"TRENCH FEVER": A RELAPSING FEVER OCCURRING WITH THE BRITISH FORCES IN FRANCE.

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Note by Colonel Sir Wilmot Herringham.

During the whole time that the Army has been in Flanders, cases of short fever have continually occurred.

In a comparatively small number there has been a little bronchitis, or some diarrhoca, or tenderness of the muscles or nerves in limited situations. These have been called bronchitis, or influenza, enteritis, colitis, myalgia, and neuritis. But as a rule the symptoms have not included more than the general aches and pains which are the common denominator of all fevers. The patients have been very slightly ill, and except in a small number of cases have quickly returned to duty.

It has been very difficult to know what to call these cases. They have been sent in as influenza, myalgia, neuritis, pyrexia of unknown origin, and even as rheumatic fever. Of genuine rheumatic fever I have seen only three instances. Its absence has been one of the most striking things in the campaign, and effectually disposes of any connexion between this fever and wet or cold.

These undetermined fevers have from the first been the hunting-ground of the bacteriologists who with their laboratories are disposed in a line along the front, together with a few in special places farther back. The bases have of course their own bacteriologists and are not now under consideration.

The diagnosis of the enteric group of fevers is of such consequence to an army that the first task of the bacteriologist is always to exclude them. In consequence these cases of pyrexia have throughout been examined from that point of view. As they were usually seen quite early in the disease, cultivation of the blood
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has been practised regularly, but cultivation of the excreta and agglutination tests have also been carried out in many hundreds of cases. In any case where either abdominal symptoms, or a dry tongue, or an enlarged spleen, or suspicious spots gave clinical grounds for suspecting an enteric fever the patient was sent down as "suspected typhoid" even if the bacteriological evidence was absent. But after all this had been done we were left with a large mass of cases in which neither the clinical nor the bacteriological evidence afforded any ground for this diagnosis.

In the early part of the summer Major J. H. P. Graham called my attention to a type of fever characterized by two bouts of pyrexia separated by a normal interval. He afterwards published two cases of the kind (Lancet, September 25, 1915). About the same time Captain Wells reported several similar cases. Colonel Sir William Leishman came round with me to see these cases. Their resemblance to sand-fly fever, and also to dengue, struck those who had had experience in these fevers, but there were several points which effectually disproved identity. Other officers were good enough to look out for similar cases. I should like especially to thank Captain Stirling and Captain Bolus for their help. In the Lancet of November 20, 1915, appeared a paper by Captain G. H. Hunt and Major A. C. Rankin, describing thirty cases, and mentioning for the first time the name "Trench Fever," which by this time has come into common use. From these papers and from the paper now published I think we can say that from the mass of cases of obscure fevers one type has been isolated, in which the clinical symptoms, the course, and to a certain extent the pathology, have been established. We are, however, still ignorant both of the nature of the infection and of the way in which it is introduced into the human system. It is still occurring, and this, I think, disproves the agency of any flying insect.

The present paper needs no praise of mine, but I may say that I have followed the work throughout with the deepest interest.

The cases of the type to be described first began to be recognized in this laboratory area about the beginning of July, 1915, although on considering the matter later it was certain that a small number of men seen during the previous month had suffered from the same disease.

It will be of interest to give an account of how our attention was drawn to the condition in the first place. In the first few days
of July a number of men, about twenty in all, were sent in to an isolation hospital labeled "suspected enteric." These men all belonged to a division which had recently arrived in the area, and all had headache and varying degrees of pyrexia in addition to other symptoms to which less attention was paid at the time. Since it was known that during the previous two months cases of paratyphoid B had occurred both in the civilian population and in the division then in occupation of the area, it was at first thought that these new cases might be of the same nature. Blood cultures were made in bile salt broth in the usual way, and thereafter the cases were immediately transferred to a stationary hospital farther from the front. These blood cultures proved one and all sterile. The men reached the stationary hospital within a week of the onset of the febrile symptoms, but on admission there their temperatures were either found normal or fell to normal within a day or two, leaving the patients apparently quite well. As the cases did not resemble clinically any of the enteric group, an inquiry was at once addressed to this laboratory to find out the results of the blood examinations. The bacteriological and clinical findings thus seemed to exclude the enteric group, although the possibility of previous inoculation modifying the course of genuine enteric had still to be considered at the time.

Cases of the same kind occurred immediately afterwards, and on these being watched it was found that the fever ceased after five to eight days. These men were examined carefully, and other symptoms recognized, which will be described in full later on. None of these early cases, however, remained under observation for long after the temperature fell to normal, so that their subsequent history is unknown. The point of this remark will be seen when the course of cases watched over a long period is considered.

As has been already indicated, all the early cases remained under suspicion of belonging in some sort of way to the enteric group. As more and more cases were observed, however, each with a similar and constant group of symptoms, the disease soon became recognizable as a definite clinical entity, and early became known to officers and men under the name "trench fever."

Since attention was attracted to the condition, great numbers of cases have come under our observation. During the months of July, August, and September, in fact, it was impossible to visit three or four field ambulances on any day without seeing at least half a dozen fresh cases.
During August and September arrangements were made, especially at one casualty clearing station, to keep a series of cases under constant observation for some weeks, as a result of which we have been able to carry out most of the clinical, pathological, and experimental work detailed below.

**Distribution of the Disease.**

The cases have been met with, curiously enough, only among two classes of men; namely, those direct from the trenches, or at least from near the trench zone (artillerymen, etc.), and men of the Royal Army Medical Corps. On looking into our records no real exception can be found to the above generalization. Thus in our experience only those who have actually lived in or near the trenches, and those who by reason of their work are constantly in contact with sick and wounded men from the firing line, have suffered from this disease. This seems important in searching for the means of transmission of the malady, and shows at any rate that the name "trench fever" is not without some justification.

No case has been met with in units such as Ammunition Columns, Ordnance, Headquarter Troops, etc., which although in the Army area are situated at some distance from the lines. Of the Royal Army Medical Corps units the personnel of both Field Ambulances and casualty Clearing Stations have suffered. No stationary or general hospitals being in the zone of the laboratory, we are unable to speak of them.

Age and service, foreign or otherwise, have had no influence, both old soldiers and newly joined men being equally involved. Officers and men, too, have apparently been affected in the same proportion.

It is important to observe, also, that in a Casualty Clearing Station, where a room was specially set apart for the observation of such cases, four of the orderlies developed typical attacks of the disease. Other men affected in the same unit included the attendant of the incinerator, the man in charge of the Thresh disinfecter, an officer's cook, as well as other men on ordinary duty. The question of the occurrence during the past summer of a similar disease among the civilian population has been gone into, and although it is difficult to get sufficient accurate information, it seems highly probable that such cases have existed.

In the course of inquiry some interesting particulars of the
types of fevers found in the Flanders area have emerged, but no help has been gained with regard to a past history of this disease.

Types of Fever.

Two types of fever will be described, and at first it was quite impossible to be certain whether both were varieties of the same disease, or were two distinct entities. When the experimental work comes to be dealt with, however, evidence will be given, which to our mind makes it practically certain that one disease alone is under consideration. Both types have identical symptoms, and the initial history of both is essentially the same. The cases only differ in their course, and that in a very curious and interesting way.

Class A.—The patient as a rule feels suddenly ill; headache, dizziness, and pains in the lower limbs being the most constant initial symptoms. Some men give a history of having been so suddenly overcome by headache and dizziness that they fell down in their trench. The headache, although always severe, is not constant in its seat of maximum intensity in different cases. A very common feature, however, is pain behind the eyes, especially when they are moved. Pain appears early in other places besides the head, the most common sites being the lower limbs, and small of the back. In the former the pain may be confined to the "shins," but is often present in the thighs and behind the knees. It is difficult to say whether the pain is periosteal or muscular or both, but all the men state that it feels deep seated in the limb. It often gives rise to an intense feeling of restlessness, so that the patient is unable to keep his legs still for any length of time.

No diarrhoea is ever present, but on the contrary a tendency to constipation is frequently observed.

The fever varies in intensity, ranging up to 103° F. or 104° F. in the first day or two. The face is flushed, the eyes generally clear and bright, and free perspiration occurs. The tongue is furred, and there is great loss of appetite. No signs of catarrh are ever present in the chest. The pulse-rate is only slightly raised, a common figure being about 100. Often about the third day there is a sudden drop of the temperature to normal or even subnormal, without abatement of the symptoms. Thereafter, however, the temperature rises at once, to fall again, in our experience, about the sixth to the eighth day. In other cases, however, there is no such intermission, the temperature remaining continuously elevated for a week. When the temperature drops at the end of this
period, there is an immediate relief from all the symptoms, which is very striking. The rate of convalescence varies, and in many of these cases, but not in all, is complicated by a single relapse. This is in contrast to the second type of case to be described, where the initial period of fever is not so long, and relapses frequent. It seems as if, granting that the same disease is under discussion, a longer initial attack may give rise to only a single relapse, whereas a shorter period of fever at the beginning may be followed by several relapses. Enough evidence has not yet been accumulated to render this supposition certain, but we wish to suggest as additional evidence in favour of the disease being a single one that the duration of the malady with its relapses may be inversely proportional to the severity and duration of the initial attack.

The relapse is met with as a rule within four days of the temperature falling to normal. The fever is never very high, reaching perhaps 100°F to 101°F. The duration is one or even two days, and during this period all the previous symptoms return, although with lessened severity.

A series of nine charts, all from cases of the type described, is given below. It seems superfluous to give a clinical account of each example, so only points of special interest will be alluded to in the text.

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**Chart 1.**

This man was admitted on the fourth day of illness. A typical single relapse is shown.

Chart 2 shows in part the tendency to remission often seen about the third day. The relapse is more gradual and prolonged than in the first chart.
This chart shows a more irregular type of fever. The patient was admitted on the second day of illness. The symptoms continued until the eighth day, after which a relapse occurred on the twelfth day.
This man had been slightly wounded in the shoulder, and came to the convalescent hospital with a normal temperature. The chart, therefore, begins on the first day of the attack. He had not been, when the illness commenced, in the ward where the other febrile cases were kept.

It will be noticed that only a slight relapse occurred nine days after the temperature fell to normal on the eighth day.
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Charts 7 and 8 are given as well-marked examples of the remission which may occur about the third and fourth day. Such a remission is well shown in two of the experimental cases.

Class B.—The chief distinction between this type and the first is the number and periodicity of the relapses, so that the disease takes on the characters of a true relapsing fever. This variety is less common than the first, only about twenty characteristic cases having been observed. Apparently, however, more have been seen so far in this than in any other zone of the British front.

This type of case begins with symptoms indistinguishable from the shorter illness already described. The headache, dizziness, pain in the legs, and tendency to constipation, all are there, and
there is high fever. In short, it is at this stage impossible to foretell into which class the case will fall. A point of importance, however, is that the initial fever does not last so long as in Class A. The duration of the initial rise of temperature is naturally the most difficult part of the disease about which to obtain accurate information, most of the cases having already passed through a field ambulance before coming under our observation. In cases seen from the very beginning however (e.g., two of the personnel of a field ambulance), the duration of the initial attack was about three days, and this bears out the story of other men who only came under observation later.

After the primary rise and fall of temperature, the patient feels perfectly well, so well indeed that in several instances he has returned to his ordinary duties. Then suddenly, after a varying number of days, the man is again aware that he is unwell. Headache is, as a rule, again the initial symptom, and is often accompanied by a sensation of cold, although no actual rigor has ever been observed. Pain in the legs and small of the back return with great severity, and on taking the temperature it is found to be high, often reaching 103.8°F. As a rule the onset of the attack is sometime in the afternoon, and the height of the fever is reached the same evening. This relapse differs from that described under Class A, in the following particulars: (1) It is the first of a series of similar attacks; (2) it is sharper, the temperature is higher, and the symptoms are just as severe as in the initial attack. The duration is short, the temperature rising quickly one day to fall to normal, or almost normal, within the next thirty-six hours. Occasionally, however, the rise is not so rapid nor the fall so sudden, so that the relapse from start to finish covers a period of about three days (vide Chart 13). The interval between the end of the initial attack and the onset of the first relapse is most frequently about four days, and once the relapse is over the patient returns again to a period of well-being. With regard to subsequent relapses the periodicity varies, as is shown in the charts, the intervals never being exactly regular even in the individual cases.

The symptoms during the second and third relapses are, as has been already indicated for the first, of considerable severity, constant in character, and just as severe as in the first days of the disease. In subsequent relapses, however, the symptoms are not so severe, nor does the temperature rise so high. It is the headache, however, which is chiefly mitigated, the pain in the shins remaining very troublesome.
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It was interesting in these cases how often the men could accurately foretell the onset of a relapse, even before the temperature was raised. They "felt something coming on" in an indefinite sort of way, and later complained of slight headache. Thus sufficient time was often given to warn us at the laboratory that a case was relapsing, in order that various blood examinations could be made during the pyrexia.

The above chart is from the case of an infantry officer, and was the first case of the kind met with. Hence a great deal of attention was paid to it, and until subsequent similar charts became available the nature of the illness remained a puzzle. Many examinations of the blood were made during and just before the attacks to see if any parasite could be found, but all proved negative. In the intervals between the pyrexial periods the patient was so well that he was out of doors all day; hence the interruptions in the chart shown by the dotted lines.

This case was observed from the outset, the man affected being one of the personnel of a field ambulance. Note the short duration
of the first febrile period, the temperature being subnormal on the morning of the third day.

This case was admitted to hospital suffering from scabies, and only fell ill after some days. The chart thus dates from the first day of the disease. On the twentieth day, when the third relapse was calculated to be due, the patient was given twenty grains of quinine. The result was interesting, as although the symptoms developed in marked degree, the temperature did not rise above 99°F.
This case, also an infantry officer, was admitted on the second day of illness. It will be observed that with each successive attack the temperature reached is, in every instance except the last, not quite so high as on the preceding occasion. This feature is also well shown in other charts, notably 11, 15, 16 and 17. This would thus seem to indicate progressive diminution of the infective agent, or the gradual establishment of immunity.
This case is included as it shows a rather irregular type of chart. The man had taken ill a week prior to admission, with characteristic symptoms, and was presumably, when first seen by us, in his second period of fever.
Charts 15, 16 and 17 show the well-marked relapsing character of the fever. In each case the first attack had occurred before the case was admitted, the men only coming under observation on the seventh, fourth, and sixth days after the onset of the illness.

Charts 18 and 19 show types of fever different in their course from any of the others described. The clinical symptoms were, however, typical enough.

**Differential Diagnosis.**

The chief diseases coming under consideration in this respect appear to be:

1. **The Enteric Group.**—This was excluded by (a) the numerous negative blood cultures; (b) the negative examinations of stools and urine; (c) the negative Widal reactions in the case of paratyphoid A and B, and (d) the periodicity of the relapses.
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(2) Malta Fever.—This was excluded by the negative agglutination tests.
(3) Dengue.—The absence of any rash seems to rule this out.
(4) Influenza.—The differentiation from this disease is very important, because probably the majority of the cases came into hospital with a diagnosis of influenza. It is quite certain that a
great many will go down permanently into Army Records under that name. Influenza is excluded by the following points: (a) Absence of all catarrhal symptoms in the chest; (b) there is not the same prostration, cases often being found walking about with
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high temperatures; (c) there are the periodic short relapses, the most distinctive feature of all.

(5) Malaria. These were both excluded by the absence of any parasites in the blood films, or of any splenic enlargement.

(6) Relapsing Fever. These were both excluded by the absence of any parasites in the blood films, or of any splenic enlargement.

Work on the Pathology of the Disease.

Work in connexion with the types of fever described has been carried on from various standpoints, and divides itself into bacteriological, pathological, and experimental. It may be said at once that the first two lines of investigation have yielded little information, but a brief account even of purely negative results must be given to complete as far as possible our knowledge of the disease. From the experimental work, on the other hand, much important information has been gained.

Blood cultures have been made in a variety of ways. At first
many of the cultures were made in the ordinary bile salt peptone broth used for the cultivation of the typhoid group of organisms. This was done because at first, as has been indicated, nearly all the cases were suspected of being enteric fever owing to the pyrexia. It is sufficient to say here that at least one hundred such blood cultures have been examined, all with negative result. All these cultures were made in the first few days of the disease, and this set of observations alone seems amply sufficient to exclude the idea first mooted that the disease might be enteric in reality, much modified by inoculation. The Widal reaction, so far as *Bacillus typhosus* was concerned, gave no assistance, owing to the high rate of inoculation. At one period a search was made for a case of this disease in an uninoculated man, but no such case on which to make agglutination tests could be found. Agglutination tests with *B. paratyphosus* A and B, and with *Micrococcus melitensis* and *para-melitensis*, were made towards the end of some cases both of long and short type, but being always found negative were not persisted with.

A considerable number of blood cultures were also made using ordinary bouillon as the culture medium, again with negative results even when the culture was left for a week or longer at 37° C. More recently anaerobic shake cultures of the blood in a large volume of glucose agar have been tried, without success.

The feces and urine have been searched culturally in a number of cases, both during and at the end of the pyrexia, but no abnormal organisms were found.

Blood films have been thoroughly searched, both in the short and especially in the relapsing cases, for the presence of any parasite, whether intra- or extra-cellular. In a few instances the blood has been examined daily, during the fever and between the febrile attacks, but nothing resembling a parasite has so far been discovered. Various stains have been employed, but especially Leishman, Jenner, and Giemsa, films being even left in the last stain for a period of several days.

Fresh films of blood from some typical cases have been searched under dark ground illumination, but no unusual appearance was detected.

The morphological changes seen in films are of some interest. As regards the red cells, only one pathological feature occurred with any degree of frequency. This was the presence of polychromatophile cells above the normal in size; and also, especially in the relapsing cases, of well-marked punctate basophilia. In
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* A Gower's hæmoglobinometer was used.
several cases this latter change was so well marked that very
careful examinations were made to make sure the appearance was
not really due to an intra-cellular parasite. An explanation of these
morphological changes was found when blood counts came to be
made, as all the men examined showed a definite defect in the
percentage of haemoglobin, the average colour index of a series of
cases being 0.8. Although the defect in the percentage of haemo-
globin was constant, there was no loss in the number of red
corpuscles, as will be seen from the Table.
The leucocytes showed no morphological changes, and differential
counts only indicated a slight relative increase in lymphocytes
(large and small) with a rather low figure of hyaline cells. The
details are given in full in the Table.

Experimental Work.
The experimental work was undertaken to satisfy any or all of
the following questions:—
(1) Is the disease transmissible by the blood (a) to animals,
(b) to man?
If so:—
(2) What part of the blood is infective—the fluid or the
cellular elements?
(3) Can the disease be transmitted by any or all of the following:
(a) whole blood, (b) plasma, (c) serum, (d) corpuscles?
(4) If the virus is transmissible, is it a "filter-passer" or not?
(5) If ultramicroscopic, is the virus in the fluid part, or only in
the cellular elements of the blood?
(6) If a virus be proved, what is the method of transmission in
Nature?
Following out this scheme, experiments were first made by
injecting the separated serum from marked cases into animals, rats
and rabbits being used. Later, whole blood (citrated) was tried, but
none of the animal experiments bore any fruit.
Thereafter, with the approval of the authorities, it was resolved
to extend the experiments to men who would volunteer for inocula-
tion. The experiments made in this way have been carried out
in a Casualty Clearing Station, which by reason of its special
situation has during the past summer acted as a convalescent
station. Until special arrangements were made, however, no case
could by rule be kept in this hospital for longer than a week, a fact
which, as subsequent events proved, militated against the success
of the first experiments. The men from whom volunteers were selected were almost all cases of minor injuries (sprained ankles, etc.), i.e., men who although unfit to return to the trenches for some weeks were otherwise healthy.

The cases from which blood was taken for transmission were carefully chosen, only those in which no sign or history of past disease could be found being used. A number of typical cases were passed over at the time for this reason.

The experiments were begun on August 11, 1915, when five cubic centimetres of blood were taken from each of two typical cases, and transferred immediately into the veins of two other men. Nothing occurred during the week these men remained under observation, and the men were then evacuated to the base and lost sight of. Positive results began to be obtained whenever permission was received to keep the cases, and the men inoculated from them, for a longer time under observation.

An account will now be given in detail of the first case in which the transmission was accomplished.

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On September 2 a Royal Army Medical Corps orderly, Pte. S., who had been on duty in the ward in which the "trench fever" cases were being kept, was in the middle of a brisk and typical attack of the disease. His temperature chart is given above.

At a time when his temperature was 101.4°F, five cubic centimetres of his blood were taken into a syringe previously washed out with citrate solution, and transferred immediately into the veins of Pte. W. Pte. W. remained well until September 11,
nine days after the inoculation. On the evenings of the third and fourth days his temperature reached 99°F., but he felt perfectly well at the time.

On the morning of September 11 he awoke at daybreak feeling unwell. He had a slight headache, and his temperature on being taken at 6:45 a.m. was 99.2°F. He got up, but could not remain out of bed for longer than an hour, as the headache became more and more severe, and he felt cold and "shivery." He returned to bed at 9 a.m., and soon after was attacked by pain, chiefly in the thighs and small of the back. Unlike other cases, he had no pain below the knees. By evening he felt very ill, and at 6:30 p.m. his temperature was 103.8°F., and pulse 88. Next morning he was rather better, the pain being easier, although the headache remained severe. His temperature, too, had fallen, being 99.8°F. in the morning and 100°F. at night. On the third morning his temperature was normal, but the headache remained, and the pain did not entirely pass off. The same evening, however, he was
perspiring profusely, and felt just as ill as on the first day of the attack. His temperature on this occasion was 100·8°F. The following morning there was again a slight remission, but only for a short time, and during the next few days he was very ill until the temperature reached normal once more on the seventh day after the onset. The complete chart is given. (Chart 21.)

Immediately the temperature became normal he felt comparatively well, and was able to sit up for a short time. His headache was completely relieved, but he still had slight pain in the thighs. Thereafter two definite relapses occurred, the one reaching its acme on September 19, and the other on September 23. During these relapses, headache and pain in the thighs and back returned with considerable severity, without being, however, quite so severe as at the beginning. It will be observed from the chart that one relapse was at its height about four days after the temperature fell to normal on the seventh day, and that the other followed at a precisely similar interval.

Various symptoms, etc., of lesser bearing have been purposely omitted in the account of this case, so as to bring those of importance into prominence. It is sufficient merely to mention that anorexia and a definite tendency to constipation, both symptoms common to many febrile diseases, were present to a considerable degree.

The subsequent course of the case was towards complete recovery, but it is a noteworthy fact that whenever the temperature rose in the least degree above normal (as for example on October 15, thirty-five days after initial fever), the pain in the thighs returned with severity. This has been observed in other cases, the patients being able to tell that their temperature was a little high by the return of the pain.

Fairly numerous blood examinations made on Pte. W. during his illness are shown in the table already given.

It was resolved to try to carry on Pte. S.'s infection through Pte. W. to a third generation, but no opportunity for doing so occurred until September 19, nine days after the beginning of Pte. W.'s attack. On this day ten cubic centimetres of blood were taken from Pte. W. into a syringe previously washed out with citrate solution and injected intravenously at once into Pte. D.

This man kept well until September 24, five days after the inoculation, when a typical attack of the disease was again reproduced. (Chart 22.)

He took ill in the evening, feeling "shivery" and out of sorts.
His temperature was found to be 99·8° F., and during the night intense headache and pain in the thighs developed. Next morning when seen he was very ill, complaining especially of pain behind the knee-joints, and at noon his temperature stood at 102·4° F. The following day his temperature was normal, and all the symptoms practically abated, so that he wished to get up. Thereafter, although a slight rise of temperature occurred on three successive evenings, he kept perfectly well until October 4. During this interval of ten days he was able to go out of doors every day, and felt quite in his usual health. A relapse then occurred, all the original symptoms returning with even more severity than in the first attack. His temperature reached 103° F. on the 5th, and then fell, all symptoms and fever having passed off by October 7. A period of well-being again followed, lasting until October 15,

when a further relapse developed with the usual set of symptoms. These were not severe, the temperature only rising to 100° F., and next day the patient was better again.

It is important to observe that the highest temperatures recorded in the three attacks occurred on the seventh, seventeenth, and twenty-seventh days after the inoculation, i.e., the interval between the height of each illness was exactly ten days. The periodicity in this case has, we also consider, a further importance in helping to establish the unity of the "short" and "long" types of disease described in the earlier part of this paper. The first case, Pte. S., represents in our original description a fairly typical "short" type. The second, Pte. W., seems merging into the other or "long" type, and the third, Pte. D., if the case had occurred naturally, would have been put without hesitation into the latter group. The results of the experiments just described, taken along with the identity of the clinical symptoms in every case, seem to constitute very strong links in the chain of evidence.
supporting the view that all are simply varieties of one and the
same disease.

The next experiment to be referred to had its origin also in
an R.A.M.C. orderly, who had also been in contact with a number
of cases. This man, Pte. C., took ill on September 15, with the,
by this time, well-recognized symptoms. His chart is appended,
and shows a fairly typical curve. (Chart 23.)

On September 19, when his temperature was 102·4°F., five
cubic centimetres of blood were transferred immediately into the
veins of Sapper M. This man kept well until October 2, thirteen
days after the inoculation, when he suddenly felt dizzy, cold, and
shivery, while going down the long hospital stairs. He had no
headache until the evening, when his temperature had risen to
102·6°F. (See Chart 24.)

Pain in the legs had come on previously (at 4 p.m.), and was at
first worst round the hips. During the night the pain became
more localized to the back of the knees and to both ankles, and felt,
so he said, deep down to the bones. The symptoms continued
until October 7 without remission, when they passed off quickly.
A relapse occurred on October 10, four days after the end of the
first pyrexial period, and a second on October 13, after a similar
interval of four days. On neither occasion were the symptoms severe, the temperatures only reaching 99.2°F. and 99.8°F. respectively.

Having shown in these three men, Pte. W., Pte. D., and Sapper M., that the disease in typical form could be transmitted from cases by immediate inoculation with "whole blood," it remained to continue work on the scheme outlined at the beginning of this section.

Serum experiments had been begun early, as the blood from typical and suitable cases could be collected at different field ambulances, the serum separated in the laboratory, and thereafter injected into volunteers when available. The first experiment with the blood serum, made on August 20, was a failure, but the two men were only under observation for about a week. The serum was, in this experiment, passed through a Doulton filter candle without dilution, before being injected. On August 22 the pooled serum from four typical cases was, after the addition of an equal bulk of saline, passed through a Doulton filter, and injected into two men. Nothing happened, although the men were kept for a fair time under observation. This attempt to prove whether the virus was a "filter-passed," before the infectivity of the unfiltered serum was tried, seems to indicate rather a cart-before-the-horse procedure, but it was adopted at the time for the following reasons: It was thought from analogy in the first place that the virus might be somewhat of the same nature as those of yellow fever or sand-fly fever, etc.; and also, the blood being at the time collected, often under difficult conditions, from field ambulances, the sterility of some of the samples might be in question. We felt safe, however, in injecting the sera after they had passed through the porcelain filter candle.

Two other men were again on August 25 inoculated with the pooled serum of three typical cases, the serum being previously filtered through a Doulton candle. A negative result was obtained. The same type of experiment was carried out on August 27, the pooled serum of four typical cases being filtered as before. A negative result was again obtained. It was then suggested to us by Sir William Leishman that our failure to get the virus through the filter was possibly due to the serum not being sufficiently diluted with saline, in none of the experiments so far described more than an equal volume of saline having been employed. In our subsequent experiments therefore, the serum was always diluted with ten volumes of saline.

These experiments now to be detailed were conducted under
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the best conditions in the casualty clearing station where so much of the work has been done, and were designed to satisfy several questions at once. They must therefore be described as separate experiences, leaving the conclusions to be drawn at the end.

On October 7, blood was withdrawn from Pte. B., on the day before his fifth attack of fever, and in the fourth week of his illness. Five cubic centimetres of blood were taken into a syringe washed with citrate solution, and injected at once into Pte. Dm. The remainder was allowed to clot, the serum separated, and divided into two parts each of three cubic centimetres. One of these parts was diluted with ten volumes of saline and rapidly filtered through a Berkefeld "V" filter. Thereafter the three cubic centimetres unfiltered serum were injected into Pte. T., and the filtered and diluted serum (now thirty cubic centimetres of fluid) was transferred intravenously to Pte. M. These two injections were made about four hours after the blood was withdrawn.

The chart of Pte. B. (Chart 25), from whom the blood was withdrawn, is given below. When admitted he gave a history of two previous attacks of fever, and four relapses, shown on Chart 25, occurred in hospital.

Pte. Dm. (Chart 26), into whose veins the "whole blood" was injected, began at once to run an irregular temperature, but without obvious symptoms, until the evening of the eighth day. Then the
usual symptoms of headache, pains in the back and legs, etc., appeared, and continued until the temperature fell to normal three days later. Thereafter three relapses occurred, each reaching its acme, as shown by the highest temperature recorded, five days after the previous one.

Pte T. and Pte M., who received respectively serum and serum after dilution and passage through a filter, kept perfectly well for four weeks under observation, their temperature charts not showing any deviation from the normal.

In this experiment, therefore, only the "whole blood" was infective, no result being obtained with serum, filtered and unfiltered.

The next experiment had as its basis the case of Pte Dm. (Chart 26) just described, whose attack followed the injection of the blood of Pte. B. The blood was withdrawn on October 15, when the temperature was 100-8° F., and the symptoms well marked. Pte. Wx. was injected at once with 5 cubic centimetres of blood, taken into a syringe washed with citrate solution. The remainder of the blood was taken to the laboratory in two parts, one being citrated to prevent clotting, and the other being allowed to coagulate. The citrated blood was centrifugalized at once, 8-5 cubic centimetres of plasma being thus obtained. The other part of the blood yielded after coagulation 10 cubic centimetres of serum. This was divided into two, 5 cubic centimetres being set aside, while the other portion was diluted with ten volumes of saline, and filtered as before through a Berkefeld "V" candle. The total bulk of the diluted fluid was thus 50 cubic centimetres. It must be pointed out here that when ready for injection, owing evidently to some fault in technique, both the plasma and the serum were somewhat hæmoglobin tinted, i.e., some red corpuscles had been damaged and the hæmoglobin liberated. The importance of drawing attention
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to this will be realized when the results of the experiment are noted. Pte. Wx. (Chart 27), into whom the “whole blood” was transferred, developed, as is shown in the chart, an extremely typical attack, with the usual relapse and the customary symptoms. The incubation period was in his case seven days.

In the case of Pte. O. (Chart 28), into whom 8.5 cubic centimetres of plasma were injected, a quite characteristic positive result was obtained after a period of thirteen days, as is shown in the chart.

A positive inoculation also resulted on the ninth day after the introduction of 5 cubic centimetres of serum into the veins of Pte. N. (Chart 29), whose chart is also given.

Clinically, the illness caused by the introduction of the “whole
blood” was much more severe than that brought about by inoculation with either serum or filtered serum—a fact well shown by comparing the three temperature charts.

The man Pte. R., into whom the filtered serum was introduced, remained absolutely without symptoms, even when watched carefully for over a month, and his temperature taken night and morning.

As it was felt that this last experiment made with plasma and serum was not perfect owing to the hemolysis which occurred in preparing the specimens for injection, it was resolved to repeat the test.

On October 21 Pte. P., an Army Service Corps driver attached to the casualty clearing station, where our experiments were carried out, was in the second day of what clinically was a typical attack. The complete chart of this man (Chart 30) shows an unusually long initial period of pyrexia, but the clinical symptoms (headache, severe pain in the shins, etc.) and the subsequent relapses were characteristic enough.

On this day (October 21) a quantity of Private P.’s blood was taken into citrate solution. Five cubic centimetres of the citrated blood were injected at once intramuscularly into Pte. A. The remainder of the citrated blood was dealt with as follows: The blood was centrifugalized and the plasma removed. Thereafter the corpuscles were washed thoroughly six times with normal saline solution to completely free them from traces of plasma. The washed corpuscles corresponding to 5 cubic centimetres of blood were then taken, suspended in sufficient saline to make up to 5 cubic centimetres, and injected intramuscularly into Lance-Cpl. B. The remaining washed corpuscles (equivalent also to about 5 cubic centimetres of blood) were mixed in a bottle with fine sand
and glass beads, and shaken thoroughly so as to break up the corpuscles as far as possible. The mixture was then extracted with saline, and the bright red hemoglobin-tinted fluid passed through a Berkefeld "V" filter. The filtrate (16 cubic centimetres in bulk) was injected intramuscularly into Grn. S. This last part of the experiment, in which an attempt was made to break up as much as possible the corpuscular elements, was undertaken to see if possibly (a thing hitherto unheard of) the virus might be ultramicroscopic, and a filter-passer confined to the cellular elements of the blood.

Of the three men injected in this experiment only one developed the disease, namely, Pte. A., into whom the citrated whole blood was injected intramuscularly. The incubation period was twenty-one days, and the attack, which was typical, is shown on the accompanying chart (Chart 31).

The other two men were watched for over a month, and they remained perfectly well.

The only positive result obtained from this experiment was, therefore, the fact that citrated whole blood is infective when inoculated intramuscularly as well as intravenously.

The last experiment of our series had, as its basis, Pte. A.
(Chart 31), who had been infected with the citrated whole blood of Pte. P., injected intramuscularly. On November 10, when Pte. A. was in his first day of illness, and his temperature 102°F., some of his blood was withdrawn into sterile citrate solution. All of the citrated blood was taken back to the laboratory for the following reason. It will have been observed that in all the previous experiments, the citrated whole blood was injected at once, whereas the remainder of the blood had to be taken to the laboratory for preparation. Thus two or three hours generally elapsed before the remaining injections could be made. It was resolved on this occasion to make all the inoculations at the same time, so as to exclude the possibility of the virus dying out in the intervening two or three hours. All the injections in this experiment were thus made at the same time, about three and a half hours after the blood was obtained.

In this, our last experiment, the following tests were made, all the inoculations being intramuscular:

1. Citrated whole blood, both as a control and for the reason referred to in the preceding paragraph.
2. Corpuscles freed from plasma by washing with saline.
3. Plasma, filtered through a Berkefeld filter candle.
4. The filtered product of broken-up corpuscles previously washed with saline.

The technique of the preparation for the last three parts of the experiment must be briefly recounted. The plasma was obtained readily enough by prolonged centrifugation, and was quite clear and free from hemolysis. After separating the plasma, the corpuscles corresponding to 5 cubic centimetres of blood were taken, and washed five times in saline. The corpuscles were always thoroughly mixed with the saline before centrifuging, and 10 cubic centimetres of normal saline were used for each washing. After the final washing the corpuscles were made up to 10 cubic centimetres with saline before injection.

For the remaining part of the experiment the corpuscles corresponding to about 10 cubic centimetres of blood were obtained by the centrifuge, and washed as before five times with normal saline. The solid corpuscles were then mixed with fine sand and pounded up thoroughly in a mortar. The mixture was extracted with saline, and the product filtered through a Berkefeld "V" filter as usual, the result being 22 cubic centimetres of a clear deep crimson fluid. The results of the inoculations in this experiment may now be given:
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Chart 32.

Chart 33.
Pte. R., into whom the citrated whole blood was injected, took ill thirteen days after inoculation, and his chart is now given (Chart 32).

Pte. Pd., into whom the washed corpuscles of 5 cubic centimetres of blood were injected took ill with the usual symptoms sixteen days after inoculation. His chart is also shown (Chart 33).

Neither of the other two men into whom, respectively, 4.5 cubic centimetres of plasma after passage through a Berkefeld filter, and 22 cubic centimetres of hemoglobin-tinted fluid (obtained by breaking up corpuscles and filtering as described), were injected, fell ill in any way during the full month they were observed.

All the men who were voluntarily inoculated with the disease have returned to normal health. Communication has been maintained with some of them and the only complaint has been a slight return of pain in the legs when fatigued, in a few cases.

Other experiments throwing some further light on the illness could have been attempted, but it had always to be remembered that soldiers were the subjects of the tests. An important point to settle, for instance, would have been the question of whether one attack of the disease conferred immunity or not, against a second inoculation.

**Summary and Conclusions.**

1. The disease is a definite entity, and of infective nature, as is proved by its ready transmission from one person to another by the blood.

2. There are two clinical types of the disease: (a) A short fever of about a week's duration, followed frequently after a few days by a single short relapse; (b) a longer illness characterized above all by the number, sharpness, and periodicity of the relapses.

3. The symptoms of both types are clinically identical, the most constant and characteristic being headache and pain in the legs and small of the back.

4. The two types described are, in our opinion, merely varieties of one and the same disease. In addition to the identity of symptoms, the experimental evidence for this is strong, a typical "short" variety having been shown capable of giving rise to a typical "long" one.

5. The incubation period varies, possibly with the dose of the infective virus introduced. The shortest incubation period in our experimental transmissions was six days, and the longest twenty-two days.

6. The disease is transmissible in every case by the whole blood, whether injected intravenously or intramuscularly.
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(7) The disease is not transmissible by the serum. In the one instance in which the serum proved infective, haemolysis of corpuscles had occurred before injection.

(8) It follows as a corollary to the preceding statement that virus is not a "filter-pass" in the serum, as we thought from analogy that it might be. All our experiments with filtered serum were negative.

(9) The plasma was infective in one experiment, but haemolysis of red cells had occurred so that the plasma was haemoglobin-tinted. The filtered plasma in another test was not infective.

(10) The above results seemed to point to the virus being contained within the blood corpuscles themselves, whether leucocytes or red cells.

(11) Blood corpuscles, after washing five times in saline to remove the plasma, were still found to be infective. This further supports our view that the virus is intracorpuscular.

(12) Very many blood films at all stages of the disease have been examined, without a parasite being detected. The blood has been examined fresh, under dark ground illumination, and dried films have been stained in varying ways, without result.

(13) Blood corpuscles were broken down, and the haemoglobin-tinted fluid passed through a filter in an attempt to prove the virus an ultramicroscopic one confined to the corpuscles. The fluid when injected, however, was not found to be infective.

(14) The only constant morphological change in the blood is the presence of punctate basophilia. This was so marked in some cases as to require very careful investigation to differentiate it from an intracellular parasite. The blood counts, differential and ordinary, did not yield any important results.

(15) As regards the means by which the disease is transmitted in nature, we have as yet no evidence to offer. The fact that only two classes of men are affected—those from the trench zone and men of the Royal Army Medical Corps—is, however, suggestive. The disease is either contagious from man to man, or, what seems much more likely, is carried by one of the common flies or parasites found in the trenches. During the past summer lice, mosquitoes, midges, and flies of other kinds, have all been common in the Flanders war zone.

We wish to express our thanks to all the officers of the Royal Army Medical Corps, who have helped us so much in this investigation, and especially to Surg.-General Porter, Col. Sir William Leishman, Col. Sir Wilmot Herringham, Lieut.-Col. W. P. Peake, Capt. G. W. M. Andrew, and Capt. Vick.