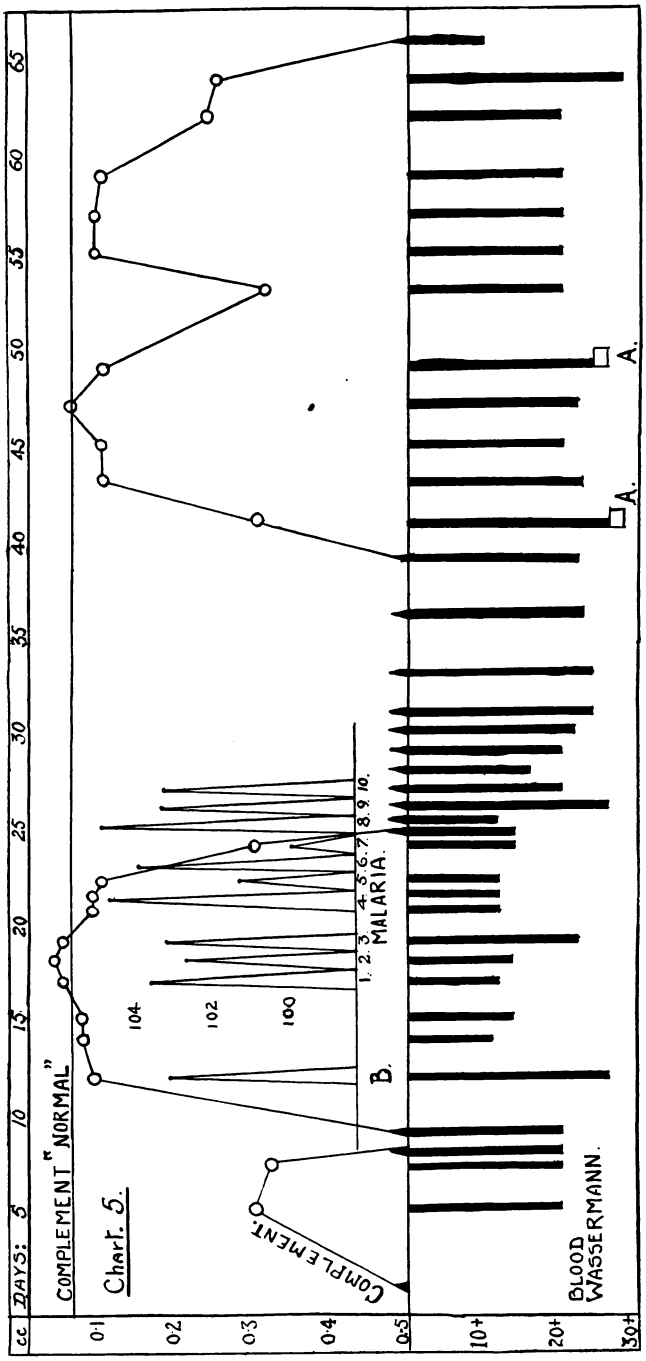
12th day: Within 36 hours he developed a temperature—103·4°. There was no rigor and no evidence of malaria. The blood injections were held responsible for this reaction, and under its stimulus the complement, at temperature 103·4°, rose quickly to 0·09, while the Wassermann increased to +26. It is difficult to explain why the Wassermann titre should have increased. Possibly it was a defensive increase.

14th day: On the 14th day the temperature remained normal. Complement rose again to 0·07, and Wassermann shortened to +12.

15th day: On the 15th day temperature remained normal. Complement remained at 0·07, and Wassermann dropped to +14.

17th day: On the 17th day the first malarial rigor occurred—temperature 103·6°. At temperature 100° (rising) complement rose above "normal" to 0·05. Patient was euphoric. Wassermann shortened to +12.

18th day: On the 18th day at temperature 97·5° and before the second rigor




The chart extends over a period of 66 days, and shows the influence of malaria therapy on the complement and blood Wassermann titres in a case of G.P.I. The patient passed into a state of remission, but at the ninth rigor he suddenly became seriously ill and the treatment had to be terminated.

Note the following points:

(1) The intensity of the Wassermann and the low and unstable titre of the complement before treatment.
(2) The complement, Wassermann and temperature reactions to the injection of blood. "B." This might be a point of difference between malarial blood infection and mosquito infection.
(3) The high titre of the complement during the first three rigors when patient experienced euphoria.
(4) The rapid fall in complement titre between the fourth and seventh rigors with patient's loss of sense or well-being.
(5) The rapid onset of a critical state from the eighth to the tenth rigors, and the total absence of complement.
(6) The prolonged negative phase in the complement titre.
(7) The tendency for the Wassermann to decrease during the first seven rigors and to increase during the negative phase.
(8) The appearance of anticomplemental serum on the 41st and 49th days. "A." It is suggested that treatment should have ceased not later than the fourth rigor.

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complement again rose to 0·04, the patient stating that he was " feeling fine ". Wassermann increased to +14. Then followed the second rigor. Temperature 102·6°.

19th day: On the 19th day at temperature 97°, and before the third rigor, complement dropped to 0·05. Patient was still euphoric. Wassermann increased to +22.

20th day: On the 20th day there was no rigor and the patient looked well and bright.

21st day: On the 21st day at temperature 98°, and before the fourth rigor, the complement dropped to 0·09. Wassermann improved to +12. The fourth rigor was severe, and at the height of the temperature, 104·6°, complement and Wassermann readings remained the same, namely 0·09 and Wassermann +12. The patient looked well and his pulse was good, but he had completely lost his euphoria.

22nd day: On the 22nd day, and before the fifth rigor, which was not severe, complement dropped to 0·1; Wassermann remained at +12. Patient stated that he felt " not too bad ", and could " stick it ". His pulse was good.

23rd day: On the 23rd day the sixth rigor occurred, and was rather severe—temperature 104°.

24th day: On the 24th day, at temperature 96·4°, and before the seventh rigor, there was a sudden fall in complement to 0·3; Wassermann increased to +14. The seventh rigor was not severe—temperature 100°. Patient looked well enough and his pulse was good, but he said he " felt tired and fed up ".

25th day: On the 25th day at temperature 96·4°, and before the eighth rigor, the complement completely vanished; Wassermann remained at 14+. The eighth rigor was severe—temperature 105°, and after it the patient looked rather tired, but his pulse was good. Readings at this point showed no complement, and Wassermann shortened to +12.

26th day: On the 26th day it was debated whether the treatment should be continued or not. The patient looked refreshed after a sleep and his pulse was good. He complained of feeling tired. There was no complement, and the Wassermann had suddenly increased to +23. From the clinical aspect, however, it was decided that he was well enough to stand another rigor. The rigor was not severe—temperature 103·4°—but with the rising temperature the patient's condition rapidly became critical. Readings showed no complement, and a Wassermann shortened to +20. Quinine was administered freely.

27th day: In spite of the continued use of quinine, the patient had the 10th rigor, during which he almost collapsed—temperature 103·4°. Readings showed no complement, and Wassermann shortened to +16. Fortunately the rigors ceased, and during the following twelve days there was a total absence of complement, tests being made on several occasions, when no complement could be discovered in the following quantities of patient's serum: 3·0, 3·0, 3·5, 3·5, 3·5, 1·0, 3·0, 3·0, 1·0, 3·0 and 3·5 c.c.

The negative complement phase, therefore, commenced on the 19th day, and extended to the 41st day. During this period there were 16 days in which there was a total absence of complement, while many of the Wassermann readings stood at a higher level than before treatment commenced. It is difficult to explain the increased Wassermann in the negative phase. It might be a defensive increase, but it is also possible that the anti-syphilitic mechanism was in abeyance.

On the 41st day the complement reappeared with a low reading, 0·3, rising to 0·6 on the 47th day. On the 53rd day the titre fell to 0·3 and the patient complained of not feeling well, but had no definite complaint. On the 55th day the titre rose again to 0·09, after which it continued to fall, until it vanished again on the 66th day.

Meanwhile, between the 41st and 66th days twelve Wassermann readings were made. On the 41st and 49th days the readings were + 28 and + 26, but on these occasions the control tubes indicated that the patient's serum was anticomplementary. Investigation revealed that the anticomplementary factor in both

instances was equivalent to two doses of complement, thus leaving the Wassermann readings at + 26 and + 24 respectively. Of the other readings, three stood at + 22, six at + 20, while on the 64th day the Wassermann suddenly increased to + 28, and on the 66th day it fell to + 10.

During the negative phase the patient was in a state of extreme exhaustion. He recovered slowly at first, but rapidly with the reappearance of the complement. Within the 66 days the patient had passed into a state of remission from his general paralysis, and treatment was continued with tryparsamide.

It is suggested that in this case the pyrexial treatment should not have gone further than the fourth rigor, since the complement titre showed definite signs of falling. Pyrexial shocks may or may not be dangerous in the negative complement phase, and again they may or may not be necessary, but until we have more knowledge on these points, it seems unreasonable to give further shocks in the negative phase. The impatient physician, anxious for a favourable clinical response, is tempted to increase the number, proximity and violence of the shocks. An examination of complement readings after protein stimulation suggests that time is required for some of the biological reactions to take place. If the complement titre swings, it seems to do so on a wave-length which is anything from one to four weeks. Other factors are probably swinging in different wave-lengths, as, for example, the malarial temperatures and the blood Wassermann in the accompanying charts. Incidentally the high temperature so eagerly sought in this form of therapy cannot be the whole story.

In general paralysis therapeutic risks may be legitimate, but in other conditions such as puerperal confusion, where the patient is usually exhausted, greater care should be exercised, especially in the use of T.A.B. vaccine, which is particularly toxic.

Non-specific methods of treatment do give results in the most unexpected cases, so the technique of the therapy is worthy of further investigation. The degree of violence required presents difficulties. Violence may not be necessary in many cases. Warren Crowe works on a minimal stimulus, and rightly points out that there is a difference between a " response " and a " reaction " to treatment. Again, if violence is used there is difficulty in recognizing the point of maximum physiological stimulation. Until this difficult question is settled, it is suggested that during a series of pyrexial shocks the complement titre should be recorded. If a sudden or persistent fall is observed, then the treatment should cease meantime, or at least be carried on with extreme vigilance.

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