An investigation into the value of the serum diagnosis of Mediterranean or undulant fever, and the treatment of the disease by means of vaccines / by P.W. Bassett-Smith.

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CRAGGS PRIZE ESSAY, 1906.

The Therapeutical Treatment of Mediterranean Fever by means of Vaccines, &c.,

BY

FLEET-SURGEON P. W. BASSETT-SMITH.

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1907.

London School of Tropical Medicine.

THE CRAGGS PRIZE.

This Prize of £50 is awarded annually in the month of October to a Past or Present Student of the School who makes the most valuable contribution to Tropical Medicine.

An Investigation into the Value of the Serum Diagnosis of Mediterranean or Undulant Fever, and the Treatment of the Disease by means of Vaccines

BY

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[Reprinted from the "Journal of Tropical Medicine and Hygiene"]

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1907

A CRITICAL EXAMINATION OF THE BLOOD OF PATIENTS IN HOSPITAL, TO DETERMINE IF OTHER THAN MEDITERRANEAN FEVER SERA WOULD AGGLUTINATE *THE MICROCOCCUS MELITENSIS.*

By Fleet-Surgeon P. W. Bassett-Smith.
Royal Navy.

The importance of placing beyond doubt the specific character of the agglutination of the *Micrococcus melitensis* when brought in contact with the blood serum of patients cannot be over-estimated, either when the test is used for diagnosis or for controlling experimental work. There have been cases, from time to time, which have led certain diagnosticians to underrate this modern method of diagnosis. These people would therefore naturally discredit all investigations based on this principle, pointing to cases in which contradictory results have been obtained from the same serum, and to statements that a positive reaction for Mediterranean fever has been met with in other diseases.

Bearing these facts in mind, I have made a careful examination of 150 samples of blood, taken systematically in the wards of Haslar Hospital, for the purpose, if possible, of demonstrating whether or not the serum of patients suffering from a great variety of diseases other than Mediterranean fever would give a reaction likely to render a mistake in diagnosis probable. It is unnecessary to describe fully the technique employed, this being so well known, excepting to say that—

(1) The tubes containing the blood were centrifugalised, and the clear serum was alone used.

(2) The emulsion was made from an agar culture

ten days old of a strain of *M. melitensis*, obtained in November, 1905, from the peripheral blood of a patient now in the Hospital, and was used living.

(3) The serum dilution of 1 in 30 was made with normal saline solution, using accurately graduated pipettes.

(4) The examination was made both microscopically, with a four-hour limit, and by sedimentation tubes with a twenty-four-hour limit.

(5) Controls were made for each batch of tubes, with a serum that reacted perfectly in dilutions from 1 in 30 to 1 in 1,000.

The whole examinations were made by myself, but the readings were confirmed by independent observers.

It will be seen that the blood of forty-one pathological conditions was tested, and that in all but four cases there was no evidence of agglutination of the *M. melitensis*. Of these four positive reactions, two appendicitis cases had lately returned from Malta Hospital, and were running a regular, undulant temperature, and had undoubted Mediterranean fever. The third case was a sick berth steward, who had Mediterranean fever two years and ten months ago. The fourth was a long time in Malta Hospital, where gastroduodenostomy was performed, and though there is no definite temperature chart of Mediterranean fever, I have no doubt that he was, like so many others, infected by the micro-organism there. His temperature is now irregular.

The results are tabulated on p. 5.

All these examinations, therefore, gave an *absolute negative* to other than Mediterranean fever blood, causing agglutination of the *M. melitensis* in a dilution of 1 in 30. The following points were also investigated with regard to this reaction :—

Will Lower Dilutions give Erroneous Results ?—Ten of the already used samples of blood were tested in dilutions of 1 in 5, 1 in 10, and 1 in 20. In one case only was there any reaction, an abscess of the knee, which agglutinated up to 1 in 10.

Are the Agglutinating Properties Destroyed by Keeping the Blood ?—Some serum from a tube of blood, which had been taken from a patient in November, 1901, was tested in the same manner.

Nature of disease	Number of cases tested	Microscopical	Sedimentation
Enteric fever	3	Negative	Negative
Tubercle of lung ..	12	,,	,,
,, testicle ..	1	,,	,,
,, joint ..	1	,,	,,
Tubercular empyema	1	,,	,,
Pneumonia	5	,,	,,
Bronchitis	2	,,	,,
Bright's disease ..	3	,,	,,
Hydronephrosis ..	1	,,	,,
Rheumatism	7	,,	,,
M.C.O.	7	,,	,,
Tonsilitis	3	,,	,,
Dilated stomach, &c...	1	Positive	Positive
Lead paralysis ..	1	Negative	Negative
Appendicitis	7	2 Positive 5 Negative	2 Positive 5 Negative
Hemiplegia	1	,,	,,
Epilepsy	3	,,	,,
G.P.I.	1	,,	,,
Alcoholism	1	,,	,,
Aneurism	1	,,	,,
Abscess, local	7	,,	,,
,, liver	2	,,	,,
,, psoas	1	,,	,,
,, mastoid ..	6	,,	,,
Cellulitis	4	,,	,,
Septic thrombosis ..	1	,,	,,
Otorrhœa	2	,,	,,
Iritis	3	,,	,,
Keratitis	2	,,	,,
Synovitis	1	,,	,,
Herniotomy	5	,,	,,
Hæmorrhoids	1	,,	,,
Varicose veins.. ..	1	,,	,,
Ulcers	2	,,	,,
Fractures	10	,,	,,
Wounds	4	,,	,,
Eczema	4	,,	,,
Gonorrhœa	5	,,	,,
Gonorrhœal rheumatism	2	,,	,,
Syphilis 1	16	,,	,,
,, 2	7	,,	,,
Normal blood	2	1 Positive 1 Negative	1 Positive 1 Negative
Totals	150	4 Positive 146 Negative	4 Positive 146 Negative

	Dilution			
	1 in 10	1 in 20	1 in 40	1 in 200
Microscopic	+	+	+	+
Sedimentation	+	+	+	+
Control, normal blood	—	—	—	—

Result.—Four-year-old blood serum agglutinated perfectly.

Are the Agglutinating Properties Destroyed by Heat?—A portion of the control serum was heated to 60° C. for ten minutes, and tested as before.

Result.—A good reaction, both microscopically and in sedimentation tubes, at 1 in 30 was obtained.

Are Dead Cultures Reliable for any Length of Time?—Using the control serum, the following dead emulsions made in the laboratory were tested, dilution 1 in 30.

	Micro-scopical		Sedi-mentation
(1) Agar emulsion of *M. melitensis* isolated at Haslar, heated to 65° C. for quarter of an hour, + 0·5 per cent. formalin. Made November 9th, 1903	+	..	+
(2) Agar emulsion from strain, given by Professor Wright, Netley. Made November 8th, 1904	+	..	+
(3) Agar emulsion, from Haslar, strain 2. Made March 20th, 1903	+	..	+
Control, normal blood	—	..	—

Thus dead cultures made here more than two years ago were perfectly reliable, though the reaction is less rapid than when living ones are used.

Reliability of the Agglutination Reaction in Mediterranean Fever.—Here it may be stated at once that, in acute cases, I have found the reaction unmistakable, the serum, in fairly high dilutions, acting on the *M. melitensis* almost immediately, clumping completely, and being generally easily visible with a 1 inch objective. With chronic cachectic cases of more than four months' duration, so commonly met with in Haslar Hospital, it is different, the reaction being often incomplete, slow, and only obtainable in very low dilutions, as shown by the following cases:—

(1) J. W. Onset of the fever, April, 1904; returned to the Mediterranean in 1905: immediate relapse. In November, 1905, the blood only agglutinated in dilutions of 1 in 10, yet the *M. melitensis* was in the same month isolated from his blood.

(2) J. P. Onset April 19th, 1905; now intense emaciation and neuritis. In November the blood agglutinated up to 1 in 10; with 1 in 5 the reaction was immediate.

(3) T. S. Onset August, 1905; great emaciation and neuritis. In November the blood only reacted up to 1 in 10.

From these results, and from a great number of the same kind, I have formed the opinion that, when using the 1 in 30 dilution (if the technique is properly carried out) a positive agglutination reaction may be considered conclusive of Mediterranean fever, past or present. On the other hand, it would not be correct to state that the patient is not suffering from Mediterranean fever when an examination of the blood gives a negative reaction with this dilution. I believe the chief sources of fallacy are:—

(1) Faulty technique; incorrect dilutions, too long time, &c.

(2) Faulty cultures; containing false clumps before use, &c.

(3) Faulty observations; mistaking false clumps for true agglutination.

(4) Faulty history; the patient having previously had the disease.

The sedimentation test appears to me to be the least likely to give rise to errors, provided *clear* blood serum is used, and the emulsion be sufficiently strong to give a visible pellet at the bottom of the tube.

———

THE TREATMENT OF MEDITERRANEAN FEVER BY MEANS OF VACCINES, WITH ILLUSTRATIVE CASES.

By Fleet-Surgeon P. W. Bassett-Smith.
Royal Navy.

FIRST SERIES.

For years we have been vainly striving to find some method of treatment for Mediterranean fever, able to prevent or cut short the relapses so constantly present and recurring. Though certain drugs have for a time seemed to act successfully, their beneficial effects are usually uncertain and transient, so that the treatment has come to be almost entirely symptomatic.

Germicidal medicines have each had many trials, lately cyllin has been said to shorten the course of the fever, which in my experience has not been the case.

Burney Yeo's chlorine and quinine mixture has undoubtedly occasionally produced very satisfactory results when given with a rising temperature, apparently cutting short the wave which we had expected to last ten days or more.

It is known that we have in this disease a constant auto-intoxication going on from a specific micro-organism, which may apparently continue and flourish in the internal organs for years, rapidly increasing when vitality is lowered from any cause, giving rise to fresh attacks of pyrexia; when the organism is easily isolated from the peripheral blood.

It would seem that, failing an effective anti-microbic serum, the most rational and successful line of treatment would be in so increasing and stimulating the "phagocytes" that they would be able to combat the influx of toxin-producing germs.

Unfortunately, one of the most constant features of the disease is a relative reduction in these active white

cells, those remaining possessing less than normal bactericidal powers.

For a month in a ward full of Mediterranean fever cases, fresh yeast was administered, in the hope of causing a rise in the number of the polymorphonuclear cells, but with no marked success, neither was there any distinct improvement in the clinical symptoms.

Sir A. E. Wright has shown that the injection of vaccines of the organism causative of a disease, when given in a suitable quantity, is able to produce protective substances in the blood, and to modify the clinical manifestations of the disease.

Staff-Surgeon A. T. Reid, R.N., by applying this method to Mediterranean fever cases has apparently been so successful, that it was desirable to give this treatment an extensive trial in the wards at Haslar, where the cases at one's disposal are fairly numerous and varied. This has now been employed for the last seven months on almost all cases, to the exclusion of any active drug treatment.

In all the cases the amount of dosage and the nature of the reaction has been calculated out by recording the opsonic index, as devised by Wright and Douglas.

Preparation of the Vaccine.

A freshly isolated strain of the *Micrococcus melitensis* was used, obtained from the spleen during life of a patient in the hospital. Agar cultures of ten days' growth were used; this was scraped off and emulsified in 100 cc. of distilled water, making a thickish opalescent fluid. The emulsion was then heated in a water-bath at 60° C. for half an hour, and finally carbolic acid was added in the proportion of 0·5 per cent., the whole being sealed up and kept as a stock vaccine.

After twenty-four hours 0·5 cc. of the vaccine was spread on an agar tube; no growth appeared in seven days, therefore it was free from contaminations and dead.

Estimation of Strength.

By Opacity.—A sample was run out into a square glass bottle, giving a thickness of fluid of 1·5 cm.; the opacity just allowing one to read ·5 Snellen's type through the fluid.

By Dilutions and Cultures.—A sample of 5 c.mm. of the fresh made emulsion was with a measuring pipette diluted fifty times, and this again in a similar way three times, giving a dilution of 1 in 6,250,000. From this high dilution 5 c.mm. plated out gave on the seventh day 150 colonies of *M. melitensis*, working out to 937,500,000 for 5 c.mm., or 187,500,000 for every c.mm.

By Weight of Dried Organisms.—From the freshly prepared emulsion, after heating, but before the addition of the carbolic acid, 20 cc. were run off in a long tube. The estimation were kindly made by Dr. C. J. Martin, F.R.S. He found that the 20 cc. of vaccine contained 4 milligrams of *M. melitensis*, or 0·2 milligram per cubic centimetre. This is, I think, the most accurate method of standardising on future occasions.

Method of Injecting.

About 10 cc. were periodically run off into a sterile bottle, having two rubber cap tops, ·5 cc. doses were drawn up into freshly prepared glass tubes by means of a sterile rubber teat, and then the tubes were sealed in the flame. These were taken to the ward for use, each dose being expressed into a sterile glass capsule as required. A 1 cc. all glass syringe was employed for injecting the vaccine. The injections were all given in the loin region, the part being prepared with spirit, soap, ether, and biniodide solution.

Generally from five to ten cases were treated at one time; in all, 101 injections have been given, so far without any sign of suppuration at the site of puncture, rarely producing slight local irritation for twenty-four hours, therefore the local toxic effects of the vaccine must be very slight.

Method of Noting the Effect of the Vaccine by the Opsonic Index.

The blood of each case was taken twice a week, or twice in ten days, generally the total number of cases under treatment at one time. The serum was separated by means of an electric centrifuge.

My own citrated blood was used throughout for the standard index, the plasma was removed, and the cells

were washed four times with ·9 per cent. saline solution.

A freshly prepared weak emulsion of a young agar culture of *M. melitensis* was made for each operation: 1 part of the patient's clear serum; 1 part of my washed blood cells; ½ a part of the emulsion of *M. melitensis* was then taken, well mixed, drawn up into small bulb tubes, sealed, and placed in the blood heat incubator for twenty minutes; the mixture was then blown out on to slides, and films were made; when dry they were fixed in alcohol for ten minutes, and finally stained with carbol-toluidin blue for half an hour.

The whole operation was completed in the morning, without delay. It was found most convenient to use my own blood as a standard index, as it was always available. I, however, tested its opsonic power with that of six of the surgeons under instruction, with the result that the average of all theirs was exactly the same as my own; therefore my serum may be taken as normal in its opsonic reaction with the *M. melitensis*.

Estimation of Phagocytosis.

Carbol-toluidin blue was found to be the most satisfactory stain, as it picked the white cells clearly, slightly staining the protoplasm in which the micrococci were seen having a deep blue colour. It was found necessary to use a high eyepiece and $\frac{1}{16}$ inch objective for the enumeration.

Not less than twenty consecutive polymorphonuclear cells were counted in each film, and the average cocci ingested taken.

In counting from twelve to twenty-four films in each series (which is most laborious and eye-straining work) one found that the leucocytes tended to congregate mostly along the margin of the film; by following this line much time is saved.

In counting hundreds of films two facts were noticeable:—

(1) That only the polymorphonuclear cells take up the organisms.

(2) When using the high powers above mentioned, the frequency with which the bacillary form of the micrococcus was met with.

Agglutination Reactions.

Besides testing the opsonic index in each case, the agglutinins were estimated for in three dilutions, 1 in 20, 1 in 200, 1 in 2,000. These, extending over many weeks, are of interest, bearing out the conclusions set forth in my paper of 1902 (*British Medical Journal*).

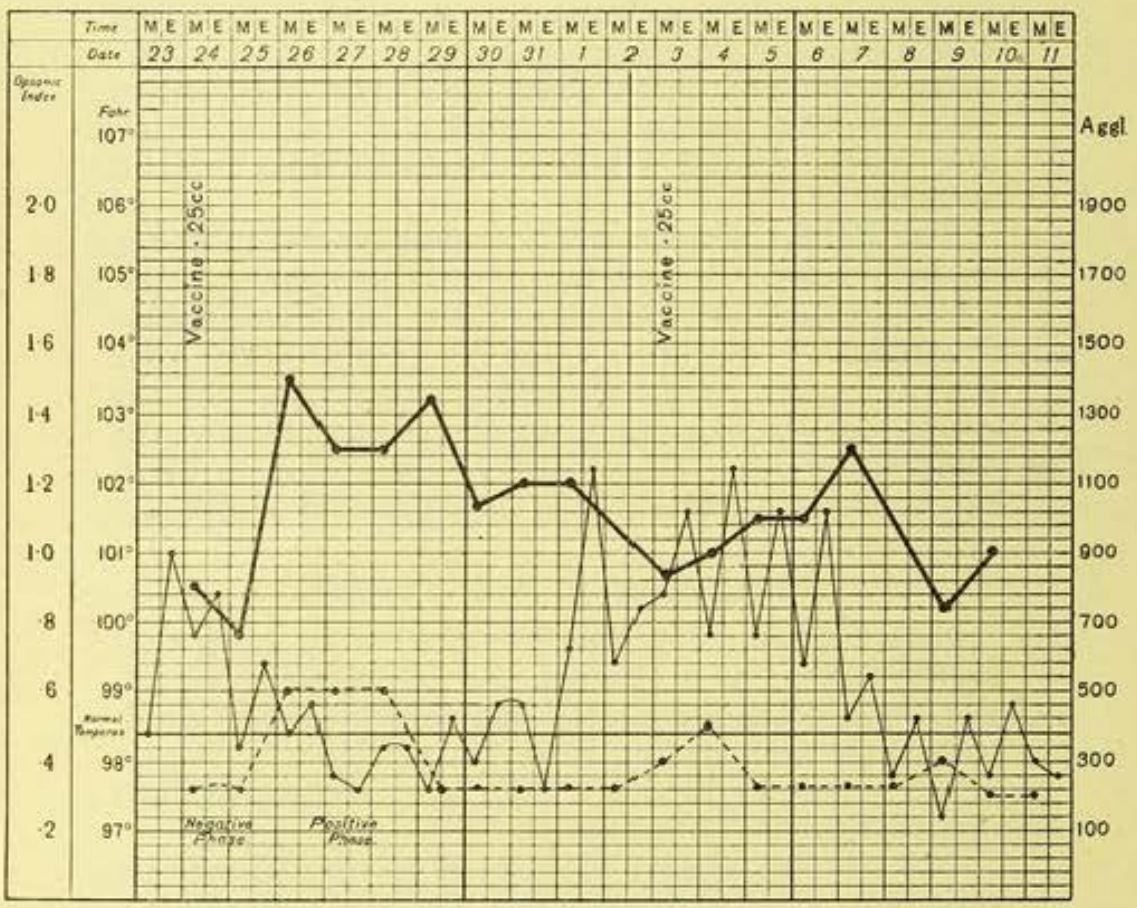

Chart 1.

Records of Temperature.

Many of the cases being very prolonged, I have reduced the temperature charts into small dimensions, as it is essential to grasp the course of the disease both before and during the administration of the vaccines if any deductions are to be drawn.

Characters of the Opsonic Curve.

Charts 1, 2, 3, show from daily observations the course of the opsonic curve after injection of the vaccines.

It will be seen in chart 1 that after the first dose of the vaccine there was a slight negative phase lasting twenty-four hours; this was followed by a rapid rise or positive phase lasting about a week. After a second injection the index rose less and was much shorter.

Chart 2.—The observations were taken after the ninth injection. Here the negative phase was slight, being followed by a high but very transient positive one; the patient was, however, feeling quite well and was discharged to duty.

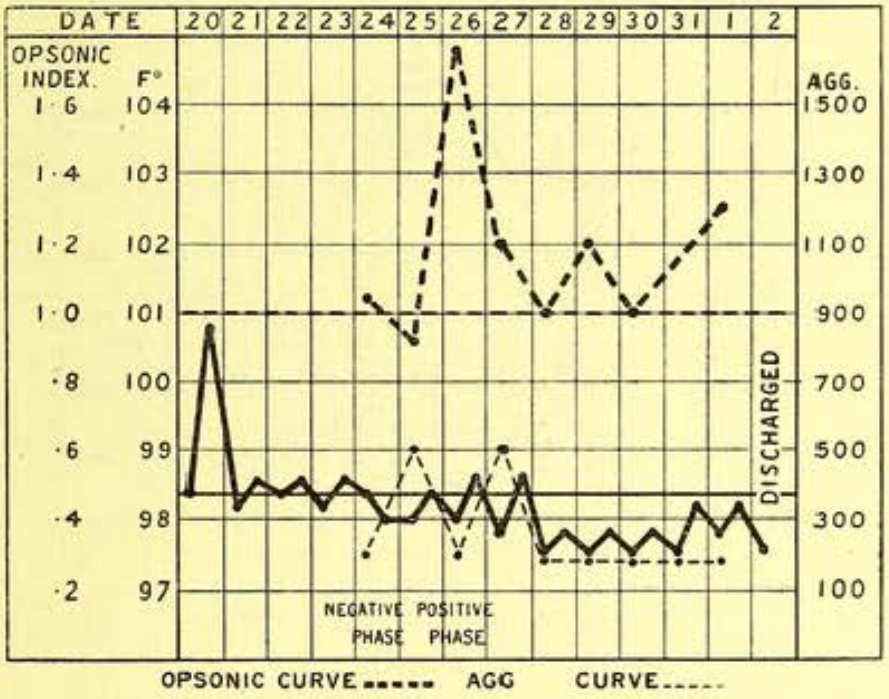

CHART 2.

Chart 3.—From a low negative phase there was a steady rise, reaching its maximum on the third day, falling to normal on the sixth.

RELATION OF THE AGGLUTINATION CURVE TO THE OPSONIC CURVE.

On the addition of an emulsion of *M. melitensis* to the mixture of normal washed cells and the serum of a patient suffering from Mediterranean fever, the possibility of the specific agglutinins in the serum causing clumping of the *M. melitensis* has to be reckoned with, rendering the ingestion of the micrococci into the phagocytes easier than normal.

In those sera which show high agglutination values, as is often the case in the early stages of the disease with high fever, one would expect that this would be very marked, and indeed that it does so occur is evident in some of the stained blood films showing high opsonic indices ; in such specimens not only are the phagocytes full of the organisms, but they are seen distinctly clumped throughout the general area of the field.

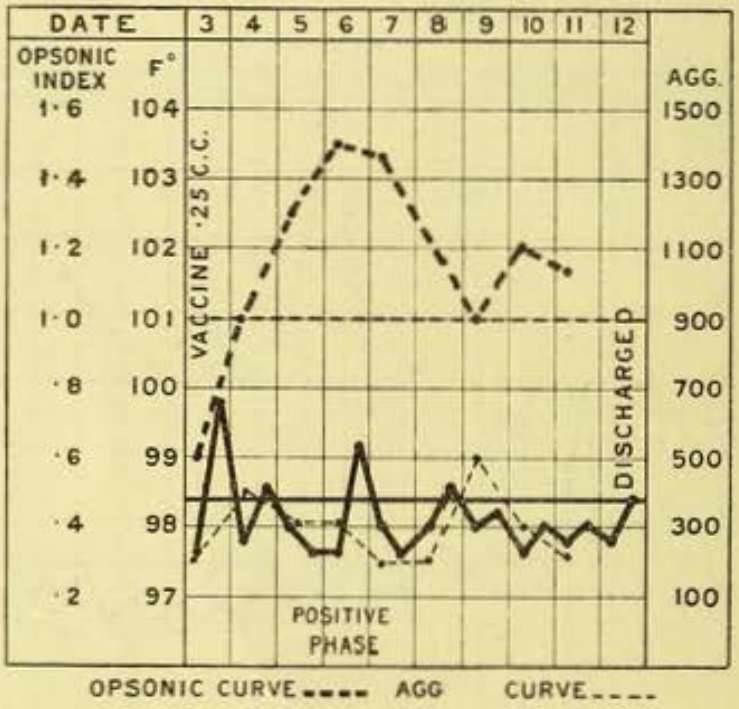

Chart 3.

From the study of many hundreds of films it was apparent that this expected agglutination reaction was rarely present sufficiently to explain the high phagocytic index of the blood examined.

A critical examination of the accompanying charts during the whole course of the cases extending over weeks shows no regular relationship of the agglutination and opsonic curves. Many of those showing very low evidences of agglutination have an opsonic index running high. To test this relationship the serum of several cases was examined daily for both agglutinins and opsonins (see charts 1, 2 and 3). In chronic cases, after the injection of the vaccine there

was a slight rise in the agglutinins, quickly falling to the usual low range.

These observations are more in conformity with the results obtained by Leishman, related in his article on "Some Experiments in Connection with Stimulins," in *Transactions of the Pathological Society*, July, 1905, than with those who found the agglutination curve running more or less parallel with the opsonic.

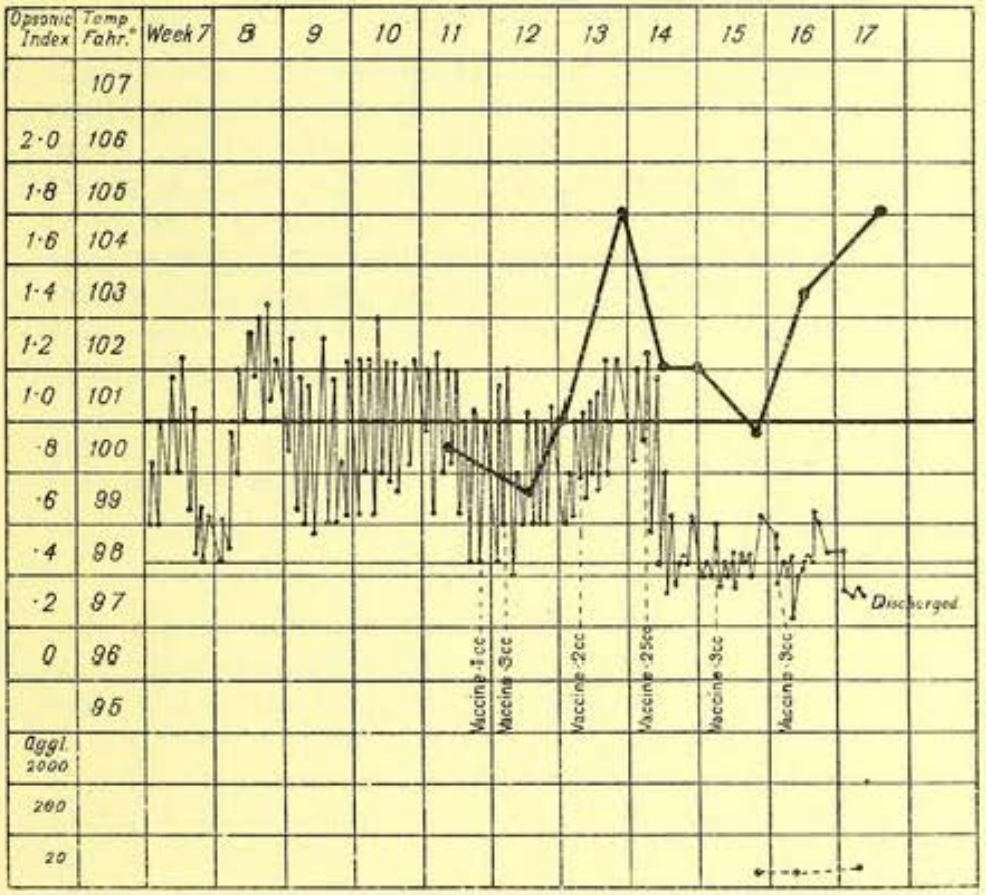

CHART 4.

RELATIVE VALUE OF SERUM AND LEUCOCYTES IN PHAGOCYTOSIS.

The following experiment is of interest; it was carried out to show the relative values of the serum and blood cells, when mixed in different ways, taken from a patient suffering from chronic Mediterranean fever, and from a healthy man.

		Average ingested in each Polymorphonuclear cell. Case 1	Case 2
(1)	Patient's unheated serum. 1 vol.		
	Patient's washed blood cells. 1 vol.		
	Emulsion of *M. melitensis.* ½ vol. (living)	23	46
(2)	Patients unheated serum. 1 vol.		
	Normal washed blood cells. 1 vol.		
	Emulsion of *M. melitensis.* ½ vol.	8·6	25
(3)	Normal unheated serum. 1 vol.		
	Patient's washed blood cells. 1 vol.		
	Emulsion of *M. melitensis.* ½ vol.	16	30
(4)	Normal unheated serum. 1 vol.		
	Normal washed blood cells. 1 vol.		
	Emulsion of *M. melitensis.* ½ vol.	19	29

From the above it would appear that the specific serum with its own washed cells was more powerfully phagocytic than when mixed with foreign (non-immune) blood cells, and that the specific serum with foreign blood cells was less powerful than when the patient's blood cells were mixed with non-specific serum; seeming to indicate that the protective power existed in the patient's white blood cells. The same mixtures with dead emulsion gave proportionately similar results.

N.B.—The low phagocytic average in No. 2 might mean that we were dealing with a negative opsonic phase.

Epitome of Cases.

(1, chart 4.) J. W. Remittent type of fever. Vaccine commenced in the eleventh week; opsonic index rose after the second injection, the temperature fell after the fourth and remained down, improvement in nutrition and power, but the agglutinins remained very low.

(2, chart 5.) J. G. B. Severe undulant type of fever. Vaccine given in the thirteenth week, at the end of a long wave, no further rise in temperature, opsonic index ran up high, he gained 16 lbs. in three weeks, agglutinins fairly high.

(3, chart 6.) J. M. Undulant type of fever. Vaccine given in thirty-third week, when a wave had well started. The temperature suddenly fell and remained down, and the opsonic index mounted high. This was a brilliant result for the time. His agglutinins fell very low.

(4, chart 7.) A. T. Undulant type of fever. Vaccine commenced in the thirteenth week of the

fever. There was no apparent effect on the fever for four weeks. The temperature then went down, and the opsonins rose high. The cachexia was very marked, and the agglutinins fell very low.

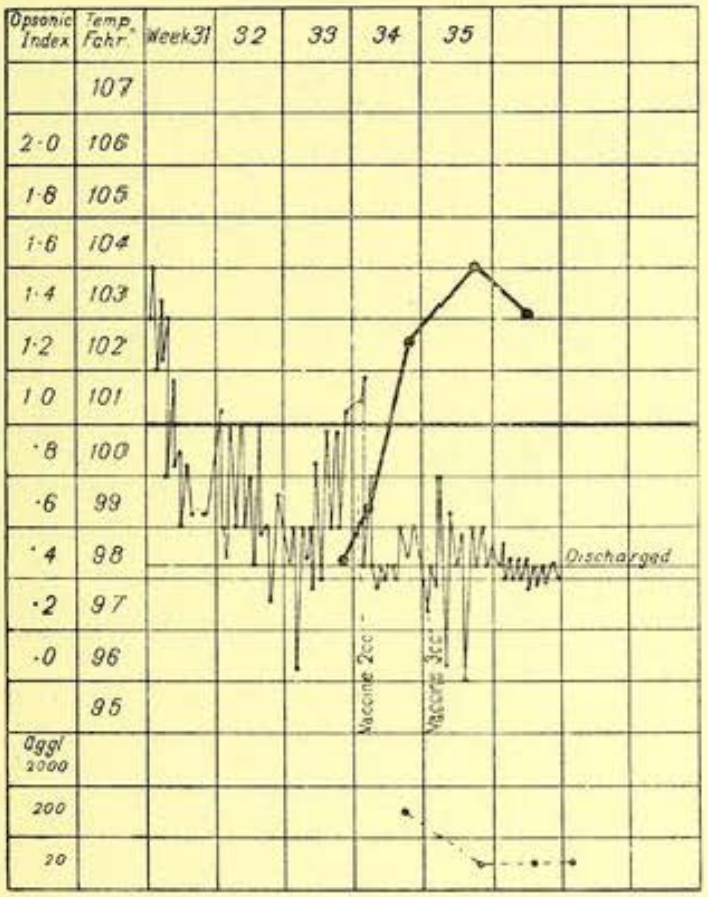

CHART 6.

(5, chart 8.) T. L. Undulant type of fever. Vaccine commenced in the tenth week; a wave of pyrexia having started, this aborted, and there was no further rise. His general condition rapidly improved, gaining 25 lbs. in twenty-one days. The opsonins rose, and the agglutinins were fairly high.

(6, chart 9.) J. W. Undulant type of fever. Vaccine commenced in the ninth week; after the second injection the temperature fell, and he steadily improved. The opsonic index rose, but the agglutinins were generally low.

(7, chart 10.) H. D. Mild undulant type, patient very anæmic. Vaccine given in the eighth week. The temperature fell, and the opsonins rose almost at once, patient gaining 14 lbs. in weight in fourteen days.

(8, chart 11.) Undulant type. Treatment commenced in the eighth week, one injection given; within

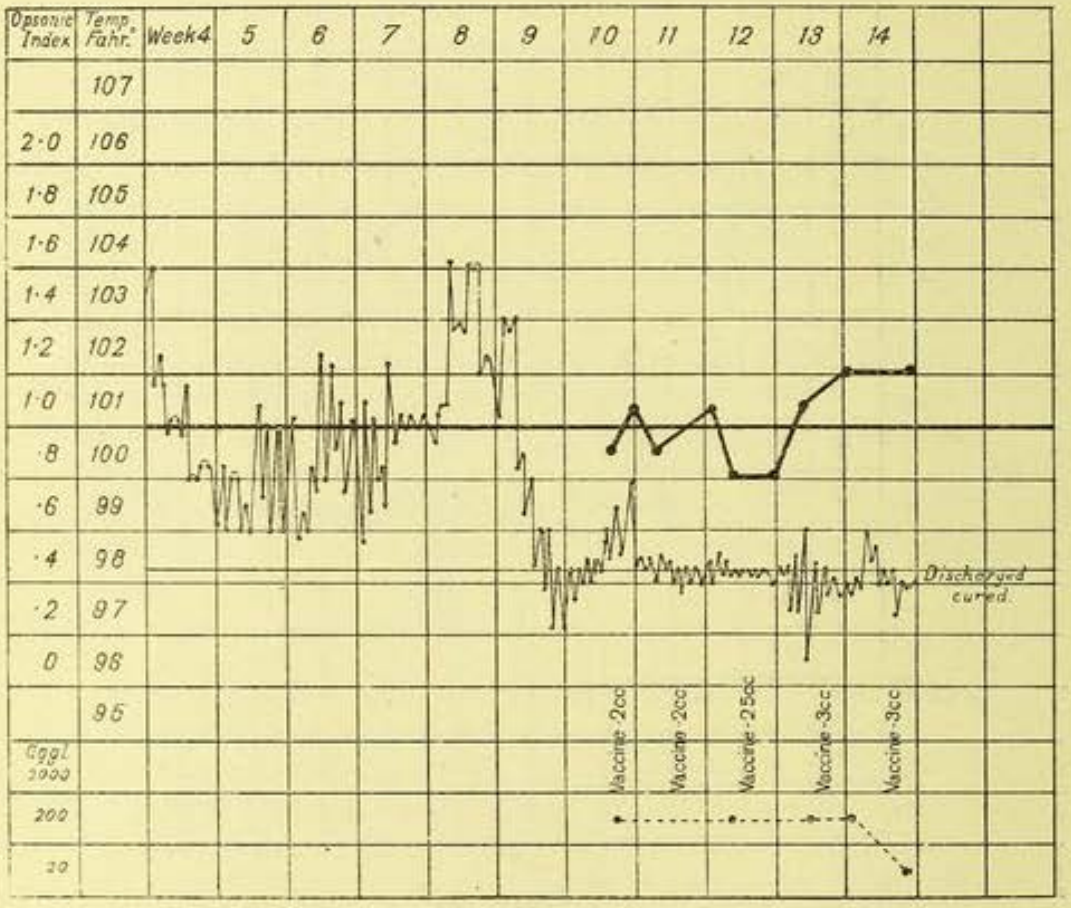

CHART 8.

three days of this the temperature had fallen, and the opsonic index risen, there was no relapse in three weeks, when he was discharged, having gained half a stone. The agglutinins from 1 in 2,000 in the pyrexial stage fell to 1 in 20 before going out.

(9, chart 12.) D. G. Undulant type of fever. Vaccine commenced in the eleventh week, the temperature fell abruptly on the second day after, and hardly rose again, the general improvement was marked. The opsonic index never rose above normal.

(10, chart 13.) J. S. Mild undulant type of fever. Vaccine commenced in the twelfth week. The temperature fell on the fifth day and remained down, the agglutinins and opsonins rose slightly together.

(11, chart 14.) C. L. Intermittent type of fever. Vaccine commenced in the ninth week, improvement commenced after the second dose, both opsonins and agglutinins rose in convalescence.

(12, chart 15.) A. W. Fever of an irregular undulant type. Vaccine commenced in the eleventh week, three injections were given at ten-day intervals. Both agglutinin and opsonic index went up, with a fall in the temperature and a gain in weight. He was discharged early at his own request, feeling quite well.

(13, chart 16.) T. F. Undulant type of fever. Vaccine first given in third (?) week. The temperature fell within a week and practically remained down; he had, however, persistent sciatica, &c. With the fall in temperature there was a rise in both agglutinins and opsonins.

(14, chart 17.) G. V. Severe undulant type of fever with severe cachexia, in an old man. Vaccine commenced in the fifth week; four doses were given, after which the temperature fell, remaining down for fourteen days, when he was discharged to his home. Neither opsonins or agglutinins showed much variation.

(15, chart 18.) H. H. Undulant type of fever, case believed to have been phthisis before admission. Vaccine commenced in the fifth week. After the third injection the temperature fell, and hardly ever rose above 100° again. He made a steady convalescence, gaining over 2 st. in weight. The agglutinins, at first high, 1 in 2,000, fell to 1 in 20 in the tenth week, rising again before he left hospital, indicating favourable result.

(16, chart 19.) A. H. Severe undulant type of fever, with great emaciation and depression. Vaccine was commenced in the fifteenth week during a high relapse. Six weekly injections were given, but there was absolutely no beneficial influence on the fever, which ran a severe course; in the twenty-first week the temperature fell, and from that time he steadily convalesced. The agglutinins, at first high, 1 in

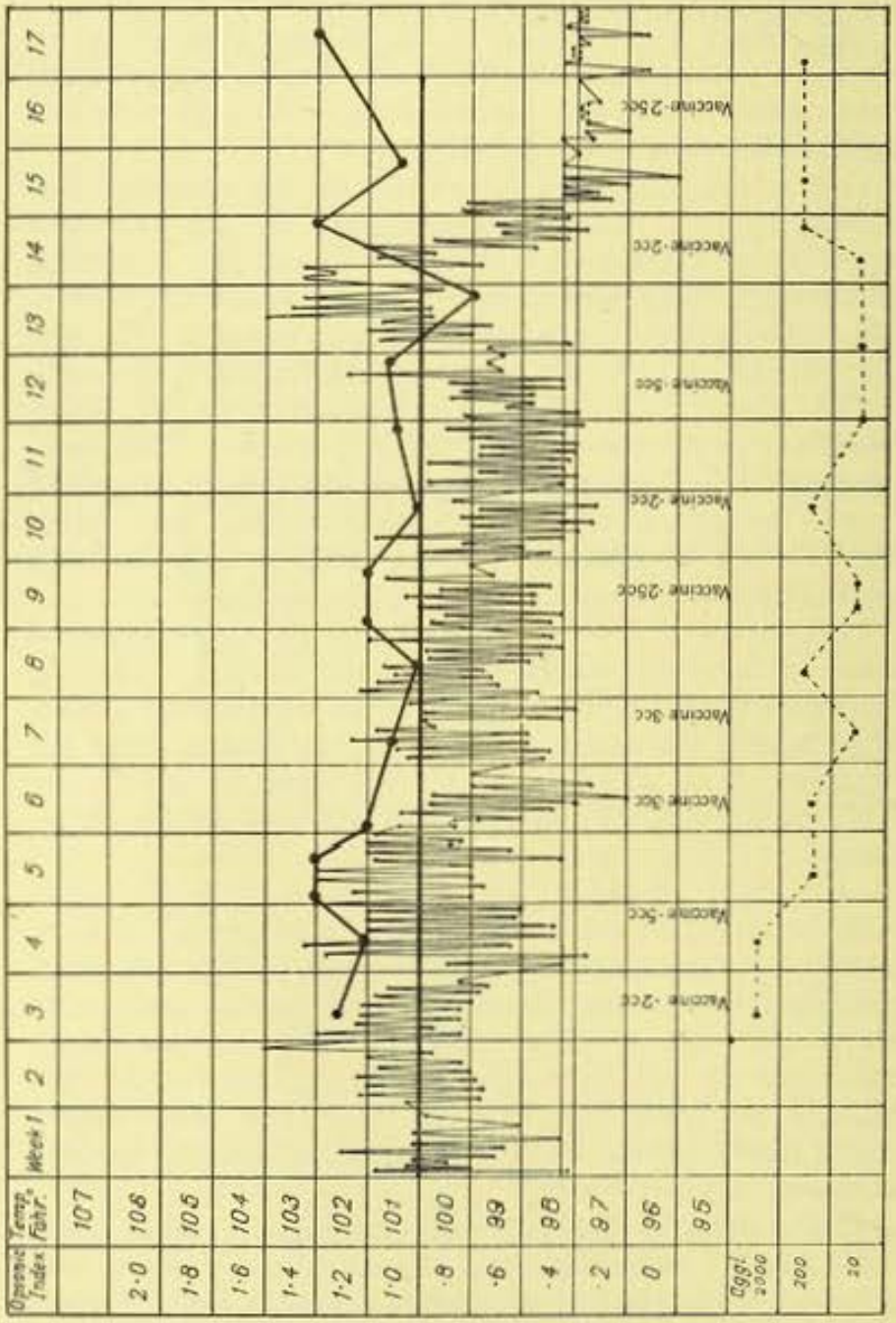
Opsonic Index
Temp. Fahr.
Week 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
2·0
1·8
1·6
1·4
1·2
1·0
·8
·6
·4
·2
0
107
106
105
104
103
102
101
100
99
98
97
96
95
Vaccine ·2cc
Vaccine ·5cc
Vaccine ·3cc
Vaccine ·25cc
Vaccine ·2cc
Vaccine ·5cc
Vaccine ·2cc
Vaccine ·25cc
Agglutination 1000
200
20

CHART 22.

2,000, fell in the twenty-third week to 1 in 20, rising slightly in convalescence. The opsonic curve was irregular, but showed a tendency to fall, with high pyrexia, and rise in the intervals.

(17, chart 20.) G. W. M. High undulant type of fever. Vaccine commenced in the fifth week at the

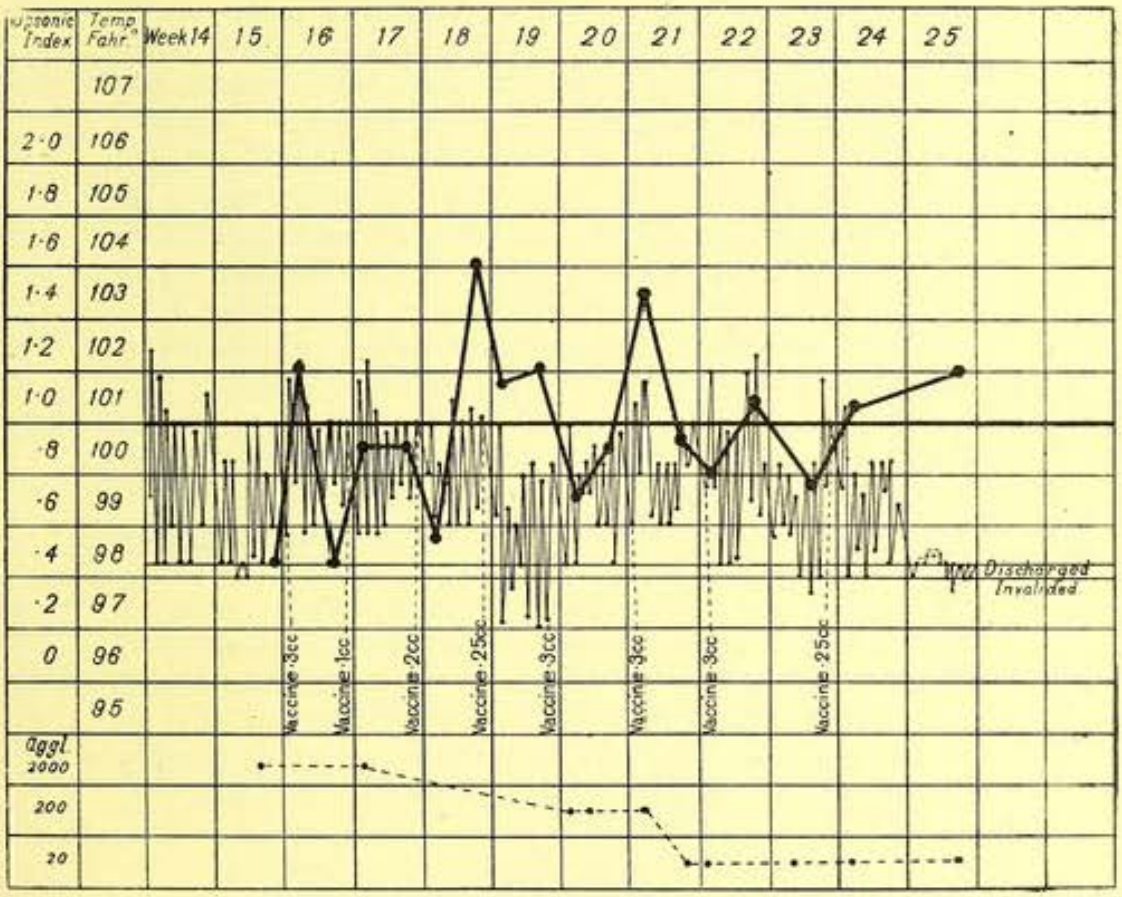

CHART 23.

commencement of a wave of pyrexia; repeated injections at long intervals did not appear to have any influence on the fever. The agglutinins, commencing at 1 in 2,000, fell in the eleventh week to 1 in 20, rising again in convalescence to 1 in 2,000. The opsonic curve was very irregular. Patient discharged to sick leave.

(18, chart 21.) J. N. Undulant type of fever. Vaccine commenced in the sixth week during a high

relapse, and was given regularly about every ten days (nine injections); it had apparently no influence on the fever or course of the disease. The opsonic index was generally above the normal, the agglutinins very low, rising slightly in convalescence. The patient was discharged in the seventeenth week, having lately steadily gained weight.

(19, chart 22.) P. A. Admitted for phthisis. Fever of an undulant type with great diurnal variations, cough, &c. Vaccine commenced in the third week, repeated about every ten days with apparently no effect on the temperature or symptoms. After a final severe relapse he made a steady convalescence, gaining weight rapidly. The opsonic index was high throughout. The agglutinins were at first high, 1 in 2,000, but fell during the course of the disease to 1 in 20, rising slightly in convalescence.

(20, chart 23.) H. H. Intermittent type of fever. Vaccine commenced in the sixteenth week; this was given weekly for five weeks, then at longer intervals. There was apparently no influence on the fever, the patient being invalided. The opsonic index made a gradual but irregular ascent, the agglutin curve steadily fell.

(21, chart 24.) C. N. Long undulant type of fever. Vaccine commenced in the thirty-second week of the disease and given weekly. During the treatment he had three relapses, the last being the most severe, the vaccine, even after many injections, being apparently powerless to prevent these relapses. He was discharged invalided in the forty-second week. The opsonic curve rose steadily, the agglutinins fell.

(22, chart 25.) H. R. P. Irregular intermittent type of fever in an oldish man. During a wave of pyrexia an injection of the vaccine was given, this was followed by marked constitutional reaction for a few hours, shivers, pain, and headache, so that he refused a further. For fourteen days the opsonic index fell, then slowly rose and remained above normal. It is impossible to say how long the one dose of vaccine influenced this curve. The general symptoms slowly improved, but the agglutinins remained very low throughout.

Thus, out of twenty-two cases, marked improvement was registered in fifteen.

The administration was in no way compulsory, the patients suffered scarcely any pain and rarely any soreness from the injections, which were generally given on the tenth day. Most of the men believed strongly in their efficacy, and asked for their repetition.

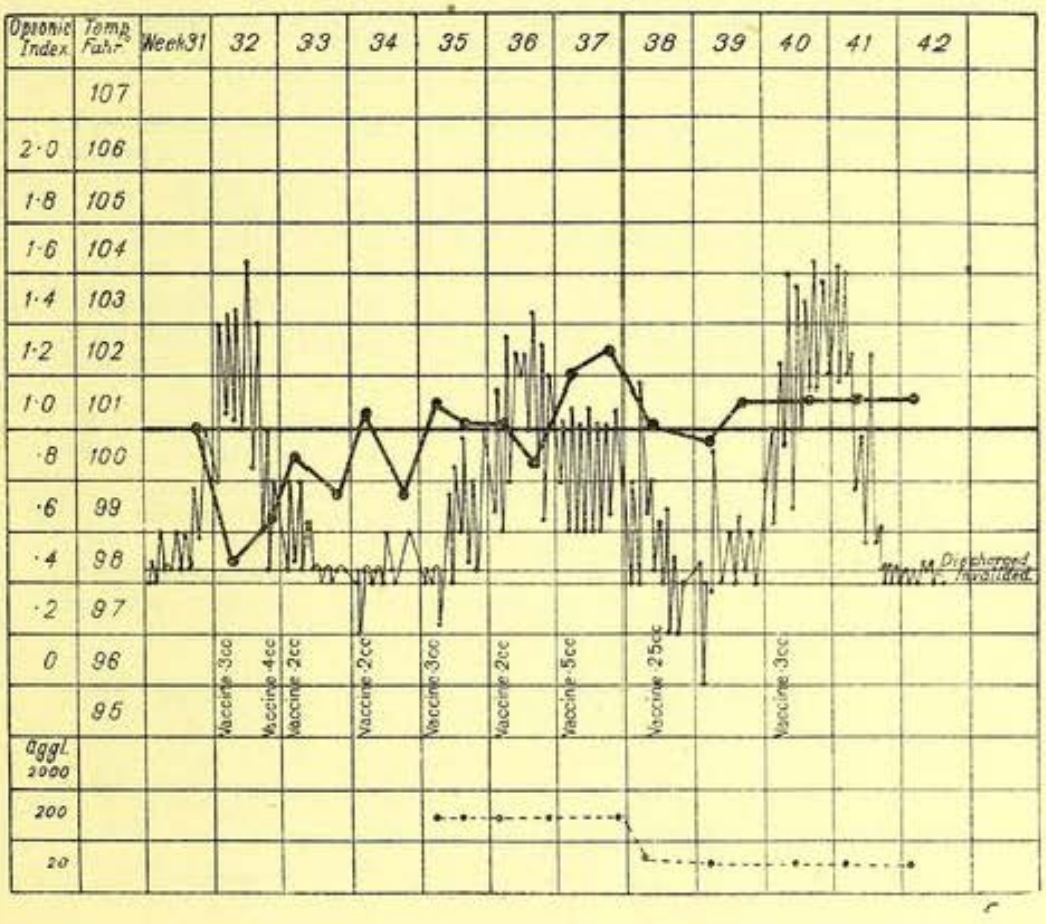

CHART 24.

The gain in weight when convalescence is once established is very rapid, from ½ to 1 lb. per diem, but this occurs also under other methods of treatment. The disease is so irregular in its behaviour, and has such long latent periods, that experience makes one careful in making a prognosis, or drawing definite deductions from any method of treatment.

In conclusion, from our present knowledge, one is justified in saying that in the administration of vaccines in Mediterranean fever we have a factor for great good; but I believe that it is unwise to think

Vaccine Record. Series I.

Table of Cases.

0·25 cc. equals 468,750,000 mm. or 0·05 milligram dried.

No. of Chart	Name	Amounts injected * in cubic centimetres.	No. of injections	Results
*4	W.	·1, ·3, ·2, ·25, ·3, ·3	6	Favourable on T. and opsonic index
5	J. G. B.	·3, ·3, ·5	3	Ditto
*6	J. M.	·2, ·3	2	Ditto
7	A. T.	·3, ·3	2	Ditto
*8	T. L.	·2, ·2, ·25, ·3, ·3 ..	5	Very favourable
9	J. W.	·25, ·3, ·25	3	Favourable on T. and opsonic index
10	H. D.	·2	1	Ditto
11	F. B.	·2	1	Ditto
12	D. G.	·2, ·4	2	Ditto
13	J. S.	·25, 5	2	Favourable
14	C. L.	·25, ·25, ·25, ·25, ·25	5	Ditto
15	A. W.	·3, ·2, ·25	3	Favourable on T. and opsonic index
16	T. F.	·25, ·25, ·25 ..	3	Ditto
17	G. V.	·2, ·3, ·25, ·5 ..	4	Improved after 4th
18	H. H.	·3, ·3, ·3, ·2, ·4, ·25, ·25	7	Improved after 3rd
19	A. H.	·3, ·3, ·5, ·5, ·25, ·3, ·25, ·4, ·3 ..	9	Negative
20	G. W. M.	·3, ·25, ·3, ·25, ·5, ·25, ·25	7	Ditto
21	J. N.	·3, ·3, ·3, ·2, ·25, ·3,† ·25, ·25, ·3 ..	9	Ditto
*22	P. A.	·2, ·5, ·3, ·3, ·25, ·25, ·5, ·2, ·25 ..	9	Ditto
*23	H. H.	·3, ·1, ·2, ·25, ·3, ·3, ·3, ·25	8	Ditto
*24	C. N.	·3, ·4, ·2, ·2, ·3, ·2, ·5, ·25, ·3 ..	9	Ditto
25	H. R. P.	·3‡	1	Ditto

* These charts only inserted.

† Marked local reaction followed the injection for twenty-four hours.

‡ Marked general and local reaction for a few hours, refused further treatment.

one's self, or allow the patient to believe, that its action will be rapid or very evident, and that in acute cases with high fever, where there is marked evidence of specific intoxication, it is not advantageous at all.

SECOND SERIES.

Since compiling the preceding paper, the method of treating almost all cases of Mediterranean fever in the wards at Haslar by the periodical administration of vaccines has been continued with varying success, the results bearing out the conclusions arrived at after a study of the first series. During this period thirty-five fresh cases have received injections of the vaccine, twenty-three of which have been discharged, and are included in this second series. Many of these were of a particularly severe type, extending over long periods.

The vaccines were generally given every tenth day, and the opsonic index was taken weekly. Some cases have, however, been daily examined for the amount of agglutinins and opsonins, the results being shown in special charts, in which the course of the two curves seems to be frequently very dissimilar. In prolonged cases, even with acute relapses, the agglutinins were rarely found to rise to any height.

During the present series, 123 injections of the vaccine have been given (a total of 224 in sixty-one cases since starting the treatment), and as in the previously recorded cases, beyond a certain amount of temporary tenderness in the loin, there were no unpleasant local effects. Occasionally the evening temperature rose slightly, but in one case this shot up to 103·6°, this was, I think, a simple coincidence, and not due to the vaccine.

It is very difficult in such a disease as Mediterranean fever to estimate how much of the variation observed in the opsonic curve is due to the addition of a small artificially introduced dose of the toxic microbe, when at any time fresh natural periods of intoxication are being produced.

Natural and Artificial Induced Variations of the Opsonic Curve.

To illustrate this, charts of the opsonic curves, &c., of two patients in very similar conditions of fever, cachexia, and period of illness were carefully recorded, one being treated with vaccines from the first, the second having no vaccine for a considerable time. In the former case (chart 5), after the first injection the opsonins rose steadily and remained at a moderately high level for about a week, then fell to normal; after the second slightly larger dose, the response was very feeble, being followed by a temporary higher rise most probably due to an auto-intoxication.

After the third dose the response was very marked, the temperature fell, and the patient in fourteen days was well enough to be discharged. In the latter case (chart 6), one saw a rising, followed by a rather high opsonic curve concomitant with the onset of a wave of fever, presumably due to a fresh influx of toxin. At this period, he being the only man in the ward not receiving the vaccine and having a relapse, he asked for the treatment, which being given was followed by a permanent fall in the temperature, general improvement in his feelings, and a rise in the opsonic index; this appeared to indicate that the vaccine was doing good.

Effect of Second Injections.—Charts 2 and 5 show how second injections failed to raise the opsonic index to the height obtained by the first, either due to a want of power of response, or possibly to too small doses being employed. In chart 3 the reaction after the second injection is seen to be very marked, though short-lived.

Presence of a Negative Phase.—Colonel Leishman, R.A.M.C., in his paper on anti-typhoid inoculations, *Journal of Hygiene*, vol. v., 1905, is sceptical in typhoid of the well-marked negative phase described by Sir A. E. Wright. A study of these charts shows that this phase is frequently absent or very short in cases of Mediterranean fever, especially when the initial reading was below normal, the rise then being apparently steady from the time of the administration of the vaccine.

Effects on the Fever.—In very acute cases with

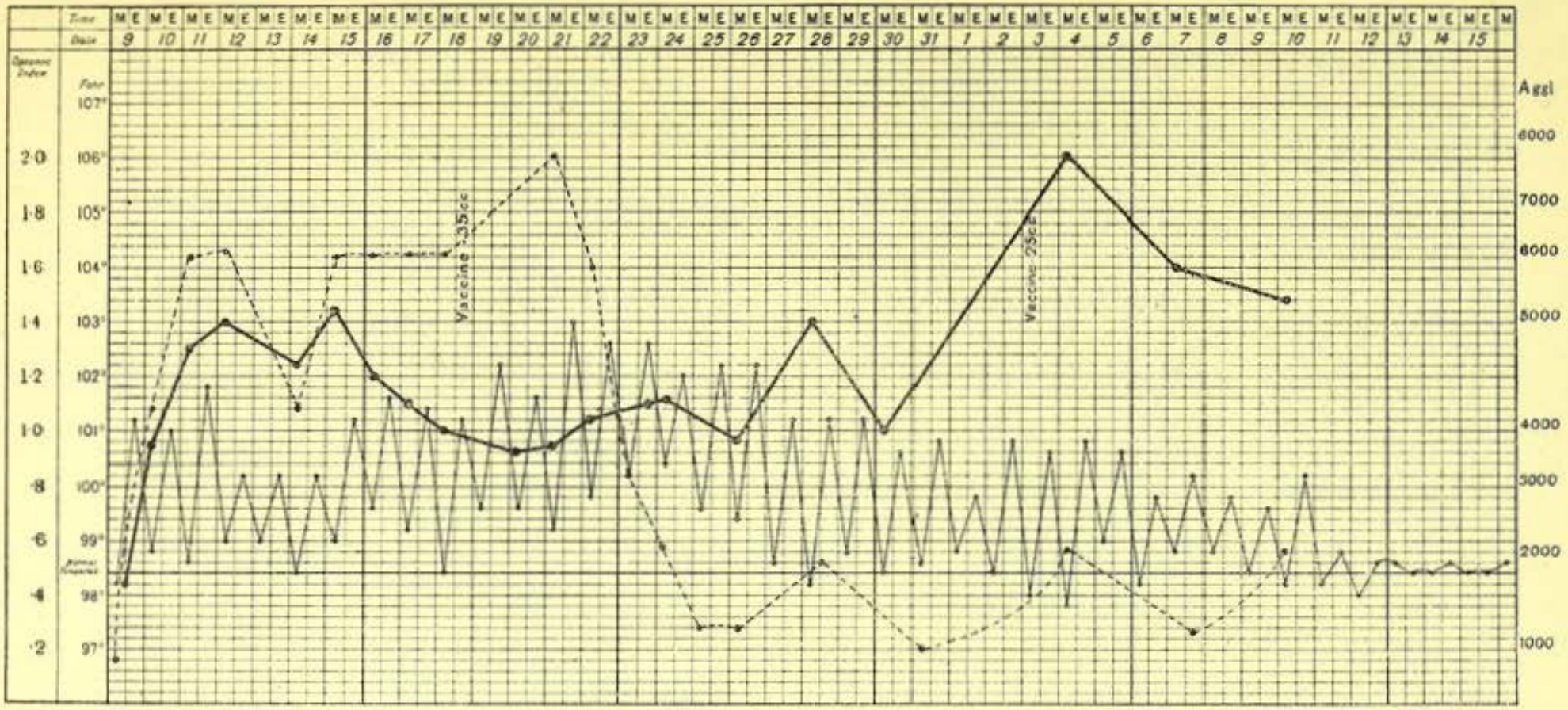
Vaccine 35cc
Vaccine 35cc
Aggl
6000
7000
8000
5000
4000
3000
2000
1000
2·0
1·8
1·6
1·4
1·2
1·0
·8
·6
·4
·2
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°

CHART 5.

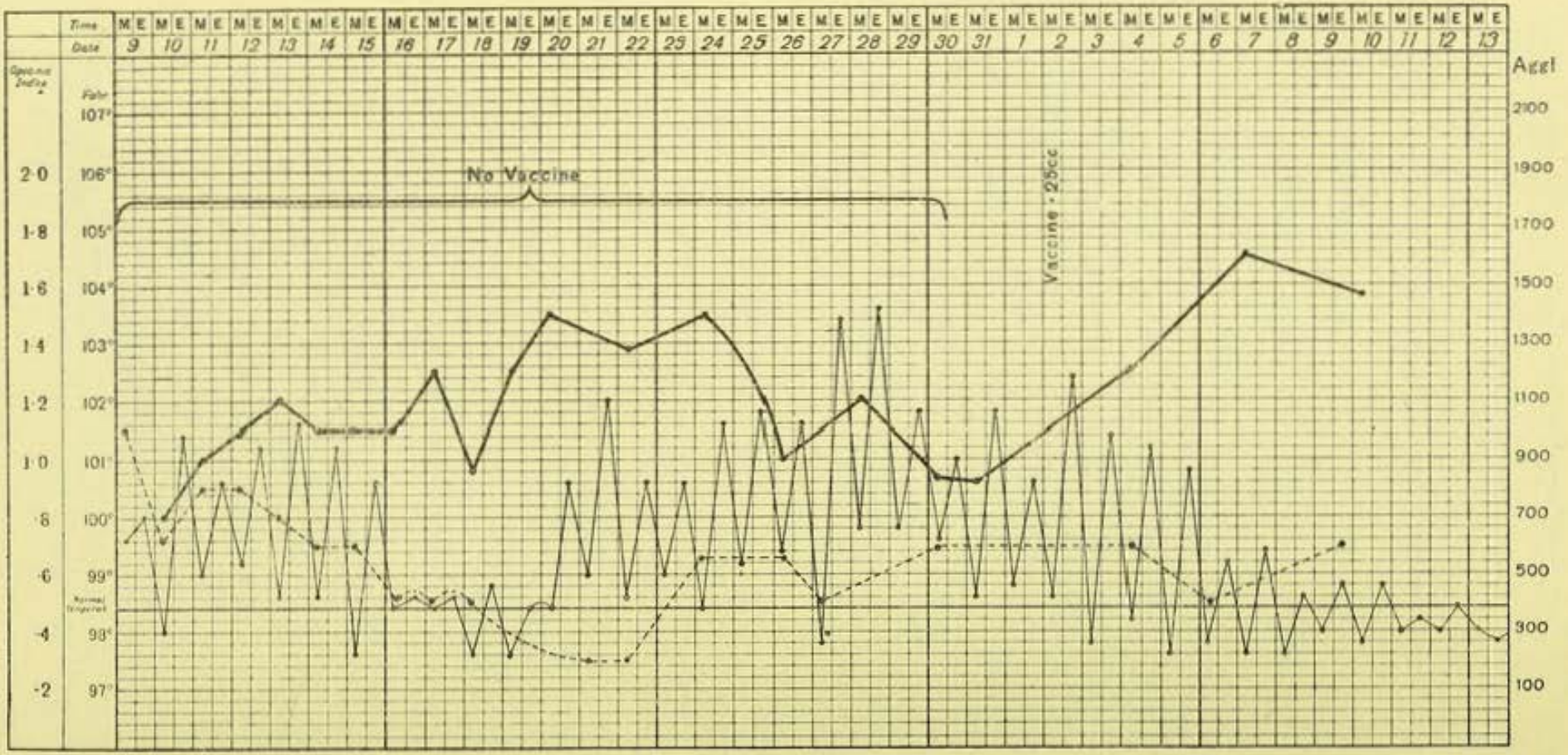
No Vaccine
Vaccine - 25cc
Agglutination Index
Fahr
Normal Temperature
Agglutination

CHART 6.

high fever one was not able to notice any benefit whatever either on the clinical symptoms or on the temperature records (charts 20, 21, 22, 23), but in slight undulatory relapses or with chronic intermittent types frequently the fall to normal seemed to be accelerated.

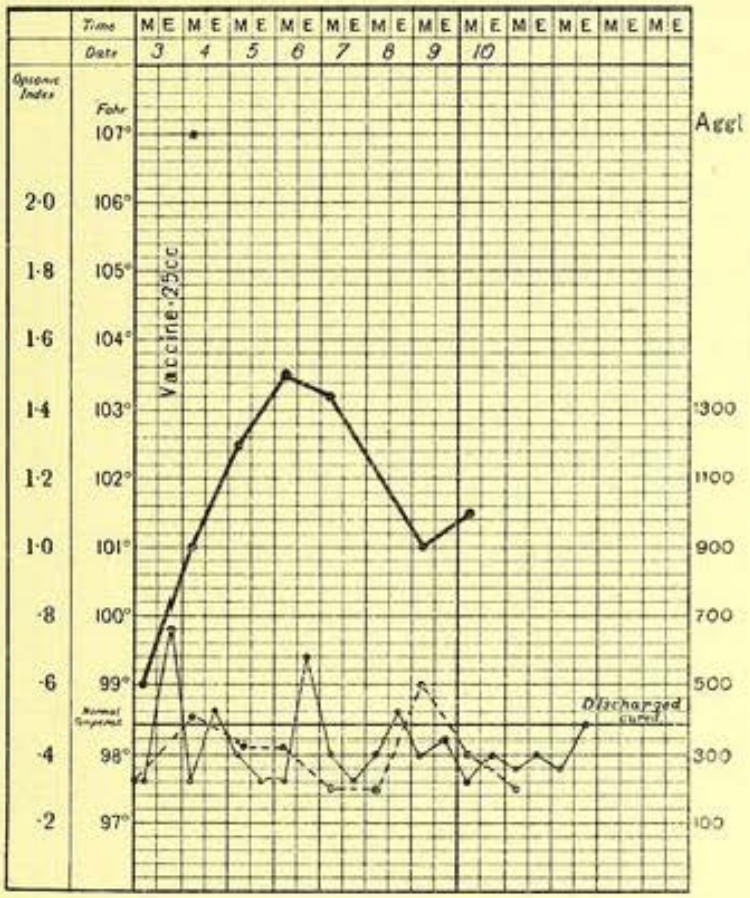

CHART 4.

Prevention of Relapses.—The prevention of relapses is perhaps the greatest desire of any one treating this trying disease. In the administration of vaccines we seemed to have a possible means of doing so. At the commencement of this investigation some very successful cases led me to think that at last there was a reliable method, but further experience has proved this hope to be without foundation, for over and over again cases under treatment, when appearing to be doing favourably, have suddenly developed another

wave of pyrexia, not differing from those which we have been accustomed to meet in cases otherwise treated.

Relief of Pain.—In the more chronic cases, with the secondary nerve and arthritic pains so frequently met with, the vaccines appeared to produce at least temporary improvement in some instances.

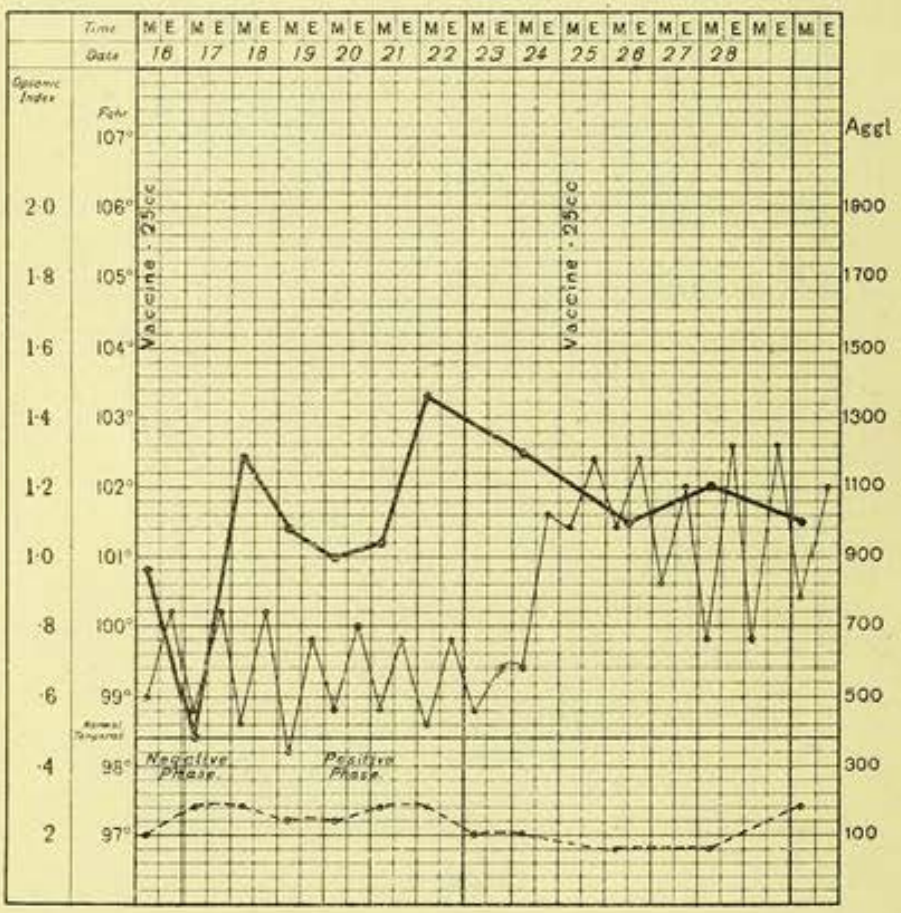

CHART 2.

Gain in Weight.—The gain in weight during this treatment was often remarkable, but, as pointed out before, during convalescence a rapid increase in body weight usually occurs under any form of treatment.

Feeling of Well-being after the Injections.—In a few cases the patient expressed himself as feeling brighter and stronger after the vaccine. This was particularly marked in the case of the man from

whom the vaccine had been withheld for some weeks (case 6).

Epitome of Cases.

(1, chart 1.) Undulant type of fever; temperature falling. First vaccine given about the fourteenth week. The opsonins rose, falling again in three days, but again rose to a higher level. The agglutinins curve followed that of the opsonins. There was no relapse and he went to duty.

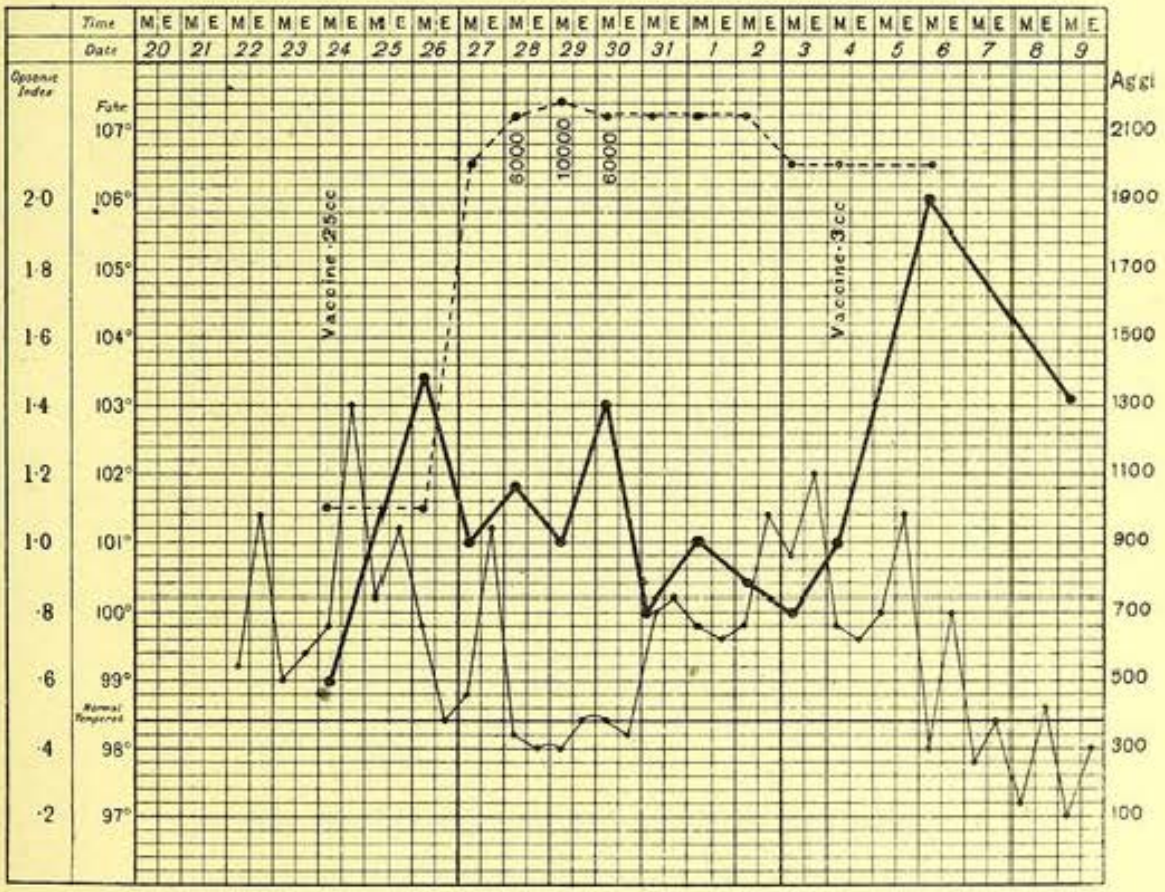

Chart 3.

(2, chart 2.) Undulant type of fever, great anæmia and emaciation. After the first dose of vaccine the temperature fell slightly, but in nine days a relapse set in. The first vaccine was followed by a short negative phase, and a very poorly marked positive one; there was no rise after the second dose, which

was given in the hope of cutting short the relapse. The agglutinins were constantly low.

(3, chart 3.) Irregular undulant type of fever, complicated with syphilis. After the first injection a slight positive phase occurred, lasting about a week, with a fall in the temperature. After the second injection there was good response, and the temperature again fell. The agglutinins rose to a great height—1 in 10,000.

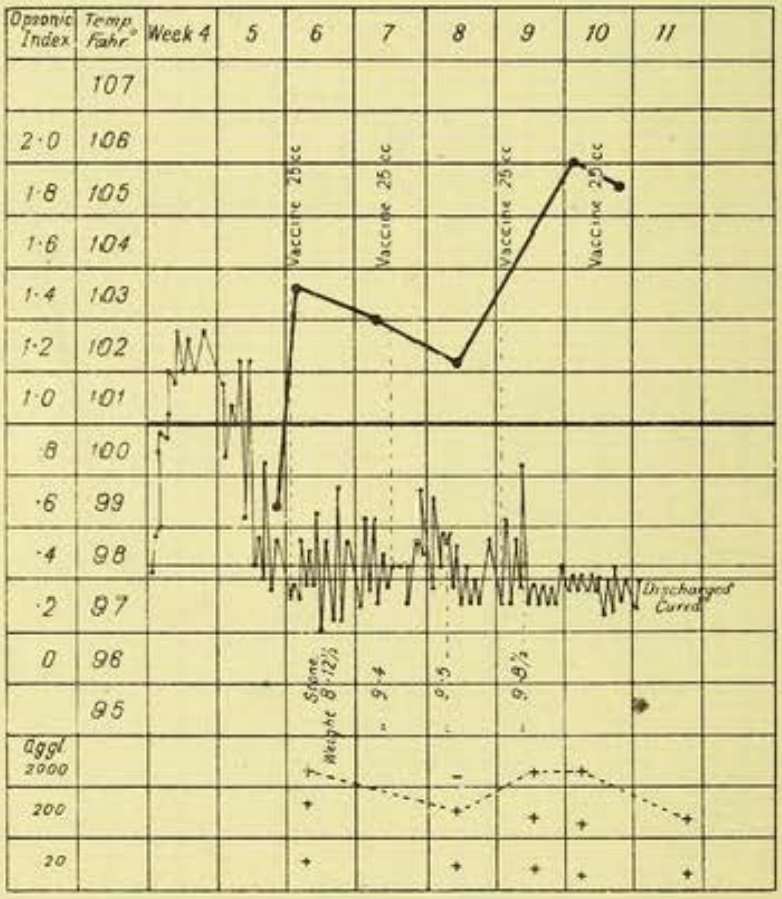

CHART 7.

(4, chart 4.) Relapsing very chronic case. Irregular rise in the opsonins, reaching its maximum on the tenth day, falling after the second dose. The agglutinins were very low. There was no improvement in his general condition and he was invalided out of the Service.

(5, chart 5.) The end of the third month of the

fever, see-saw type of temperature with considerable anæmia and debilty. Vaccines were commenced at once; opsonins rose at once, remaining up for a week, then fell; after the second injection the reaction was less, but after the third the rise was much more marked; his temperature fell and he was discharged. The agglutinins were high throughout, for ten days varying from 1 in 4 to 8,000, when they suddenly fell to 1 in 2,000, and remained at that level (this was unusual so late in the course of the disease).

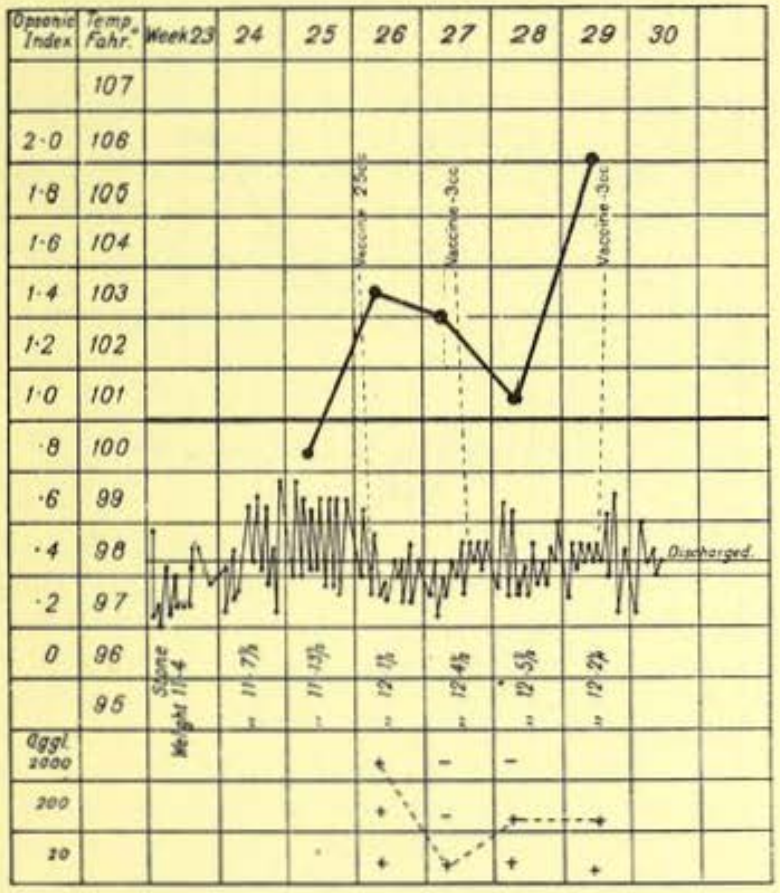

CHART 8.

(6, chart 6.) Undulant type of fever at the end of the third month, with orchitis. For twenty days he was treated without vaccines, the daily opsonic and agglutinin reactions being taken for the purpose of showing the variations produced by the disease alone, which are seen to be considerable. After the first

dose of vaccine the opsonic index rose to a greater height than previously, and the temperature fell, the patient being discharged fourteen days after feeling well.

(7, chart 7.) Undulant type of fever. Vaccine commenced in the sixth week; he had marked purpuric eruption on the lower limbs. Four doses were

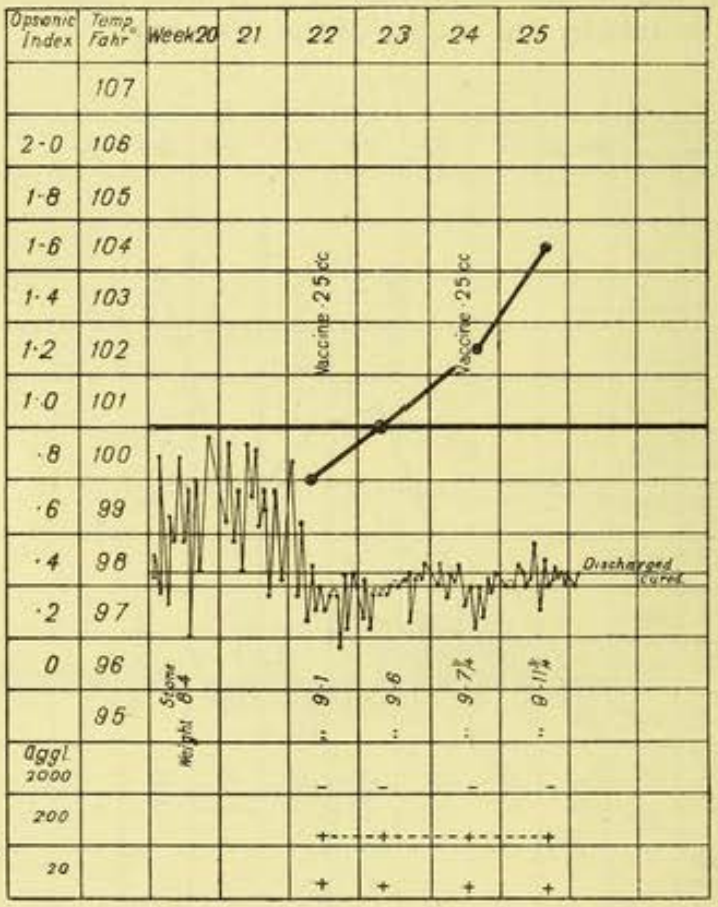

CHART 10.

given; his opsonins rose very high, and the temperature fell; the agglutinins were moderately high. He steadily gained weight and was discharged.

(8, chart 8.) Slight irregular fever, neuritis and effusion into the left knee. Vaccine commenced in twenty-sixth week; the opsonins rose high and the temperature fell; he gained in weight and his general condition improved markedly.

(9, charts 9 and 3.) Undulant type of fever, with secondary syphilis. Vaccine was commenced in the tenth week; both opsonins and agglutinins were high and he made a good recovery.

(10, chart 10.) Late undulant type with neuritis. Vaccines were commenced in the twenty-second week; there was no further rise of temperature, and the opsonins steadily rose.

(11, chart 11.) A late relapse after being apparently one year free from fever. Vaccine was commenced in the third week of the relapse. There was very slight rise in the temperature after; the pains decreased, and there was a gain in weight. The opsonins and agglutinins did not vary much.

(12, chart 12.) A mild case with a low irregular fever chart. Vaccines commenced in the ninth week. His opsonins were at first very high, then very variable; the general condition improved; he gained 1 st. in weight, and the agglutinins went up.

(13, chart 13.) Undulant type of fever, not severe. Vaccine commenced in the third week, six injections were given. The pyrexial waves were very short, and he was discharged at the end of the thirteenth week, having gained 1 st. in weight. The opsonins were generally above normal, the agglutinins very variable.

(14, chart 14.) Undulant type of fever. Vaccines were commenced in the twelfth week. The opsonins rose at once; after the second injection the temperature fell and there was no further fever; he gained 2 st. in weight, but had to be invalided for pre-existing heart disease.

(15, chart 15.) Slight irregular fever following high early waves. Vaccine was commenced in the ninth week. The opsonins went up and the temperature remained down; his weight increased and he made a good recovery. The agglutinins were very high.

(16, chart 16.) Mild undulant type of fever. Vaccines were commenced in the ninth week. The temperature remained slightly irregular. His opsonins and weight went up, but the agglutinins kept very low. There was some anæmia and œdema of the legs when he was discharged.

(17, chart 17.) Undulant type of fever of long duration. The vaccine was commenced in the nine-

teenth week; after the second dose he commenced to improve and rapidly gained weight in spite of two slight relapses; he made a good recovery.

(18, chart 18.) Prolonged undulant type. Vaccine commenced in the twelfth week; after each injection the temperature rose markedly, on one occasion to 103·6°; there was only a slight gain in weight, but he steadily gained strength and looked better, being discharged quite well.

(19, chart 19.) Very irregular fever with emaciation and depression when admitted. Vaccine was commenced in the eleventh week; following the second injection he had a three-week wave of fever, when the vaccine was stopped, but continued later. His opsonins, agglutinins and weight all went up, and he made a good recovery.

(20, chart 20.) A very prolonged and severe type of fever, at first intermittent, then undulant, with great depression, &c. Vaccines were commenced in the fifteenth week, his opsonic index fell, and after the third injection a severe relapse set in; he had two further relapses, and in the thirtieth week, being considerably improved, was sent out. The three injections did not appear to do good, though the opsonic curve was maintained at a high level. A further relapse occurred after leaving the hospital.

(21, chart 21.) A very severe undulant type of fever. The first vaccine was given in the eighth week during an acute relapse; no improvement. Second and third doses were given in the interval, but acute relapses followed for a period of twelve weeks. Two other doses were given between the waves, when the morning temperature was normal, without effect. The opsonic index remained above normal, both during the administration of the vaccines and after. The agglutinins were very high almost the whole time. After twenty-eight weeks of treatment he went out, feeling almost well.

(22, chart 22.) Severe continued type of fever, passing into the undulant form. The first vaccines were given in the twelfth week. The opsonic index at first rose, but rapidly fell; vaccine stopped. After the next relapse three injections were given, there being a normal morning temperature, followed by a

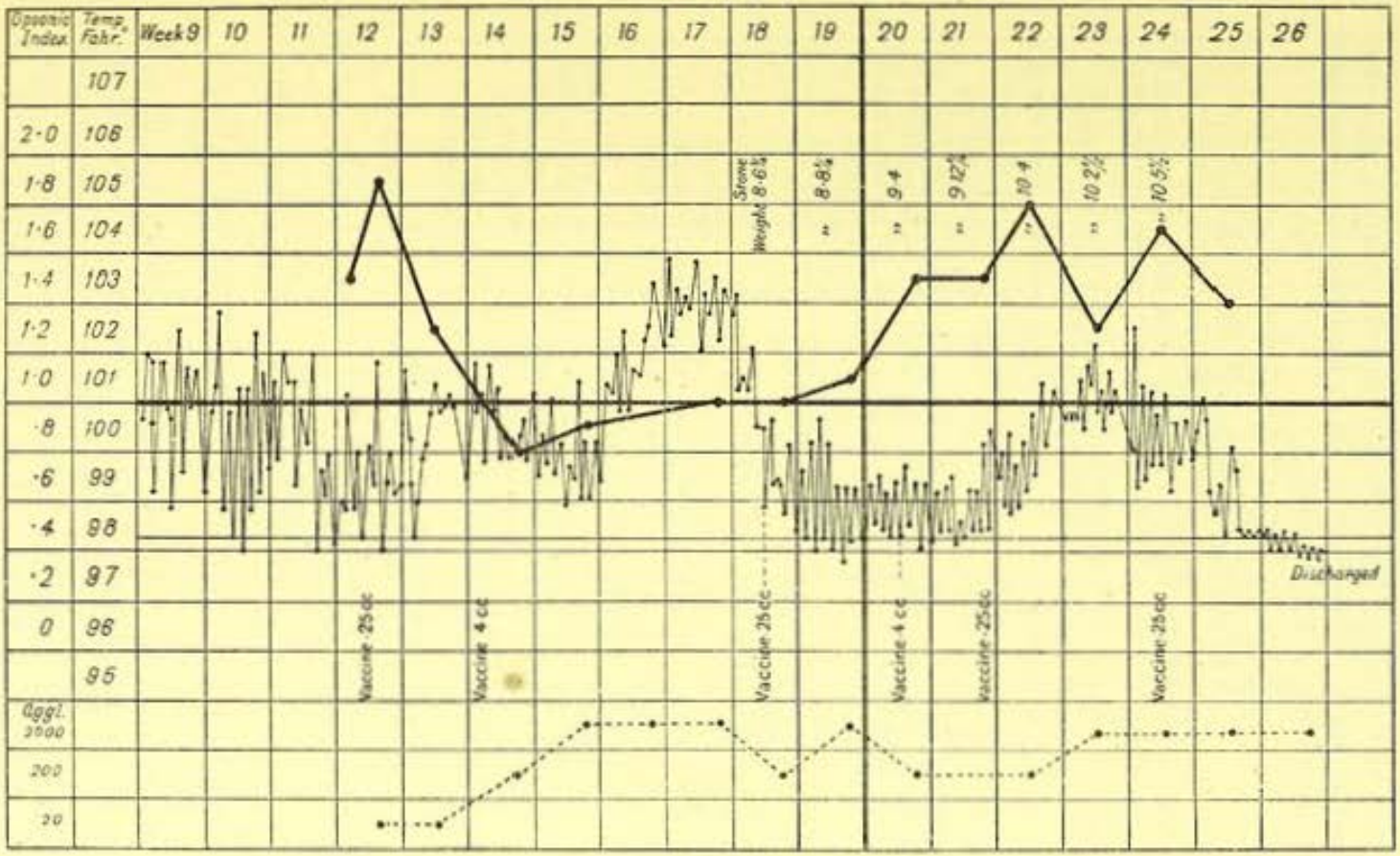
Opsonic Index
Temp. Fahr.
Week 9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
107
106
105
104
103
102
101
100
99
98
97
96
95
2·0
1·8
1·6
1·4
1·2
1·0
·8
·6
·4
·2
0
Aggl. 2000
200
20
Stone Weight 8·6½
" 8·8½
" 9·4
" 9·12½
" 10·4
" 10·2½
" 10·5½
Vaccine 25 cc
Vaccine 4 cc
Vaccine 25 cc
Vaccine 4 cc
Vaccine 25 cc
Vaccine 25 cc
Discharged

CHART 22.

further wave of pyrexia, in spite of a high opsonic index. He, however, gained 2 st. in weight, and felt much stronger during this four-week relapse, and was discharged to sick leave. His agglutinins rose, and remained high, 1 in 2,000.

Vaccine Record. Series II.

Table of Cases.

0·25 cc. equals 468,750,000 mm., or 0·05 milligram dried.

No. of Chart	Name	Amounts injected in cubic centimetres	No. of injections	Results
1	C.	·23	1	Good
*2	S.	·25, ·25	2	Negative
*3, 9	F. C.	·25, ·25, ·25, ·3 ..	4	Good
*4, 25	Q.	·3, ·3, ·3, ·3, ·3 ..	5	Negative
*5	B.	·25, ·3, ·35	3	Favourable
*6	H.	·25, ·3	2	Good
*7	B. C.	·25, ·25, ·25, ·25 ..	4	Good
*8	G. G.	·25, ·3, ·3	3	Good
*10	T. B.	·25, ·25	2	Good
11	F. M. W.	·25, ·25, ·1, ·4 ..	4	Good
12	G. F.	·25, ·25, ·25 ..	3	Good
13	F. H.	·25, ·25, ·25, ·3, ·35	5	Good
14	W. H.	·25, ·25, ·25, ·3, ·25	5	Good
15	J. I.	·25, ·25	2	Good
16	J. P.	·25	1	Favourable
17	E. J.	·25, ·25, ·25, ·3, ·3	5	Favourable
18	T. D.	·25, ·25, ·25, ·25, †·3	6	Favourable
19	G. B.	·25, ·25, ·3, ·25, ·3	5	Negative
20	W. M.	·25, ·3, ·25 ..	3	Negative
21	M.	·25, ·25, ·3, ·25, ·25	5	Negative
*22	V. H.	·25, ·4, ·25, ·4, ·25, ·25	6	Negative
*23	G.	·2, ·4. ·25, ·25, ·2, ·2, ·25	7	Negative
24	C.	·25, ·2, ·25, ·3, ·2, ·2, ·25, ·25 ..	8	Favourable

* These charts only inserted. † Temperature rose to 103·6°.

(23, chart 23.) Severe case with a high continued type of fever, followed by slight undulations. Vaccines were commenced in the eighth week, and were repeated for six weeks without appearing to do good; they were therefore stopped, but two further doses were given in the twenty-fourth and twenty-fifth weeks. This patient improved and was able to go out in the twenty-ninth week. The opsonic index, which had

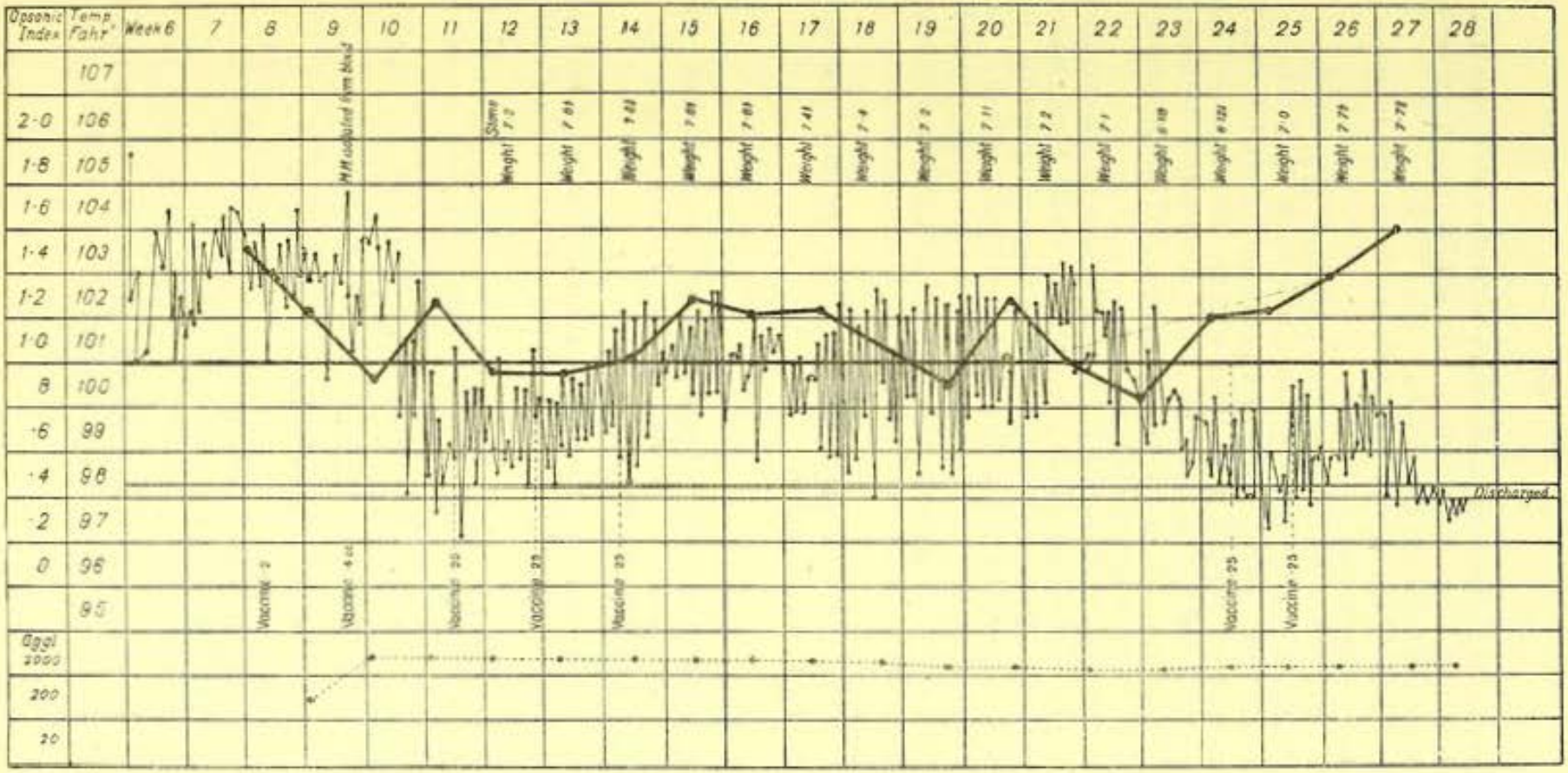
Opsonic Index
Temp. Fahr°
Week 6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
107
106
105
104
103
102
101
100
99
98
97
96
95
2·0
1·8
1·6
1·4
1·2
1·0
·8
·6
·4
·2
0
Oggi
2000
200
20
Discharged.

CHART 23.

remained about normal, rose considerably after the two last doses of vaccine. The agglutinins were very high throughout, 1 in 2,000.

The *M. melitensis* was isolated from the blood in the ninth week.

(24, chart 24.) Irregular undulant type of fever. Vaccine commenced in the ninth week; eight injections being given. The temperature slowly fell, each attack of pyrexia becoming shorter and milder; he gained 3 st. in weight, and was discharged to duty. The opsonins remained about normal. The agglutinins rose high in convalescence.

(25, charts 25 and 4.) A relapse of a long undulant type, readmitted in the fourteenth week, fever intermittent, pains severe. Vaccines were commenced in the sixteenth week, five injections being given; no improvement was noted, either of symptoms or weight. The opsonins responded fairly well, but the agglutinins remained persistently very low. The case was finally invalided.

Thus, out of twenty-three cases, marked improvement was noted in sixteen.

Experiments to Demonstrate the Amount of Sensitising Substance in Heated and Unheated Serum.

The serum was heated to a temperature of 60° for a quarter of an hour, then added to my washed cells and emulsion.

(1) *Acute Mediterranean fever case.*		Average cocci ingested	Index
Unheated serum	1 part		
My washed blood cells	,,	11	1·2
Emulsion	,,		
My heated serum	,,		
My washed blood cells	,,		
Emulsion	,,	9	1·0
My unheated serum	,,		
My washed blood cells	,,		
Emulsion	,,	9	1·0

The heated serum of the patient still contained substances favourable to phagocytosis "stimulins."

			Average cocci ingested	Index
(2)	*Chronic Mediterranean fever case.*			
	Unheated serum	1 part		
	Washed blood cells	,,		
	Emulsion	,,	7 ·	1·2
	Heated serum	,,		
	Washed blood cells	,,		
	Emulsion	,,	2·5	0·41
	My unheated serum	,,		
	My washed blood cells	,,		
	Emulsion	,,	6	1·0
(3)	*Chronic Mediterranean fever case.*			
	Unheated serum	1 part		
	Washed blood cells	,,		
	Emulsion	,,	10·2	0·94
	Heated serum	,,		
	Washed blood cells	,,		
	Emulsion	,,	2·8	0·16
	My unheated serum	,,		
	My washed blood cells	,,		
	Emulsion	,,	10·8	1·0
(4)	*Chronic Mediterranean fever case.*			
	Unheated serum	1 part		
	Washed blood cells	,,		
	Emulsion	,,	7·2	1·2
	Heated serum	,,		
	Washed blood cells	,,		
	Emulsion	,,	1·9	0·33
	My unheated serum	,,		
	My washed blood cells	,,		
	Emulsion	,,	5·7	1·0
(5)	*Healthy surgeon.*			
	Unheated serum	,,		
	Washed blood cells	,,		
	Emulsion	,,	13·6	1·04
	Heated serum	,,		
	Washed blood cells	,,		
	Emulsion	,,	3·0	0·23
	My unheated serum	,,		
	My washed blood cells	,,		
	Emulsion	,,	13·0	1·0
	My heated serum	,,		
	My washed blood cells	,,		
	Emulsion	,,	2·6	·2

In all these last, the sensitising substance was almost entirely destroyed by heat.

Experiment to demonstrate whether the removal of the serum, and replacing the contents with normal saline solution, would cause an equal diminution in the phagocytic action of the washed blood cells.

			Average cocci ingested	Index
(1)	My washed blood cells	1 part		
	Normal saline solution	,,		
	Emulsion	,,	5	·37
	My washed blood cells	,,		
	My unheated serum	,,		
	Emulsion	,,	13·5	1·0
(2)	My washed blood cells	,,		
	Normal saline solution	,,		
	Emulsion	,,	2·9	0·78
	My washed blood cells	,,		
	My unheated serum	,,		
	Emulsion	,,	3·7	1·0
(3)	My washed blood cells	,,		
	Normal saline solution	,,		
	Emulsion	,,	2·2	0·5
	My washed blood cells	,,		
	My unheated serum	,,		
	Emulsion	,,	4·0	1·0
(4)	My washed blood cells	,,		
	Normal saline solution	,,		
	Emulsion	,,	7·0	·7
	My washed blood cells	,,		
	My unheated serum	,,		
	Emulsion	,,	10·0	1·0

These seemed to show that moderate phagocytosis still occurred after removal of all the sensitising substances with the serum.

These experiments demonstrate that though sensitising thermolabile substances for *M. melitensis* are found in the serum in varying quantities, yet, when these have been removed by heat or replacing the content with normal saline solution, the cells themselves still contain or produce a quantity of stimulins, which assist phagocytosis, as shown by Metschnikoff, who states "that the absorption of the microbes may be effected without the help of opsonins, or that—should such help be indispensable—the opsonins may be supplied by the leucocytes themselves.

General Conclusions arrived at from a Study of the Total Cases Treated.

In dealing with a systemic infective disease like Mediterranean fever, the addition of further quantities of artificially produced toxin to a patient in acute phases of the fever not only appears to me to hold out little likelihood of acting beneficially, but would act detrimentally (*vide* charts 20, 21, 22, 23). On the other hand, in chronic conditions, where one has only slight relapses or a mild see-saw temperature without marked hectic symptoms, then a slight addition of the toxic product just adds that quantum of stimulation which places the patient in a more favourable condition for combating the infective organism present in small quantities.

It is to these latter cases that I now restrict its administration, and if, after the injections, one finds a rising index, there is *bonâ fide* reasonability in continuing the dosage with advantage to the patient.