

Memorandum by the Director-General, Army Medical Service, on the transmission of enteric fever by the "chronic carrier" / Army.

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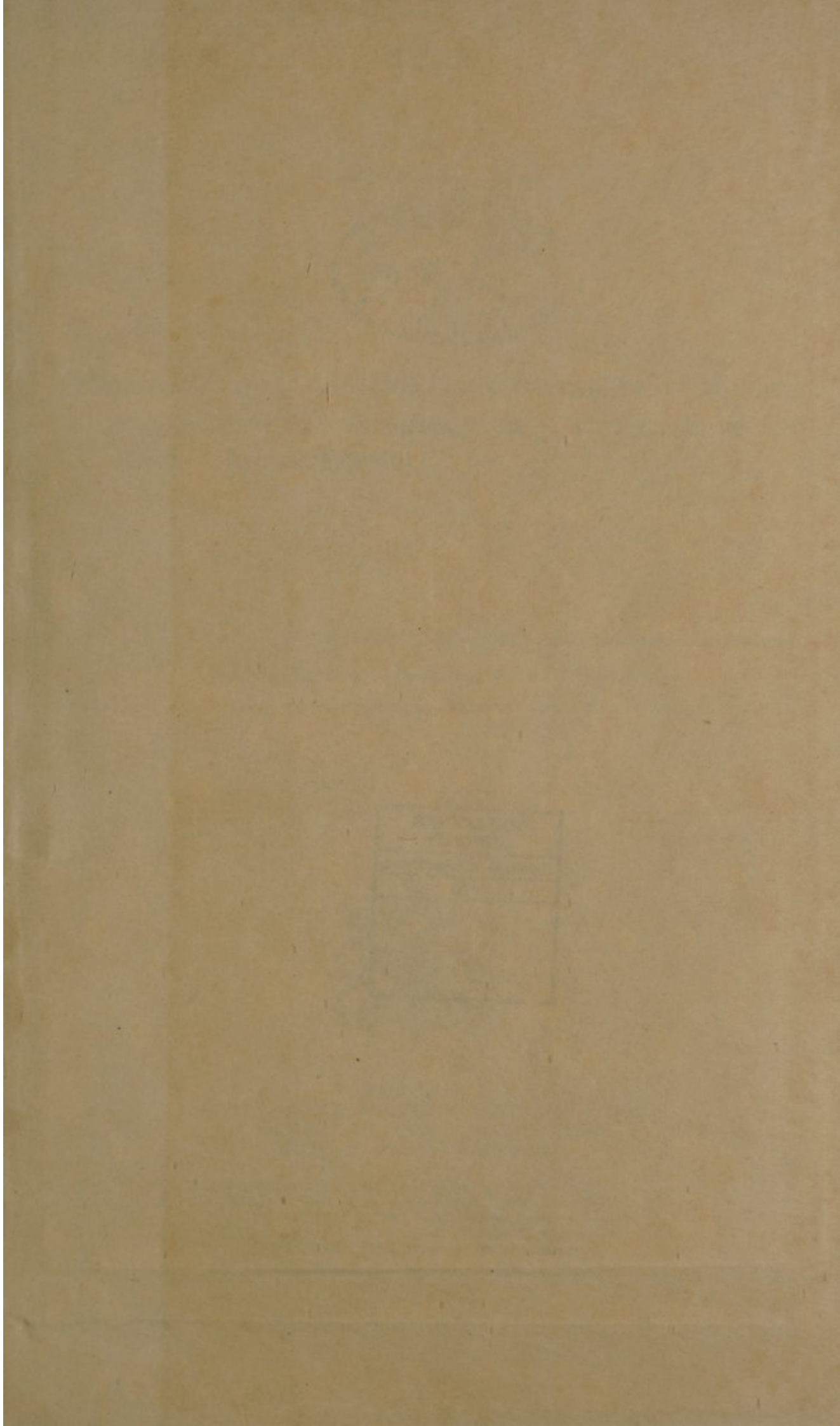
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The Transmission of Enteric Fever by the



Memorandum by the Director-General, Army Medical Service, on the Transmission of Enteric Fever by the "Chronic Carrier."

Presented to both Houses of Parliament by Command of His Majesty.



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1909.

The Transmission of Enteric Fever by the "Chronic Carrier."

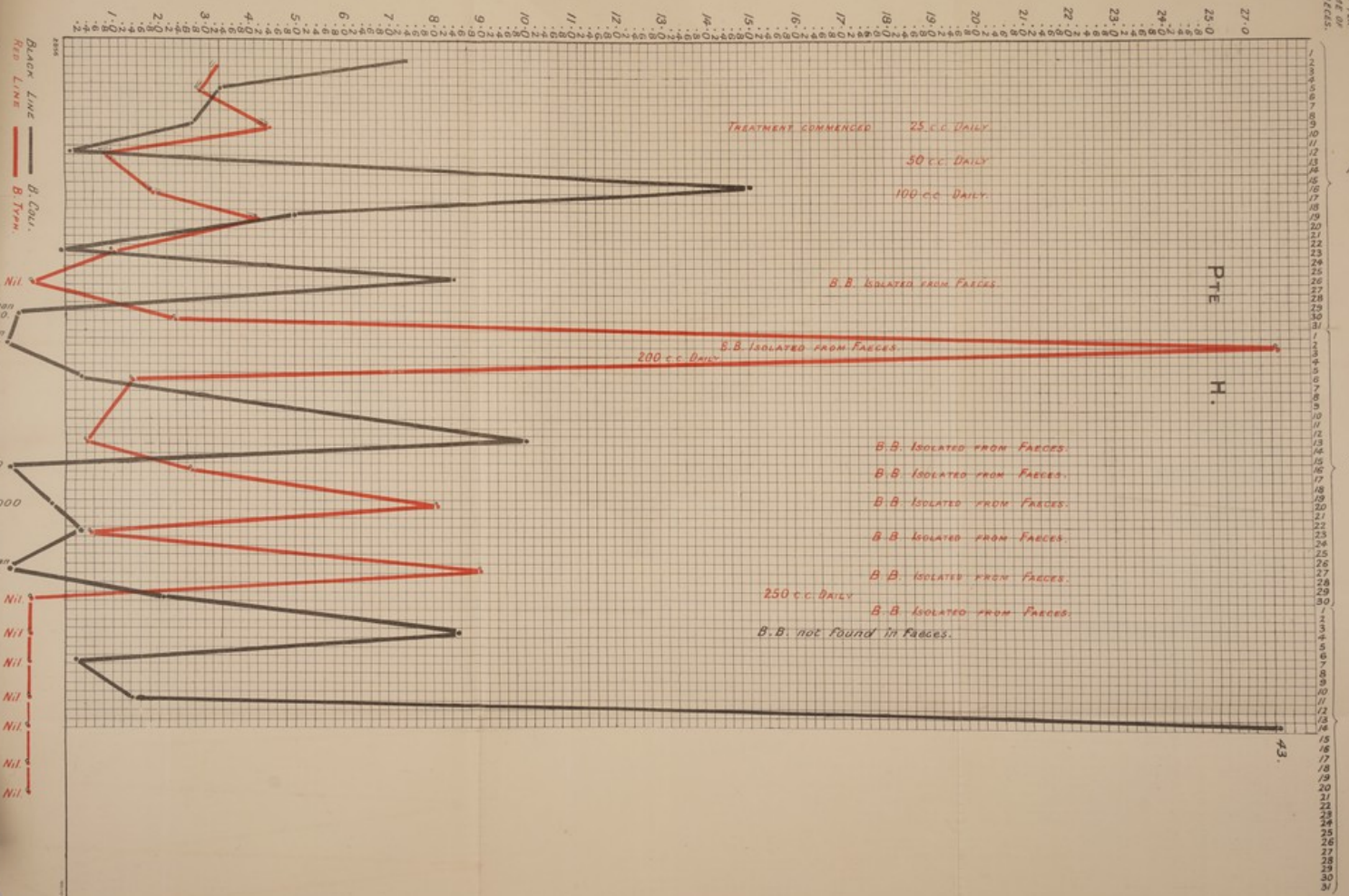
I.—INTRODUCTION.

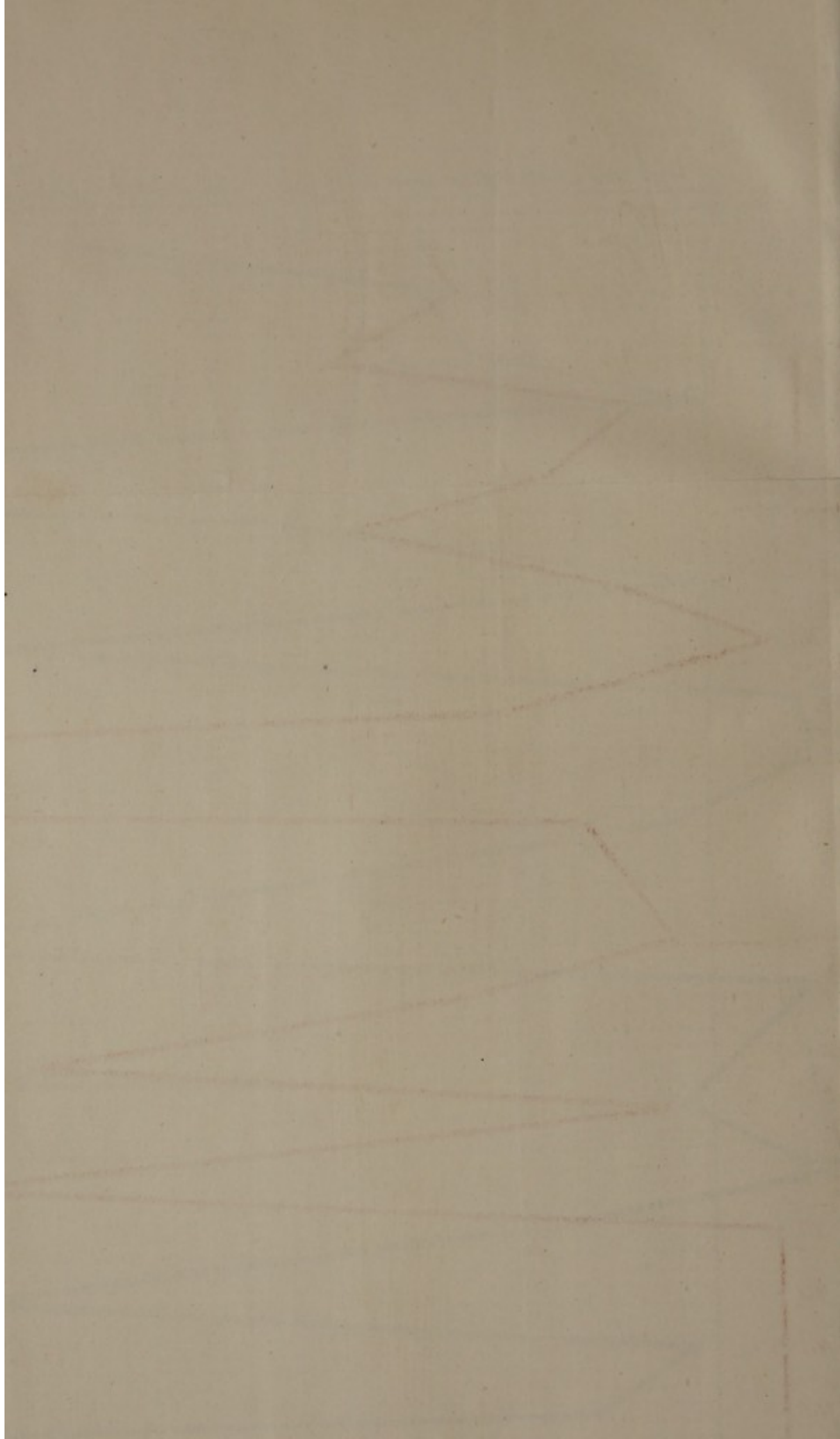
For many years the causes of epidemics of enteric fever were supposed to be either (1) infection by water, (2) infection by food, or (3) infection by contact. Infection by water or food produces a morbidity curve characterized by a sudden rise, the sharper and more elevated according as the pollution has been more abundant. When, however, infection depends on contact, the prevalence shows a curve only slightly elevated and often prolonged over many months. The importance of contact infection was not realized until Koch commenced his researches in 1901. Repeated outbreaks of enteric fever had occurred in Westphalia, and in some parts of the Rhine province the disease had become endemic. The German Government accordingly called upon Koch to conduct an enquiry and to advise as to the measures to be taken to combat the disease.

Experiments having shown that the life of the typhoid bacillus outside the human body is comparatively short—probably not more than one month in water and two months in soil—Koch came to the conclusion that the human body, either suffering from enteric fever or convalescent from it, is the starting point of all typhoid infection, and pointed out the necessity of preventing contact infection, in other words, of searching for and isolating the human host of the bacillus. Frosch, Donitz and others, working in south-west Germany, proved the danger due to contact infection. They were puzzled, however, by the constant occurrence of enteric fever in a house, the so-called "typhoid house," which had hitherto been free from infection. In explanation of this occurrence Frosch suggested the possibility of a prolonged or indefinite excretion by a convalescent patient, but it was left to Conradi, Kayser and their collaborators to demonstrate the existence of the chronic "typhoid carrier." Kayser collected 101 cases of cured typhoid fever cases declared to be free from typhoid bacilli, and yet at a period of two years after convalescence three cases were found to be still harbouring the bacillus, and were therefore chronic carriers. More recent work has confirmed these observations, and it may be taken as established that about 3 to 4 per cent. of convalescents from enteric fever become chronic carriers, and that in the neighbourhood of enteric cases a small percentage of the community may be temporary harbourers of the bacillus. It has also been noted that chronic carriers excrete the typhoid bacillus in an intermittent fashion, and in certain cases several months of intermission have been observed.

The results of the German investigations have been received with great interest everywhere, and especially in India, where in spite of the provision of a pure water supply, enteric fever has remained endemic in many stations. In 1906 the Government of India appointed a committee to investigate the channels by which enteric fever is propagated. In 1907 the committee stated "it has been proved that a proportion of those who have suffered from enteric fever, either in a form recognized as such or so slightly as to escape recognition, and of those who have been in close contact with them, harbour and excrete typhoid bacilli for considerable periods while showing no symptoms of illness." They recommended that "accommodation should be provided in the hills for isolating convalescents from enteric fever away from other troops. The places selected for this purpose must have at their command bacteriological laboratories where cultivations from the excreta can be made daily, to determine when the individuals are free from infection." Naini Tal Depôt was reserved for convalescents from enteric fever, and during 1908 several chronic carriers were detected and subsequently invalidated to England.

In France the question of the bacillus carrier has been carefully studied, and it is now ordered: (1) That typhoid fever cases shall be kept in hospital until a bacteriological examination of the stools and urine has shown that the *B. typhosus* is absent from these excreta; and (2) that every soldier returning to his corps from leave after convalescence from enteric fever shall be carefully examined with the object of ascertaining if he is still a carrier.





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BLACK LINE — B. GOLD
RED LINE — B. TYN

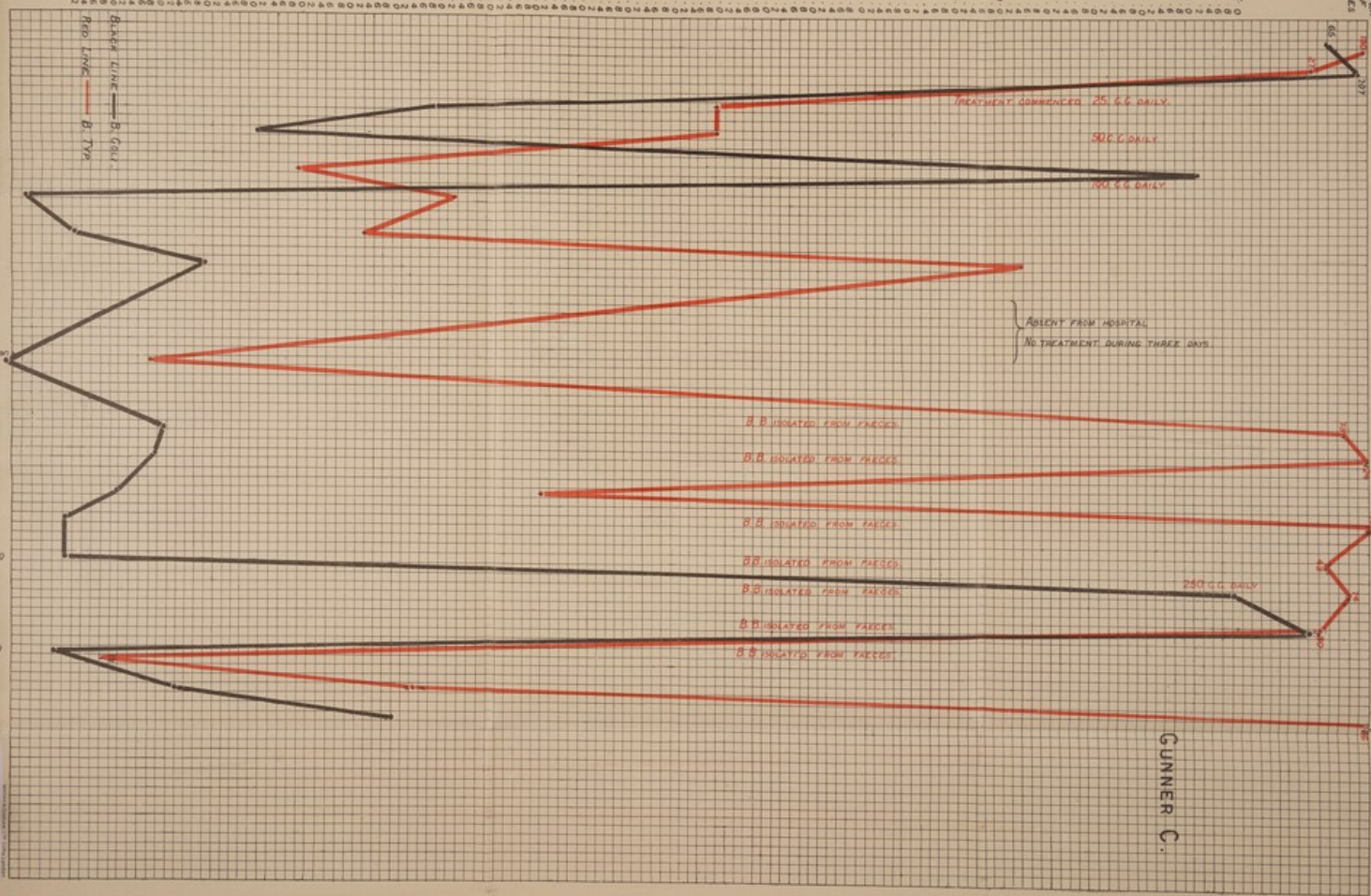
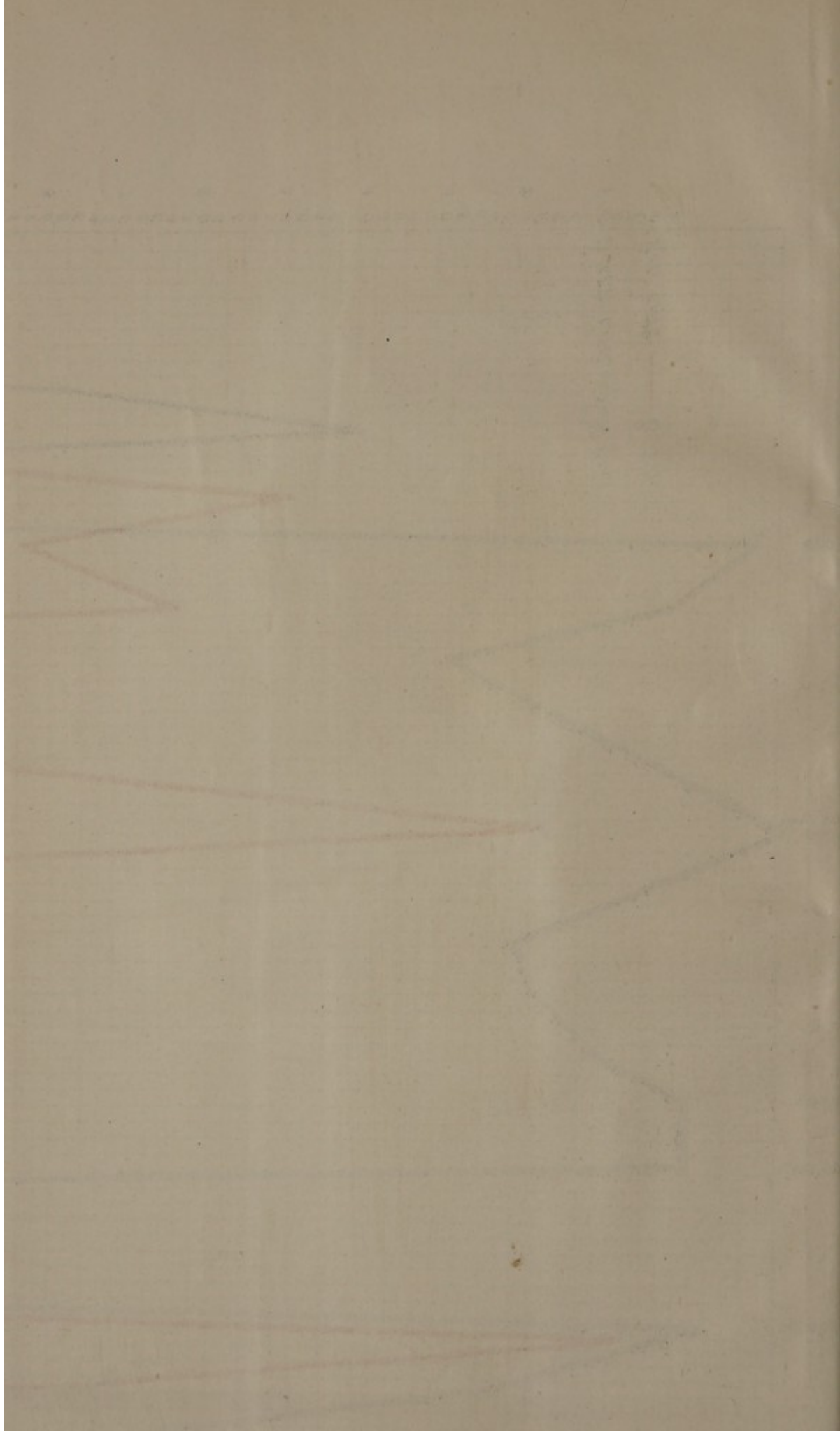
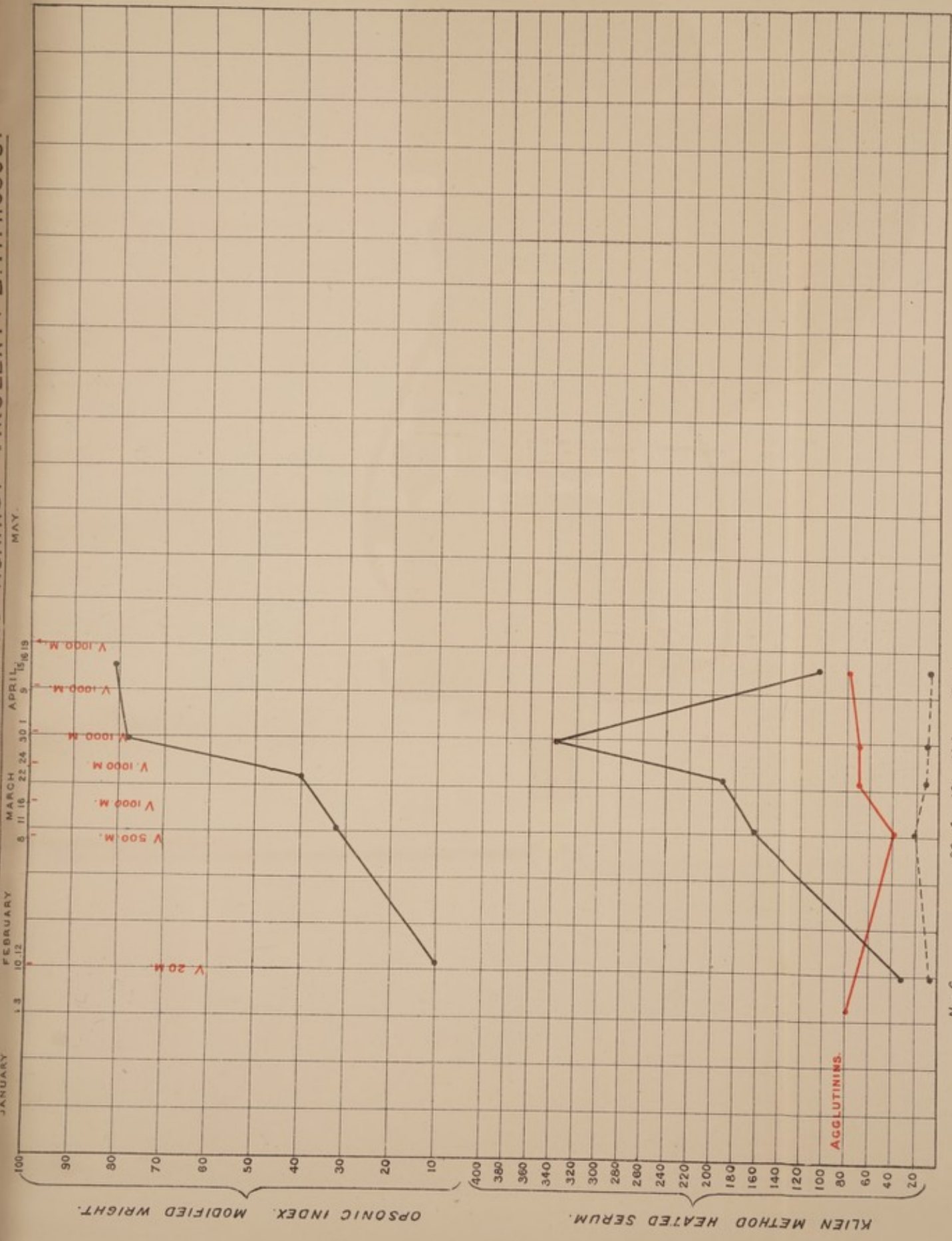


CHART 2.

GUNNER C.



OPSONIC AND AGGLUTININ AGAINST VIRULENT B. TYPHOSUS.



OPSONIC INDEX. MODIFIED WRIGHT.

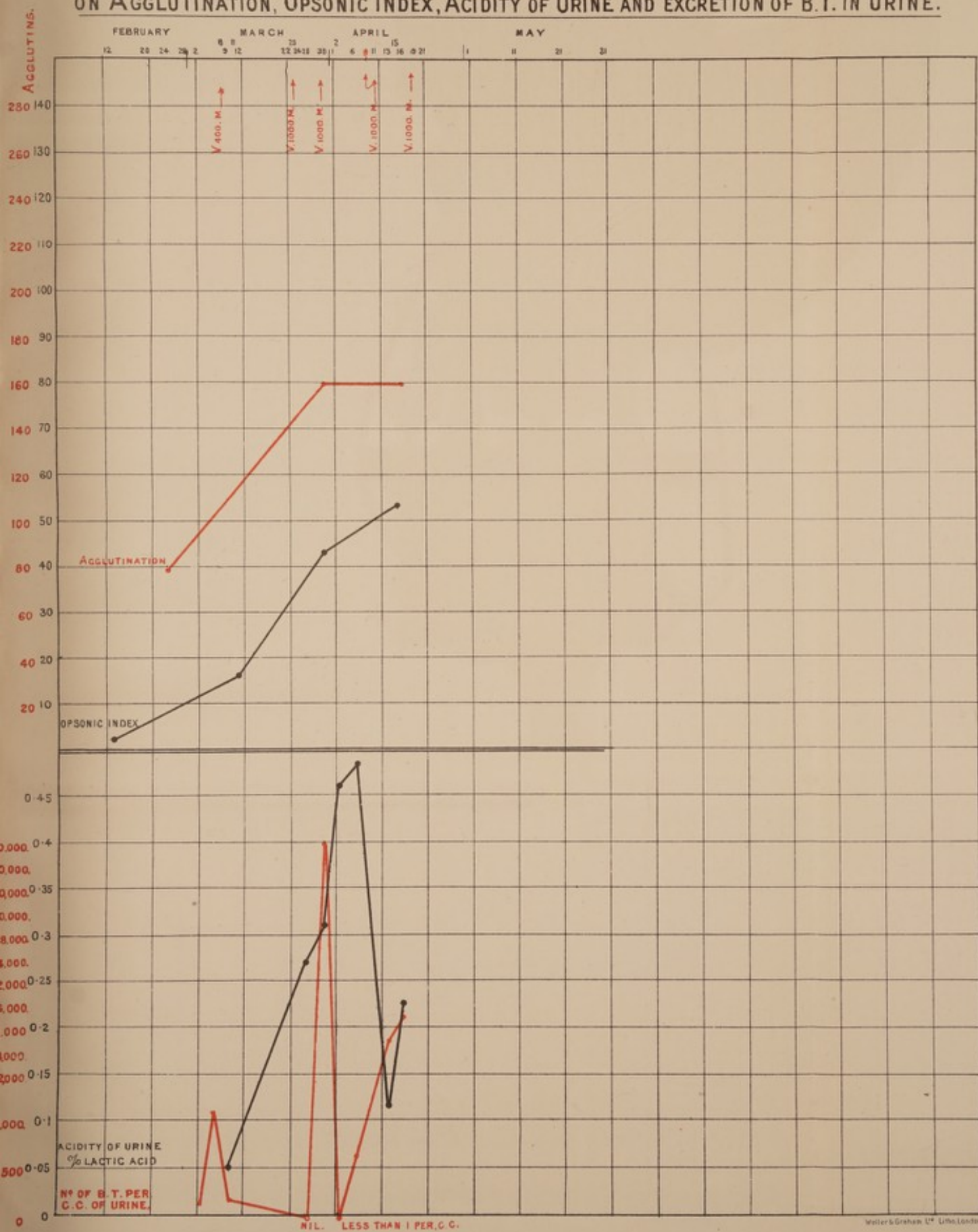
KLIEN METHOD HEATED SERUM.

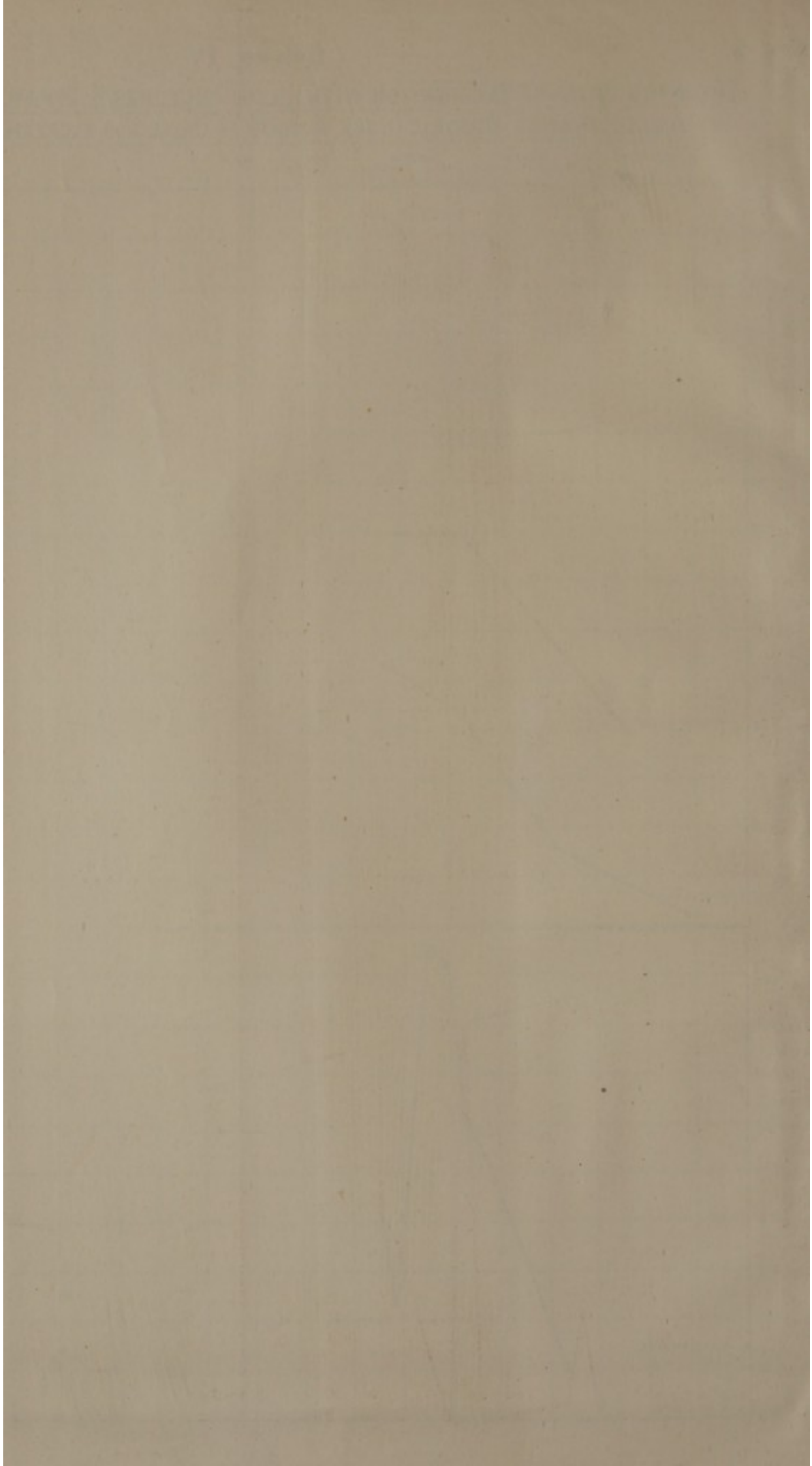
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CHART IV

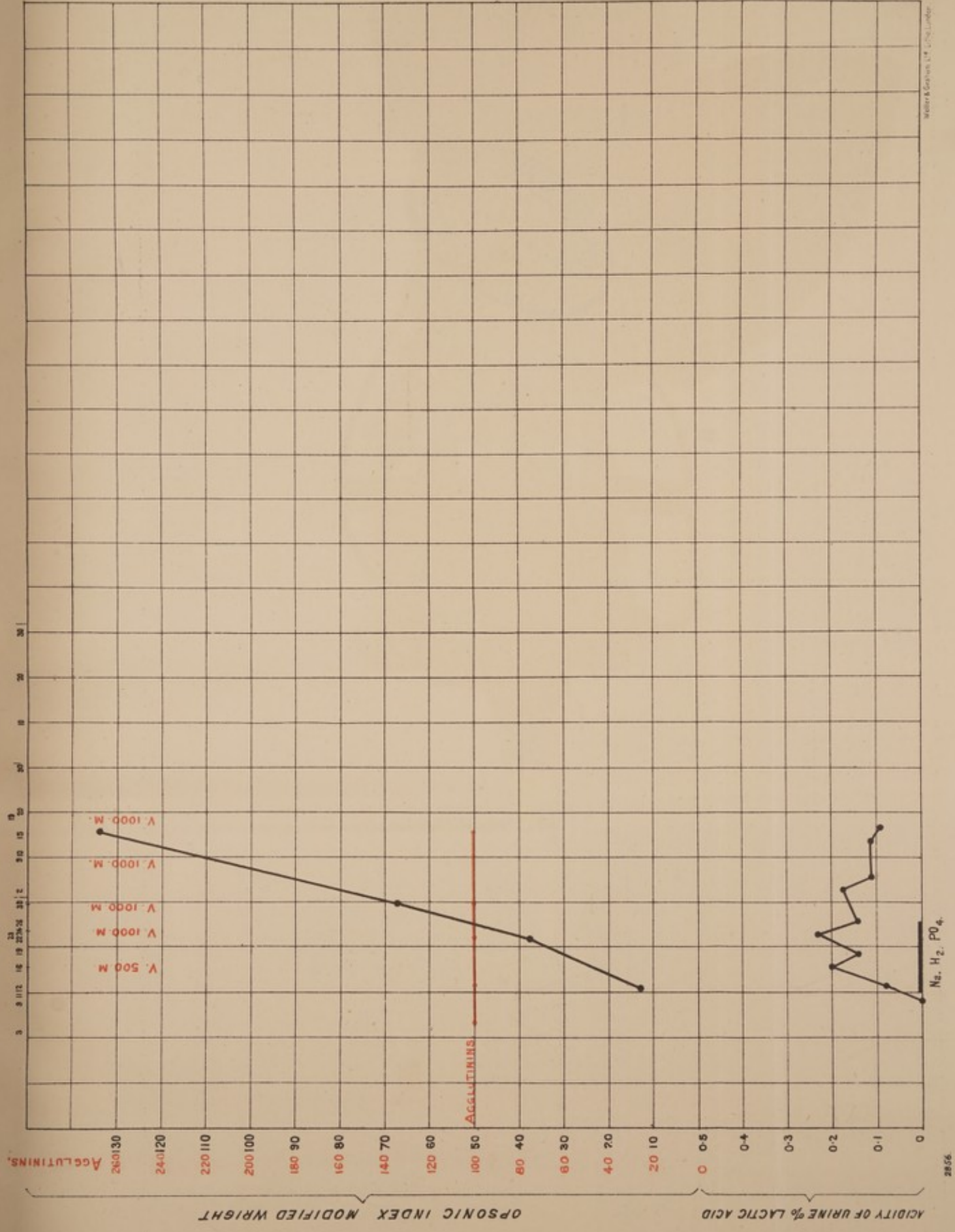
SHOWING DATES OF VACCINATION WITH KILLED CULTURES B. TYPHOSUS, AND THE EFFECT ON AGGLUTINATION, OPSONIC INDEX, ACIDITY OF URINE AND EXCRETION OF B.T. IN URINE.





OPSONINS AND AGGLUTININS AND ACIDITY OF URINE.
HEATED SERUM AGAINST B.T. VIRULENT.

Sgt. I.



Waters & Gwynne, Ltd., London



TABLE I.
RESULT OF EXAMINATION OF STOOLS FOR B. TYPHOSUS.

	JANUARY					FEBRUARY					MARCH					APRIL					MAY									
	13 TH	20 TH	27 TH	3 RD	11 TH	15 TH	19 TH	23 RD	26 TH	2 ND	5 TH	9 TH	12 TH	16 TH	19 TH	23 RD	26 TH	30 TH	6 TH	9 TH	13 TH	16 TH	20 TH	23 RD	27 TH	30 TH	4 TH	7 TH	11 TH	14 TH
FAECES	+	+	-	+	-	+	+	+	+	-	-	○	-	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-
L	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C	+	+	+	+	+	+	+	+	+	+	+	*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
H	-	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINES	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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+ = B. TYPH. FOUND
 - = B. TYPH. NOT FOUND
 * = TREATMENT WITH LACTIC ACID BACILLI COMMENCED
 ○ = VACCINE TREATMENT COMMENCED



Hitherto all attempts to render carriers typhoid-free by medicinal treatment have been unsuccessful. Salol and other intestinal antiseptics, also urotropine, have been tried, but the bacilli have not been found to disappear completely. Accordingly, the Army Medical Advisory Board deputed a sub-committee to investigate methods of treatment of typhoid carriers.

After a careful consideration of the cases invalided from India and of the case of Lance-Serjeant I., who had been responsible for the outbreak of several cases of enteric fever in his own regiment and of several cases in other units quartered with his regiment, the committee came to the conclusion that chronic carriers might be arranged in several groups:—

- Group (1) Pure intestinal cases. Bacilli excreted only in the faeces.
- „ (2) Urinary cases. Bacilli excreted only in the urine.
- „ (3) Intestinal cases with symptoms of inflammation of the gall bladder.
Bacilli excreted in the faeces, but obviously having a focus in the gall bladder.
- „ (4) Mixed intestinal and urinary cases. Bacilli excreted in both urine and faeces.

Group (1).

In the pure intestinal cases it was thought that it might be possible to disinfect the gastro-intestinal tract by the aid of lactic acid bacilli. Professor Elie Metchnikoff, of the Paris Pasteur Institute, and his pupil Cohendy, have recently directed attention to the remarkable therapeutical effects obtained by the use of certain lactic acid producing organisms administered in the form of curdled milk or in malt extract. The action of these lactic acid germs has been shown to be strongly inimical to the organisms of cholera, dysentery and infantile diarrhoea. The idea of treating typhoid carriers with lactic acid bacilli also occurred to Professor Drigalski, who, in conjunction with Professor Fraenkel, has carried out observations on two cases with apparently successful results.

The Advisory Board Sub-committee arranged that two carriers, Gunner C. and Private H., should be treated on these lines.

Groups (2), (3) and (4).

In cases where the typhoid bacillus has invaded the urinary tract it appears unlikely that the administration of lactic acid bacilli will prove beneficial, as when given by the mouth they do not appear to be excreted by the urinary passages.

Cases complicated by symptoms of inflammation of the gall bladder are also unfavourable for the lactic acid treatment. Recent work in Germany on this class of case has shown that the typhoid bacilli may gain access to the gall bladder in three ways: (1) by passage from the small intestine, (2) by passage from the liver by the hepatic duct, and (3) by direct passage from the capillaries of the gall bladder itself. It appears also that when the typhoid bacillus has invaded the gall bladder changes go on in its walls, which become thickened, covered with fringe-like processes, and lose their epithelial lining. The typhoid bacilli are found in the midst of necrotic areas in the thickened tissues; in course of time they are set free by the death of the altered tissues, and gaining access to the bile probably multiply there, as that fluid forms a favourable medium for their growth.

It is evident that though the lactic acid bacilli in the intestine might also reach the gall bladder, they would only prove effective against the bacilli floating in the bile. They could not be expected to influence the bacilli enclosed in the necrotic areas in the walls of the gall bladder. Under these circumstances the Germans have suggested that the gall bladder should be removed, and this has been done with success in certain cases. Such an operation should be performed only as a last resource, and the committee thought that before considering such an heroic procedure an attempt should be made to cure these cases by calling in the aid of the protective substances, which naturally exist in the human body and can be increased in amount by the injection of a suitable vaccine. It was accordingly decided to commence the treatment of cases in groups (2), (3) and (4) by injecting gradually increasing doses of anti-typhoid vaccine. At first the general vaccine, prepared in the Royal Army Medical College, was employed. This vaccine has proved a very effective prophylactic for enteric fever, and has also given encouraging results when employed for the treatment of the disease. But though the injection of the vaccine has increased the protective substances in the patients, the

excretion of typhoid bacilli has not been arrested. It appears that races of typhoid bacilli, probably in relation to their virulence, show marked variation in their resistance to the action of the protecting substances, and if the best results are to be obtained vaccines made from the infecting bacilli in each case must be employed. Instead of a general vaccine, specific vaccines are now being used, and it is hoped that through their agency the excretion of the typhoid bacilli may be completely arrested.

II.—DETAILS OF THE CARRIER CASES ADMITTED TO Q.A.M. HOSPITAL, MILLBANK.

Seven supposed typhoid carriers were sent to Millbank for treatment on the lines already indicated :—

- (1) Gunner C., R.A., age 22, service 3 years, acquired enteric fever in Meerut in March, 1908. He was sent to Naini Tal Depôt on the 25th of June, and was found to be excreting typhoid bacilli in his faeces. He was invalided to Netley, and transferred to Millbank on the 8th of January, 1909.
- (2) Private H., Bedford Regiment, age 22, service $3\frac{6}{12}$ years, acquired enteric fever at Jhansi on the 15th of May, 1907. He was transferred to Kasauli Sanatorium on the 14th of July, 1907, and to Naini Tal Depôt on the 10th of April, 1908. On the 23rd of December, 1908, he was admitted into Netley Hospital, and transferred to Millbank on the 18th of February, 1909. He was found to be excreting the typhoid bacillus in his faeces.
- (3) Bombardier S., R.A., age 25, suffered from enteric fever in India in May, 1908. He was sent from Netley to Millbank on the 5th of February, 1909, and was said to be excreting typhoid bacilli in his urine.
- (4) Private L., Bedford Regiment, age 22, acquired enteric fever in Jhansi on the 24th of April, 1907. He was sent to Kasauli on the 14th of July, 1907, and whilst there suffered from two severe attacks of inflammation of the gall bladder. He was transferred to Naini Tal Depôt on the 10th of March, 1908, and found to be excreting typhoid bacilli in the faeces. He was invalided to Netley, and admitted into Millbank on the 8th of January, 1909.
- (5) Lance-Serjeant I., East Kent Regiment, age 26, acquired enteric fever in Aden in 1904. In 1908 several cases of enteric fever occurred in the barracks at Aldershot occupied by the man's regiment. As the outbreak could not be explained by any of the usual causes, a careful examination was made of all the men living in the rooms where the cases had occurred, and Serjeant I. was found to be excreting the typhoid bacillus in his urine. He was isolated, and no further cases of enteric fever developed. Treatment by drugs was carried out, but no good results being obtained, the man was transferred to Millbank on the 2nd of March for further treatment.
- (6) Private O'N. suffered from enteric fever in India in May, 1908, and was transferred to Naini Tal Depôt. Here he was found to be a typhoid carrier, and was sent to Netley, being transferred to Millbank on the 6th of February, 1909. Since his admission to Millbank repeated examinations of his dejecta have been made, but the typhoid bacillus has never been recovered. He was discharged to duty on the 5th of April, 1909.
- (7) Private S. suffered from enteric fever in June, 1907. He was examined in Secunderabad in January, 1909, and said to be a "carrier." He was invalided to Netley, and transferred to Millbank on the 29th of March, 1909. Since his arrival in England repeated examinations of his dejecta have been made, but the typhoid bacillus has never isolated. He was discharged to duty on the 29th of March, 1909.

III.—DETAILS OF THE TREATMENT OF THE FIVE "CARRIER CASES" NOW IN MILLBANK HOSPITAL.

(a) *Treatment by cultures of lactic acid bacilli.*

The cases in group (1), Private H. and Gunner C., have been treated by this method. Before the treatment was commenced careful enumerations were made of the numbers of *B. coli* and *B. typhosus* in the stools. A pure culture of Metchnikoff's Bulgarian bacillus was isolated from Lacto-bacilline powder and then grown in a diluted extract of malt for 48 hours at 37° C. At first only 25 c.c. of the 48 hours' culture were given daily to each patient, later the amount was increased to 250 c.c. daily,

divided into three doses. Extract of malt, instead of milk, was selected for the medium, as one of the investigators found by personal experience, that the exhibition of considerable quantities of acid milk gave rise to some irritation of the stomach. The faeces were carefully examined from time to time so as to determine when the Bulgarian bacillus had become established in the alimentary canal.

Experiments were also carried out *in vitro* to determine after what period of growth of the lactic acid bacilli the toxins produced by them would destroy the typhoid bacillus. It was found that the toxins produced in 48 hours sufficed to destroy the strain of *B. typhosus* excreted by Private H., but in the case of Gunner C. the bacilli required to be grown for five days before the toxins destroyed the infecting organism. These observations have a practical bearing on the results obtained.

Case of Private H.—A reference to Chart I shows that this man was excreting 3,200,000 typhoid bacilli in each gramme of faeces before the treatment was begun. On March 8th, 25 c.c. of the malt culture were given, but the Bulgarian bacillus was not established in the alimentary canal until March 26th. This long interval was probably due to the small dose of the Bulgarian bacilli given, and in future it would be well to avoid this long delay by giving large doses at once, as was done by Cohendy, under Metchnikoff's direction, without any harm resulting. On April 2nd, the excretion of typhoid bacilli rose to 28,000,000 per gramme of stool, and the chart shows very clearly that though the excretion of typhoid bacilli was continuous the numbers varied extremely. At the end of April the typhoid bacilli disappeared from the faeces, and no signs of them have been discovered up to the present date. It is hoped that this patient is cured, but the treatment must be stopped and the patient must be kept under observation for a few weeks before the real result can be ascertained.

Gunner C.—Chart II shows that this man was excreting 190,000,000 typhoid bacilli per gramme of stool when first examined, and though the treatment with Bulgarian bacilli was carried out exactly as in the case of Private H. no cure has resulted. The Bulgarian bacilli are well established in his alimentary canal, and yet at the last examination he was still found to be excreting 86,000,000 bacilli per gramme. The explanation of this disappointing result is to be found in the resistance which the infecting organism shows to the toxins of the lactic acid bacillus. As already stated the accumulated toxins produced by five days' growth of the lactic acid bacilli *in vitro* were required to destroy the strain of *B. typhosus* which had infected this man. Unfortunately the lactic acid culture has a slightly aperient effect, and it appears probable that the toxins are discharged from the bowel before the desired effect has been produced on the typhoid bacillus.

(b) Treatment by anti-typhoid vaccine.

The cases in groups (2), (3), and (4) have been treated by subcutaneous injection of the anti-typhoid vaccine prepared in the Royal Army Medical College. Charts iii, iv and v show that under this treatment there has been a rise in the opsonic index of each patient, that is to say the substances which act on the bacilli and render them more easily destroyed (phagocyted) by the white corpuscles of the blood have been developed. As regards the agglutinins—*i.e.*, the substances which cause the typhoid bacilli to come together in masses, and in this way probably assist in their destruction—there has been a distinct rise in the case of Private S., but in the case of Lance-Serjeant I. and Private I. there has been no increased production of these bodies up to date.

Table I. shows that the excretion of the typhoid bacilli has been distinctly intermittent in the case of Private S. and of Private L., and continuous in the case of Lance-Serjeant I. Following on the injections Private S. ceased to excrete the specific bacilli for about three weeks, and during this month there has been a corresponding intermission in the case of Private L. These results, which were not observed before the vaccine treatment was commenced, lead us to hope that if the protecting substances could be produced in greater amount a permanent cure would result. The elaboration of protecting substances appears to be related to the virulence of the particular race of the typhoid bacillus which has invaded the human body. The opsonins produced by the injection of a comparatively non-virulent strain do not seem to have much power of rendering a virulent strain of the same organism vulnerable to the attacks of the white corpuscles of the blood. Consequently it has been determined to discontinue the general vaccine employed hitherto and to inject each patient with a vaccine prepared from the particular strain of the typhoid bacillus which has infected him.

divided into three parts. The first of these parts was devoted to the study of the effect of the various factors on the growth of the bacteria. The second part was devoted to the study of the effect of the various factors on the survival of the bacteria. The third part was devoted to the study of the effect of the various factors on the virulence of the bacteria.

Experiments were also carried out to determine the effect of various factors on the growth of the bacteria. It was found that the growth of the bacteria was increased by the presence of certain factors. These observations have a practical bearing on the results obtained.

Case of Typhoid H.—A reference to Case 1 shows that this case was a typical case of typhoid fever. The patient was a young man who had been ill for several weeks. The symptoms were those of typhoid fever, and the diagnosis was confirmed by the examination of the blood.

On March 23rd, 1900, the patient was admitted to the hospital. The temperature was 101.5° F. The pulse was 100. The patient was very ill, and the diagnosis was confirmed by the examination of the blood. The patient was treated with salicylic acid, and the temperature gradually fell. The patient was discharged on April 10th, 1900, and was well at the time of writing.

Case 2.—Case 2 shows that this case was a typical case of typhoid fever. The patient was a young man who had been ill for several weeks. The symptoms were those of typhoid fever, and the diagnosis was confirmed by the examination of the blood. The patient was treated with salicylic acid, and the temperature gradually fell. The patient was discharged on April 10th, 1900, and was well at the time of writing.

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