PHLEBOTOMUS FEVER IN MALTA AND CRETE.

By LIEUTENANT-COLONEL C. BIRT.
Royal Army Medical Corps.

PHLEBOTOMUS FEVER IN CRETE.

The task of unravelling the tangled skein of "continued fever" in Crete is beset with greater difficulties than that of Malta. In the year of occupation, 1897, there were 785 cases of "simple continued fever" among 1,152 troops. It is stated that "febricula" was prevalent, but the incidence of enteric, Malta, and malarial fever was considerable.

In 1898 149 admissions for "simple continued fever," 39 for Malta fever, and 131 for enteric fever are recorded.

In 1899 108 cases of "simple continued fever," 1 of Malta fever, and 340 of ague appear in the Report.

In 1900 the "simple continued fever" admissions were 47 only; Malta fever, 7; ague, 133.

In 1901 147 cases of "simple continued fever" were returned in June, July, and August, but 1,393 admissions for ague in a strength of 564 men were also shown. It is stated that "ague" assumed an epidemic form in the summer. The earliest cases were observed in June, but the month of maximum prevalence was October. It seems probable that phlebotomus fever was epidemic at the same time as malaria.

In 1902 1,036 admissions among a body of 460 men are entered under the heading of "Ague." It is stated that a notable feature of the epidemic was the falling-off of the admissions shortly after the end of August. This suggests that "pappataci-fever" was then prevalent.

The year 1903 was more healthy. "Ague" had fallen to 222 attacks among 410 men.

The year 1904 was not remarkable. There were 8 admissions for "simple continued fever" and 133 for ague.

In 1905 the admissions for "simple continued fever" rose to 137, or 190 per 1,000 of strength. The average duration of each case was under a week. There were also registered 246 attacks of ague.

In 1906 the admissions for ague had fallen to 60, and those for "simple continued fever" to 39; the average stay in hospital of these latter was less than fourteen days.
In 1907 there were 71 cases of "simple continued fever," each of which had a mean duration of thirteen days while under treatment. Ague was responsible for 64 admissions.

In the Report for 1908 is the following table of admissions by months for "pyrexia of uncertain origin."

<table>
<thead>
<tr>
<th>Month</th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>Apr</th>
<th>May</th>
<th>June</th>
<th>July</th>
<th>Aug</th>
<th>Sept</th>
<th>Oct</th>
<th>Nov</th>
<th>Dec</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>84</td>
<td>12</td>
<td>2</td>
<td>12</td>
<td>17</td>
<td>17</td>
<td>9</td>
<td>17</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>

It is remarked that "A large number of cases of mild fever occurred amongst the troops, both at Canea and Candia. They occurred during the summer months, and chiefly among young soldiers lately arrived from England. The fever had a duration from two to four days. In Canea 26 cases occurred among 56 men, from May 24th, 1908, to September 9th, 1908. They practically ceased as soon as the troops were moved to camp. Malaria was not prevalent in Canea. The blood of those attacked was free from parasites. In Candia febrile seizures were diagnosed 'pyrexia of uncertain origin' only after negative blood examinations."

1909. The seasonal prevalence of "pyrexia of uncertain origin," influenza, and ague till the close of July, 1909, is here shown:

<table>
<thead>
<tr>
<th></th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>Apr</th>
<th>May</th>
<th>June</th>
<th>July</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;P.O.U.O.&quot;</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>—</td>
<td>8</td>
<td>28</td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ague</td>
<td></td>
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<td></td>
<td></td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

At the end of May, 1909, I was permitted to accompany the Principal Medical Officer, Malta and Crete, Colonel J. G. MacNeece, on his tour of inspection to the latter island. We found both in Canea and Candia cases of pyrexia, lasting three or four days, characterised by severe frontal headache, flushed face, heavy half-open eyes with injected conjunctive and tender eyeballs, pains in the back and limbs, tongue coated with white fur, constipation. No malarial parasites were detected. In short, we met with phlebotomus fever, identical with the Malta infection. Canea is exempt from malaria, yet these short febrile seizures have been noted every summer since the occupation not only amongst our own troops, but also in the Russian, French, and Italian contingents. We also discovered Phlebotomus papatasii in Candia and Canea similar in every respect to the Malta fly.

Major A. E. Master, R.A.M.C., informs me that in 1905 and 1906, when he was residing in Crete, he and other medical officers had no difficulty in immediately distinguishing cases of phlebotomus fever, then known as "simple continued fever," from ague, by clinical symptoms alone. The former obtained the slang name of
Phlebotomus Fever in Malta and Crete

"pink-eye." In his Report of the Medical Transactions, Crete, 1905, he describes this ailment as forming an epidemic characterised by high fever, lasting four days on the average, headache, pronounced lassitude, and congestion of the conjunctive, and sudden cessation of the symptoms with some subsequent debility. He notes that the seasonal prevalence of "pink-eye" occurred in the early summer months, whereas ague did not appear before July.

PHLEBOTOMUS FEVER IN MALTA.

The seasonal prevalence of fevers in Malta during 1909 is thus shown:

<table>
<thead>
<tr>
<th>Month</th>
<th>Pyrexia of uncertain origin</th>
<th>Enteric fever</th>
<th>Malta fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>February</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>March</td>
<td>1</td>
<td>-</td>
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<tr>
<td>April</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>May</td>
<td>8</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>June</td>
<td>94</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>July</td>
<td>89</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>August</td>
<td>47</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>September</td>
<td>39</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>October</td>
<td>26</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>November</td>
<td>0</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

In 4 per cent. of the "Pyrexia of uncertain origin" there was fever for 1 day, 2 days.

Therefore in 85 per cent. of the cases of "pyrexia of uncertain origin" the temperature was raised for five days only or under.

Composite charts have been prepared by taking the mean of the observations recorded at corresponding periods of the illnesses lasting one, two, three, four, five, six, and seven days respectively.

COMPOSITE CHARTS OF PHLEBOTOMUS FEVER.
Sixty-five per cent. of the attacks of "pyrexia of uncertain origin" occurred in soldiers who had resided less than a year in Malta. If we add the admissions among the troops in their second year, then 92 per cent. of the total number of cases of "pyrexia of uncertain origin" is the proportion of seizures in men with less than two years' service in Malta.

Spot maps show that the cases of "pyrexia of uncertain origin" were widely distributed. C Block, Floriana, Verdala, and the Royal Army Medical Corps' quarters, Cottonera, gave the largest proportion of admissions. Intarfa, 630 feet above sea level, and St. Elmo Fort—strength 350—were almost exempt.

The onset of the fever returned "pyrexia of uncertain origin" is usually sudden, though sometimes a history of a few days' malaise makes it difficult to determine the beginning of the pyrexia. Chills, nausea, headache, heaviness and discomfort about the eyes, lumbar pain and stiffness of the muscles of the lower extremities, and somnolence, induce the patient to take early to his bed. He finds himself unfit for his duty next morning and comes for relief. His temperature will then be 101° to 102° F., and pulse slow, 70 to 80. His face will be flushed, eyes suffused and heavy, the tongue rather large and coated with a thin white fur, except at the tip and edges. There is no rash except from the effects of biting insects. The same evening the temperature may rise to 103° F., though without a corresponding increase in the frequency of the pulse. A fall of two degrees takes place next morning, which often is continued without a further rise until the normal standard is attained. Convalescence is rapid.

Nervous System.—There is marked drowsiness with disinclination to be disturbed. The headache is severe, but the severity is rarely so great as to cause the sufferer to clamour for its relief. The frontal region is chiefly affected. There is some mental depression. Hysterical symptoms have been noted once in a girl, convulsions in a child, and delirium occasionally in the adult. Tenderness along the course of nerves has been observed a few times.

Eyes.—The movements of the eyeballs, opening and closing the lids, which are often swollen slightly, are attended with discomfort. The eyeballs are tender on gentle pressure. The injection of the conjunctiva on either side of the cornea is marked, and is a prominent symptom. No subconjunctival hemorrhages have been recorded. There is no watering of the eye, nor an icteric tint of the conjunctiva.
Nose.—Epistaxis has occurred but seldom. There is no coryza at any time.

Mouth, &c.—The tongue is large, moist, flabby, and is coated with a thin whitish fur, except at the tip and edges. Taste is impaired. It is rare that any soreness of the throat occurs. Sometimes small vesicles may be observed on the mucous membrane, but they give rise to no subjective symptoms. There is no expectoration from the throat or bronchi; loss of appetite is constant. Nausea is very frequent. Vomiting ushers in the attack in about a quarter of the cases. It may be repeated more than once. The matter ejected is tinged with bile. Constipation is commonly observed at some stage. Diarrhoea with watery stools has been noted in about 20 per cent. of the cases. It has never been very excessive or protracted. Occasionally blood has been present in the feces.

Vascular System.—A slow pulse is a well-marked feature of the ailment. A pulse-rate of under 90 has been recorded when the temperature was 104.7°F. Rates as low as 40 have been registered during the course of the pyrexia. There is a moderate degree of leucopenia. The average of 35 estimations was 5,428 leucocytes per c.mm. Several counts have been under 2,500. There does not seem to be any great fluctuation in the number of the leucocytes from day to day. The leucopenia may continue into convalescence. The polynuclear leucocytes are diminished; they number about 56 per cent., instead of the usual 65 to 75 per cent. The large and medium sized mononuclears are increased; the lymphocytes and eosinophiles are decreased. No parasites are found in the living or stained films. The spleen is not palpable, nor is the splenic dulness increased. The urine sometimes contains a trace of albumin.

The skin is usually dry, though the patient may at times perspire freely. But the profuse sweating such as ends a fit of ague does not occur. There is often much dilatation of the capillaries of the face, which causes some puffiness of the eyelids and features, and gives a dissipated look to the sufferer. The erythema may extend to the neck and upper part of chest. Rashes are absent, except those caused by biting insects. Herpes on the lips has been noted twice. There is no jaundice.

Stiffness and pain in the back and calves of the legs are rarely wanting. The discomfort is increased by movement. Hence the patient usually lies quite motionless in bed, and may be averse from looking round about him on account of the uneasy sensations in
the external muscles of the eye. Tenderness on pressure of the muscles is infrequent. The joints are not swollen; pain is sometimes referred to the knees.

Every case has ended in recovery. The fever has not left any after-effects, such as neuritis, cachexia, &c.

Second attacks have occurred in 6 per cent. A recrudescence of the fever on the fourth or fifth day has been once or twice charted.

Blood has been abstracted from the veins in front of the elbow in twenty-three instances. Cultures on agar and in peptone broth and in peptone bile have remained sterile for weeks. If the needle of the syringe be sharpened on a hone and its point examined with a lens, the method of drawing blood from a vein in the forearm is less painful than a finger-prick. A blunt needle is a frequent cause of failure.

Serum agglutination examinations have been made in 47 instances. Neither the Micrococcus melitensis nor Bacillus typhosus, nor B. paratyphoid A and B have been clumped by dilutions of the blood higher than what obtain in health.

Blood films have been stained by many methods, including that for deep chromatin, and have been examined with a Zeiss apochromatic 2 mm. N.A. 1.4. No malarial or other parasites, nor any structural alterations in the blood elements, have been discovered. Specimens of the living blood under the same power have shown no abnormality.

The following diseases have been excluded by these negative results: malaria, relapsing fever, trypanosome fever, Malta, typhoid and paratyphoid fevers, streptococcic, staphylococcic, tetragenous, pneumococcic and influenzal infections, and Rogers' "seven-day" fever, which he states is caused by a typhoid-like bacillus.

In sifting the patients' histories of the probable causes of the illness, the statement that they had been bitten by "sand-flies" occurs with the greatest frequency.

The "sand-fly" of Malta and Crete is the P. papatasii, which makes its appearance in scant numbers at the end of April and beginning of May, and becomes more numerous as the summer advances. It has been found in all places where those who have contracted the fever have resided. There is a correlation between the distribution of P. papatasii and the ailment. Where phlebotomi have been few or wanting, there has been also an absence of febricula; and where the phlebotomus has been abundant, there the fever has prevailed, often in the form of an explosive outbreak. In a large barrack-room which gave a daily supply of about a dozen
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"sand-flies" to the laboratory, one case occurred, and was followed in quick succession by others, until most of the occupants of the beds adjoining the haunts of the fly had been attacked.

A small room in an old building on Suda Island, Crete, was used as a quarter for a detachment which consisted of an N.C.O. and five men. They all became infected, and passed through typical attacks of phlebotomus fever. Though none of them were aware of the existence of the phlebotomus, they bore marks of the bites, and Captain R. G. Meredith, R.A.M.C., and I captured over a dozen phlebotomi distended with their blood. The minute size of *P. papatasii* and their lightly coloured wings and body render them almost invisible in their flight, and therefore they often escape observation. Negative evidence as to the absence of the phlebotomus in a habitation must be taken with reserve. Only after a thorough examination of likely spots in the daytime is it possible to arrive at a reliable conclusion.

The phlebotomi select dark corners and recesses, away from light, glare, and noise, in which they settle during the day. Clothing hanging from pegs on the wall affords them a favourite retreat. They are attracted by the human odour. Many may be found in an inhabited room, but none in one next door which is vacant. Spider webs have no terrors for them; we have never seen them immeshed, and we have watched them fearlessly enter corners festooned with these traps. They elude capture with great facility on account of their sudden and rapid side movements. Large-sized glass-bottomed cardboard pill-boxes are the means we have employed in collecting the flies. A phlebotomus resting on the wall is slowly approached and then quickly covered with the pill-box. A card is inserted between the box and the wall. The fly, nevertheless, frequently effects escape while the card is being replaced by the cover of the box. By this means ten or a dozen flies may be caught in half an hour in a favourable locality; nearly 3,000 have been thus captured. The phlebotomus avoids painted surfaces. Its choice leans to white-washed, stone, or plaster walls. The study of the habits and life-history of *P. papatasii* has been pursued with great interest by the officers, non-commissioned officers, and men of the Royal Army Medical Corps. Colonel J. G. MacNeece, Lieutenant-Colonel H. Esmond White, Lieutenant-Colonel J. J. Gerrard, Major G. Crawford, Captains H. S. Anderson, M. H. Babington, P. J. Marett, J. B. G. Mulligan, P. S. Stewart; Lieutenants W. K. Beaman, H. G. Gibson; Serjeant-Major R. Stanley, Staff-Serjeant Storey, Corporal T. Kerr, and Private W. J. Scorey, have been most
enthusiastic in trapping and preserving in captivity this insect, and in hunting for its ova and larvae. Following Grassi’s observations, we have collected the most varied materials—human and animal dejecta, earth and rubbish, stones from cellars, dust, cobwebs and mortar from walls, scrapings of ventilation pipes of sewers, water, slime and putrid matter from wells, cesspools and sewers, seaweed, decaying leaves, fragments of paper, straw, shavings from dark moist corners, the bark, fruit, leaves, and roots of trees, &c., &c.—and after submitting them to microscopical examination we have placed these substances in Petri dishes or gauze-covered bottles, where they have remained for weeks and months. Unfortunately, we have not yet succeeded in detecting the ova or larvae in any of our samples, nor has the adult *P. papatasii* ever hatched out from larvae which might have been hidden in the materials. Grassi admits that he has only rarely found the ova and larvae in nature, “Non avendo potuto avere che un piccolissimo numero di larve.”

We have endeavoured to entrap the fly in the open, by placing flat objects, such as tin plates, boards, &c., the surfaces of which have been covered with fresh paint, linseed oil, paraffin, or other greasy material, over drains, holes in walls, crannies in rocks, clefts in woodwork, fissures in the bark of trees, &c. Though many flies have been ensnared by the oily substance, *P. papatasii* has not been found among them. We have never discovered phlebotomus on the under surfaces of the air-tight covers of the inspection chambers of sewers. The harmless psychoda has been abundant in this situation. Phlebotomus has not been caught in chiffon-covered frames applied to the openings of the ventilation pipes of sewers, or to the seats of latrines.

By placing female *P. papatasii* on leaves in bottles, Major Crawford, Captain Anderson, Captain Marett and I have obtained a few larvae hatched out of ova deposited on the leaves. They have never reached maturity, and survived for a few days only. This is not altogether surprising, since many diptera require special conditions for their development. Giles, in his work on mosquitoes, states that he has not yet succeeded in rearing anopheles from egg to imago. The Imperial Entomologist with the Government of India (Bulletin No. 7) used wet blotting-paper soaked with the decayed pulp of cucurbitaceous fruits for hatching the eggs of phlebotomus, but his larvae soon died. He states that the larvae have not been found in the field in India.

Grassi recently has been able to rear the phlebotomus from ovum to maturity. He allowed me to inspect the chamber in Rome.
in which he had conducted the experiments which succeeded only after several years of failure. It was a dimly-lighted room, somewhat below the level of the street. The floor was damp and covered with fragments of stone, mortar, brick, &c., which retained a considerable amount of moisture. He gave me a piece of mortar, in a crevice of which a nymph-case can just be discerned with the unaided eye. On returning to Malta we redoubled our efforts in the search for similar vestiges in bits of stone from old walls, cellars, caverns, &c. Although we failed to verify our suspicion, it seems that crannies and crevices in walls or rocks are the places in which the P. papatasii selects to breed.

Doerr¹ has been equally disappointed in his search for the breeding places of phlebotomus in Mostar during the summer of 1909.

It was hoped that by following the life-history of a harmless member of the same family, Psychoda phalaenoides, a key to the problem would be obtained. The larvae of this psychoda are abundant in the slime of sewers, and of walls which are constantly wet. They develop rapidly to the imago stage in captivity, and a fresh generation can be reared under artificial conditions. These larvae perish if they are allowed to dry, but complete submersion also kills them. Judging by analogy, the rudimentary stages of Phlebotomus papatasii cannot be passed in any but damp places. The phlebotomus larvae we have reared were soft-bodied and unable to bear exsiccation. The habits of the two species are, however, distinct. P. papatasii are not found associated with the psychoda, so less was learnt than was anticipated.

The phlebotomus has thrived best in cages, the dimensions of which are 18 inches × 12 inches × 12 inches. The top and sides are covered with the finest chiffon; a sleeve of the same material is fixed at one end. Fragments of porous stone moistened with water, or wet blotting-paper on a plate, together with fruit of various sorts, are placed in the cage. The phlebotomi only rarely have been seen to feed on this vegetable matter, nor have they been attracted by raw lean meat. The cage must be kept in a sheltered spot. Exposure to the sun rapidly destroys the phlebotomi. Under the most favourable circumstances they have survived no longer than a fortnight. Many expire within a few days of capture, though still seen to be distended with blood. If an observer introduces his forearm into a cage containing twenty or thirty flies, it is

only rarely that he finds more than one or two punctures have been inflicted on him, though he may continue the experiment for half an hour, and though the "sand-flies" may have had no food since their capture. It is therefore apparent that there is considerable difficulty in infecting phlebotomis, in preserving them for a week after infection, and in inducing those that survive to bite at the end of that period.

It had been proposed to carry out the experimental part of the investigation on monkeys which had been brought from England for this purpose, but they proved to be immune. Four cubic centimetres of virulent blood caused no symptoms. Neither had broth-cultures of virulent blood or filtrates through Chamberland candles any pathogenic effect on monkeys, rabbits, or guinea-pigs. It therefore was necessary to enlist volunteers for the research. Many willingly came forward and offered themselves.

Science and humanity owe a debt of gratitude to the self-sacrificing courage and zeal of the gunners of the 99th Company of Royal Garrison Artillery. When the object of the research was explained to them, they vied with one another in offering themselves as cheerful victims for the sake of mankind. The men of this company are of splendid physique, and they rejoice in rude health, which they maintain by the enthusiastic pursuit of athletics. Those volunteers who were selected for experiment had resided less than a year in the island. They were all exceptionally healthy, strong, and muscular men. The aches and pains during the acme of phlebotomis fever make the sufferer an object of our profound pity. Those who, of their own accord, knowingly submit to them, are martyrs indeed.

**Experiments with Infected Phlebotomi papatasii.**

Gunner Finn was admitted to the Military Hospital, Valletta, on June 12th, 1909, complaining of pain in the stomach, vomiting, and purging, which had come on suddenly that morning. His temperature was 102° F. (see Chart 4). His face was deeply flushed, and his eyes suffused in the manner characteristic of phlebotomis fever. His tongue was covered with thin white fur, except at the tip and edges; it was moist. He complained also of much headache and of pains in his back and in the calves of his legs. There was no rash, nor evidence of his having been bitten by insects. On the same evening he put his hand and forearm into a cage containing about fifteen *P. papatasii*, which had been caught in the Royal Army Medical Corps barrack-room,
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Valletta. They eagerly attacked him. On withdrawing his forearm half an hour later there were marks of seven punctures, which rapidly became the centres of urticarial spots, a centimetre in diameter, accompanied with much itching. These disappeared in a few hours. Next day no trace of the bites could be found.

FEVER EXPERIMENTALLY INDUCED BY MEANS OF INFECTED PHLEBOTOMI PAPATASII.

FEVER CAUSED BY BITES OF INFECTED PHLEBOTOMUS PAPATASII.

![Chart 4](chart4.png)

The gastric symptoms soon ceased. His temperature fell to the normal on the second day, and his convalescence was rapid (see Chart 4).

Experiment 1.—Seven days later,¹ at 1 p.m., Lieutenant H. G.

¹ Since Doerr showed that phlebotomi were not immediately infective after sucking virulent blood.
Gibson, R.A.M.C., introduced his forearm into this cage and was bitten by one phlebotomus. A small, irritable papule was the result, which remained visible for forty-eight hours. On June 26, seven days after submitting to the bite, he began to feel unwell. Severe vomiting, repeated three times with much nausea, came on. Headache, pains in the back, lower extremities and abdomen caused him to pass an almost sleepless night. Movements in bed were attended with much discomfort. On the following day he had the typical look of “Pappaticifeber,” deeply flushed face, and injected conjunctiva. His tongue was coated with a thin white fur, his taste was impaired, and he had much nausea, giddiness, and anorexia. General stiffness of the muscles of the back and lower limbs continued. His temperature was raised to 100°2 F., but his pulse was slow. He was constipated. He was inclined to somnolence, and was obliged to lie quite quiet in bed on account of the discomfort attending movements of any kind, and of giddiness when he attempted to raise his head. His eyeballs were tender. On the following day most of his symptoms had disappeared, and his convalescence was unimpeded (vide Chart 4).

Private Stansbury was admitted on June 29th, 1909, complaining of severe frontal headache, discomfort in the eyes, lumber and calf pains. He had been taken ill at 11 a.m. of that day. His face was much flushed, his conjunctivae injected, his tongue was coated with a thin white fur, it was rather large, and moist. He was constipated. His temperature was 101°5 F. and his pulse 88. Ten hours after the onset of the fever he submitted to the bites of *P. papatasii* confined in a cage. Several sucked his blood, though they left no trace on the following morning. His febrile symptoms were still severe next day. The frontal headache, intolerance of light and muscle pains became more pronounced. He resented being disturbed, and lay with his eyes closed, attempting to sleep. His pulse was slow. Improvement began on the third day. On the fourth day his temperature was still raised over 100°5 F., though his pulse was only 50 to 60. There was a crisis on the morning of the fifth day, with rapid convalescence (see Chart 5).

*Experiment 2.*—On July 9th, 1909—that is, ten days after the sand-flies were infected—Corporal H. Griggs, R.A.M.C., put his arm into their cage and was thrice stung. Six days eight hours later he began to shiver and to suffer from severe headache, especially over his eyes; weakness and pains in his legs and back, anorexia, thirst and high fever. Next day he remained much the same, but weaker, and became faint when he attempted to stand up.
He was constipated, and had complete loss of appetite. On the morning of the third day he was unable to stand on account of weakness and giddiness, his temperature was 100.5°F., and his pulse 80, which was irregular. His face was flushed and his conjunctivae injected. His tongue was large and flabby, and was coated with a pale, white fur, except at the tip. It was moist. There were no malarial or other parasites seen in films of his blood stained by Giemsa's fluid. His serum diluted ten times gave no reaction with the Micrococcus melitensis or Bacillus typhosus. His leucocytes were reduced in number—4,050 per c.mm. It will be seen on referring to Chart 5 that the pyrexia continued until the morning of the eighth day. There was no notable change in the character of his symptoms until they abated on the seventh day, when the stiffness of the muscles of his back and limbs and headache disappeared. He regained his usually robust health in a few days.

Experiments at the Royal Army Medical College, London, with Phlebotomi Infected in Malta.

Patients while in the first day of typical attacks of phlebotomus fever introduced their forearms into a cage containing seventy or eighty P. papatasii on August 22nd, 23rd, and 24th. (Vide Charts 6, 7, 8). Some of the phlebotomi sucked blood on each occasion.

Lieutenant-Colonel J. J. Gerrard undertook to convey these flies to London by the quickest route. He left Malta on the night of August 24th, 1909, and delivered the cage to Sir W. B. Leishman on the afternoon of August 28th, when he arrived in London. Sir W. B. Leishman, Lieutenants H. S. Ranken and F. W. M. Cunningham, R.A.M.C., at once endeavoured to feed the flies, which were now reduced to eight or ten, with their blood.

Sir W. B. Leishman is in doubt whether they attacked him. He could find no trace of a puncture on his skin.

Experiment 3.—Lieutenant H. S. Ranken was twice bitten. Minute ecchymoses formed round the site of the stings. Five days later he felt cold and uncomfortable and complained of frontal and temporal headache. The feeling of chilliness continued for about an hour after going to bed. On the second day his malaise remained. He had diarrhoea, and passed three profuse watery evacuations. On the third day he still retained the feeling of weariness, and suffered from diarrhoea. Improvement began on the fourth day and he speedily regained his health. No pyrexia was noted throughout the attack.
Charts of Patients who infected the Phlebotomi Papatasii despatched to Royal Army Medical College, London.

Chart 6.

Chart 7.

Chart 8.
Experiment 4.—Lieutenant F. W. M. Cunningham was bitten by one phlebotomus only. The small mark of the puncture disappeared in twenty-four hours. Five days after exposure to infection he began to suffer from slight headache, general malaise, feeling heavy and tired; diarrhoea set in. He had five actions of the bowels. On the second day he felt better, though the diarrhoea continued. On the third and fourth days he felt well. At 5.30 on the morning of fifth day he woke up with a slight degree of shivering, which passed off in a few seconds. A few minutes later it was repeated with greater severity, his teeth chattered and his head and shoulders trembled. His pulse was 90 and his skin was clammy. No thermometric observation was then made. He fell asleep again and woke up feeling quite well. Pyrexia was not noted at any time.

Franz, on p. 32 of Doerr’s monograph, “Das Pappatacifieber” notes the occurrence of cases of phlebotomus fever in which the intestinal symptoms are pronounced, with little or no elevation of temperature: “Auffallend war, dass hauptsächlich jene Fälle, die mit reichlichen diarrhoischen Entleerungen einsetzten, wiederholt nur von geringen Temperaturerhöhungen begleitet waren; desgleichen ging die Entfieberung rascher vor sich, wenn wässerige Stühle auf der Höhe des Fiebers auftraten.”

Later he says: “Ja es gibt Fälle, die zur Zeit der Epidemie einzelne Symptome des Pappatacifiebers aufwiesen, dabei jedoch gänzlich fieberfrei blieben.”

It was mentioned previously that diarrhoea is a symptom of the ailment in about 20 per cent. of the attacks in Malta.

Experiments with Blood.

No. 8242 Private J. Matthews, 2nd Somerset Light Infantry, was attacked with head- and backache on the morning of August 13th, 1909. His temperature was raised to 101° F.; his face was flushed, his tongue was large, moist, and coated with a thin white fur. His bowels were confined. He had not previously suffered from any infectious disease. His leucocytes were somewhat reduced in number—5,900 per c.mm. The serum did not agglutinate the M. melitensis, or the typhoid bacillus. His blood proved sterile on culture in broth. His was considered to be a favourable case for providing blood for experimental purposes; 9 cc. were withdrawn from the median basilic vein eighteen hours after the onset of his illness. His febrile symptoms continued throughout the second
day, and some epigastric tenderness and pain was noticed by him. Nevertheless he made a rapid recovery. (See Chart 9.)

Experiment 5.—No. 3568 Gunner Thomas Carey, 99th Company, Royal Garrison Artillery, volunteered to receive Matthews' blood. Accordingly 1.5 cc. of the blood withdrawn from Private Matthews at 6.30 p.m., August 13th, 1909, were immediately injected beneath the skin of Carey's forearm. Three days sixteen hours later, on the morning of August 17th, he was seized with a feeling of chilliness, malaise, rapidly followed by severe headache and pains in the lumbar region. He was incapacitated from work and lay on his bed, constantly moving himself, trying to get relief from his aches. His temperature in the evening was 101.4° F. His face was deeply flushed and his eyes were injected and tender and sensitive to light. His tongue was moist, but was coated with a thin layer of white fur. He was constipated and had complete loss of appetite, and was very thirsty. There was no rash or traces of bites of insects. On the morning of the second day his fever was unabated, but his pulse was reduced to 50 per minute. His leucocytes were few—5,950 per c.mm. The polynuclears were diminished to 57 per cent., while the medium-sized mononuclear and transitionals were increased to 19 per cent. No malarial parasites were present. His temperature fell on the evening of the second day and he made an uninterrupted recovery. (See Chart 10.)

Experiment 6.—No. 27733 Gunner Albert Edward Bradley, of the same company, Royal Garrison Artillery, was also a willing volunteer; 2 cc. of the blood withdrawn from Matthews at 6.30 p.m., August 13th, were forthwith injected beneath the skin of Bradley's forearm. He remained quite well until the morning of August 18th, four days sixteen hours after inoculation, when he began to suffer from aching in his head, back, and limbs, which caused him to toss restlessly in his bed, whither he was compelled to go. He had nausea, and he vomited once in the evening. His temperature was raised above 103° F., though his pulse was below 90. He passed a restless night, troubled with the pains in his head, eyes, back, and knees. Next day his face was still flushed and his conjunctive were injected. His tongue was moist, but coated with white fur, except at the top and edges. He complained of much stiffness in his limbs. His leucocytes were reduced to 5,600. The polynuclears were diminished to less than 50 per cent.; the deficiency was supplied by an increase in the medium-sized mononuclears and transitionals. Improvement set in on the third day. The attack ended without complication or delayed convalescence. (Vide Chart 11.)
FEVER INDUCED BY MEANS OF FILTERED AND UNFILTERED BLOOD.

Charts 9 to 13.

No. 1.—Fever caused by inoculation with fresh infected blood.

No. 2.—Fever caused by inoculation with fresh infected blood.

No. 3.—Fever caused by inoculation with filtered infected blood. Filtrate one day old.

No. 4.—Fever caused by inoculation with filtered infected blood. Filtrate eight days old.
EXPERIMENTS WITH FILTERED BLOOD.

Experiment 7.—Five cubic centimetres of Matthews' blood extracted at 6.30 p.m., August 13th, were mixed before coagulation had taken place with 45 cc. of sterile physiological salt solution. This mixture, which remained permanently free from clot, was immediately placed in a Cobbett's filter which had been sterilised. This was fitted with a "Chamberland F. candle contrôlé." The apparatus had been proved to be reliable by testing it with *M. melitensis* emulsion, which was kept back. Filtration of the blood and salt solution was conducted under the pressure of gravity only at a temperature of 78° F. About 20 cc. of filtrate was collected in twenty-four hours; this filtrate proved to be sterile on culture on agar. After the completion of the process the filter was again tested with the *M. melitensis*, and was found to be proof against this small micro-organism.

Seven cubic centimetres of this diluted filtered blood of Matthews, representing 0.7 cc. of fresh blood, were injected under the skin of the forearm of 28,086 Gunner Edwin George Bennett, 99th Company, Royal Garrison Artillery, who with great alacrity offered himself for experiment at 7.15 p.m. on August 14th, 1909. In the afternoon of August 19th, four days and twenty-one hours after inoculation with the filtered blood, he began to feel unwell. His head and back ached; his face became flushed, his eyes were suffused and the globes tender on gentle pressure. His temperature was raised to 101° F., but his pulse remained below 60. He passed a restless night on account of the discomfort in his head, eyes and back, though his fever was less next day. Loss of appetite and constipation were noted. His leucocytes amounted to 10,100, but there was a relative diminution in the polynuclears, which amounted to 61 per cent.; the medium-sized mononuclears were increased to 15 per cent. On the third day he felt much better. The improvement continued, but his temperature did not reach the normal morning level till the eighth day. Convalescence was rapid. (Vide Chart 12.)

Experiment 8.—Six cubic centimetres of the same filtrate, which had been preserved in the dark at a temperature of 75° F. to 80° F. for a week, were injected beneath the skin of the forearm of 27786 Gunner James McCauley, 99th Company, Royal Garrison Artillery, who, without solicitation, came to the laboratory requesting that he, too, might aid the investigation by submitting to inoculation. This corresponded to 0.6 cc. of undiluted blood. The injection was made at 7 p.m., August 21st. Four and a half days later, on the morning
of August 26th, he began to feel unwell, lost his appetite, and complained of headache. He was inclined to lie down all day. In the evening his temperature was 99.4°C and his pulse 72. His tongue was slightly furred and he had a heavy appearance in his eyes. Next morning his symptoms had passed off; his evening temperature was 98.2°C, and he looked almost well. He rapidly recovered his usual good health. (See Chart 13.)

Private T. Gillespie, 2nd Somerset Regiment, was admitted to hospital on September 15th, 1909. He came from a regiment and barracks where numerous cases of phlebotomus fever had occurred. His forearms bore traces of phlebotomus bites; notwithstanding this, he attributed his illness with great confidence to exposure to the sun on the rifle range on the day of his admission. The theory that most of the febricular attacks in hot climates are due to the sun has held sway so long and tenaciously that it was considered advisable to put it to the test of experiment. The attack came on suddenly with pains in his head, back, and in the calves of his legs. He could walk only with difficulty, and his comrades noticed that he looked very ill. He bore the characteristic aspect of phlebotomus fever; hot, dry skin, temperature 103.2°C, pulse 72, flushed face, heavy half-open eyelids, conjunctiva injected. He complained of a racking headache, chiefly confined to the forehead and eyes, which were sensitive to light, movements of the head, and gentle pressure. His tongue was large, moist, coated with a thin fur except at the tip and edges; his blood contained no parasites; the leucocytes were somewhat diminished, 6,500 per cubic millimetre. The polynuclears were decreased to 42 per cent., but the medium-sized mononuclears were increased to 22 per cent. Next day, though his fever was less, his symptoms were unabated; he vomited once, and was constipated. Twenty-three hours after the onset 9 cc. of blood were withdrawn from the median basilic vein; 3 cc. were injected immediately beneath the skin of the forearm of 28038 Gunner George Dyer, 99th Company, Royal Garrison Artillery; and 3 cc. were administered subcutaneously to 28884 Gunner Albert Meades, 99th Company, Royal Garrison Artillery; 3 cc. were inoculated into 200 of peptone broth. This remained sterile. Gillespie began to improve on the second day; his pulse was slow, 48 only, when his temperature was 102.6°C. His temperature fell on the third day; the pains in his head, back, and limbs were less, and his tongue began to lose its furred coating. On the fourth day he was almost well; his convalescence was unbroken. (See Chart 14.)

Experiment 9.—28884 Gunner Albert Meades, 99th Company,
Royal Garrison Artillery, voluntarily received 3 cc. of the blood of Gillespie beneath the skin of his forearm at 3.10 p.m. on September 16th, 1909, immediately after venesection had been performed. He was in excellent health and had never been ill. On the following evening he felt somewhat languid. Next day he had slight headache, some loss of appetite, and disinclination for exertion. His bowels were sluggish and his tongue was rough and furred in the centre. Purgatives gave some relief, but his ordinary vigour did not return. The morning of September 22nd, five and a half days after inoculation, marked the onset of a very severe attack of phlebotomus fever. Headache commenced, with pains in his arms,
legs, knees, and back, which continued with increasing severity. On the evening of that day his flushed face, half-closed palpebral apertures, suffused conjunctivæ, and look of distress were typical of the fever. One-third of a grammè of phenacetin was given to alleviate his headache, which had now become almost unbearable. On the second day of the attack the symptoms were unrelieved. He had much nausea, distaste for food, and he vomited once: his tongue was coated with a white creamy fur except at the tip and edges; he could hardly move in bed on account of the pain and stiffness in his body and limbs; his headache was intense; his eyes were sensitive to light and were tender on pressure; ocular movements were attended with discomfort; he was drowsy, but restless. Notwithstanding four degrees of fever his pulse remained below 80. His leucocytes were diminished to 4,125 per cubic millimetre. There was a diminution in the number of polynuclears and an increase in the medium-sized mononuclears. No malarial or other parasites were found in films stained by Giemsa. On the third day improvement began, though he was much harassed by the stiffness and pain on movement of his back and leg muscles. He slept the greater part of the day. On the fourth day his temperature had fallen below 100° F., and his symptoms were becoming less pronounced; his tongue remained dirty. He expressed himself as feeling nearly well on the fifth day. His convalescence was unbroken. (Chart 15.)

This case affords a good example of a prodromal stage which has been observed by Pick in "pappataci fever." A few examples of malaise and slight disorders of digestion preliminary to the onset of the pyrexia have been noted in this Malta epidemic.

Gunner Meades at no time exhibited any rash, nor marks of biting insects.

Experiment 10.—No. 28038 Gunner George Dyer, of the same company, was Meades' companion in offering himself for an experiment by which he might benefit his fellow-men; 3 cc. of Gillespie's blood immediately after withdrawal were injected subcutaneously into his forearm at 3.10 p.m. on September 16th, 1909. Dyer was in perfect condition and had always enjoyed robust health. He had not been bitten by phlebotomi. On the morning of September 22nd, five and a half days after inoculation, he complained of chilliness, headache, malaise, and distaste for food and impaired taste. The same evening his temperature rose to 102.4° F. The pains in his head, back, and calves of his legs were more marked. He passed a restless night. On the second day all his symptoms were aggra-
vated. His face was much flushed. His headache was worse, confined chiefly to the forehead and eyes, which he could hardly open. The general stiffness of the muscles in his trunk and limbs limited his movements in bed. His tongue was thickly coated with brownish white fur, except at the tip and edges. He had vesicles on the mucous membrane of his mouth and palate. His pulse was slow and rather irregular. His leucocytes were 8,575 per c.mm. There was a decrease in polynuclears and lymphocytes and an increase to 38 per cent. in the medium-sized mononuclears. There were no malarial or other parasites evident in blood-films. Though his seizure was not quite so acute as Meades', he bore the aspect of suffering great distress during the height of the fever. On the third day the intensity of his symptoms was becoming subdued and he spent many hours in sleep. His mouth and tongue were still abnormal. The fever subsided on the fourth day. (Chart 16.) A leucocyte count gave 5,970 per c.mm. On the fifth day he had nearly recovered his usual health, but his pulse was still slow and irregular. No rash was observed. He rapidly regained his vigour.

All those gunners who volunteered for experimental inoculation were quartered in St. Elmo Fort, where we were unable to discover any *P. papatasii*. Although about 350 was the number of troops occupying this fort, only three cases of phlebotomus fever had occurred among them. Moreover, nearly two months had elapsed since the date of the last admission, at the time of the experiments. No vestige of a midge-bite was detected on any of these soldiers just mentioned. By these means it has been proved—

1. That the blood of a person suffering from phlebotomus fever is virulent during the first day;
2. That the virus can pass through a Pasteur Chamberland candle "F";
3. That the *P. papatasii* can convey the infection;
4. That the incubation period has varied from three days sixteen hours to seven days;
5. That *P. papatasii* are infective seven to ten days after sucking virulent blood;
6. That the virus retains its activity for a week *in vitro*.

The phlebotomus fever of Malta and Crete is a milder ailment than that of Herzegovina described in R. Doerr's classical mono-

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1 Negative results were obtained with flies which had been infected under a week. It was seldom that they survived longer than ten days in captivity. Experiments with survivors were also unsuccessful.
phlebotomus fever is an infection distinct from dengue, which, too, is caused by an invisible virus conveyed by the culex. Dengue has well-marked clinical signs in the rashes and joint pains, which are of a much severer description than the aches of phlebotomus fever. Moreover, dengue has occasionally visited Malta. In the autumn and winter of 1881 it was epidemic. But there is no record of an outbreak during the summer.

Ophthalmo and skin reactions with the virulent blood of phlebotomus fever gave negative results. Mixtures of serum of patients in the course of the fever with that of convalescents resulted in no precipitation. So far, therefore, no specific test for diagnosing the infection has been discovered, except human inoculation.

R. Doerr’s researches on “Pappatacifieber,” in Dalmatia and Herzegovina, instigated similar investigations on the cause and nature of the kindred febrile ailments in the British Mediterranean possessions. The experiments which have been described above confirm in every respect Doerr’s results.\(^1\)

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