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MALTA FEVER

by
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MALTA FEVER.

In the April and June numbers of this Journal for 1904, there appeared Editorials bringing up to that date our knowledge of Malta Fever. A good deal of work has been done since then, and many new facts and observations obtained. It will be well, then, to again make a survey of this subject, which is of such importance to the Army and Navy in Malta, this fever being said to give rise, yearly, to some 120,000 days of disease among the soldiers and sailors stationed there. The same arrangement of the new matter will be made as in previous papers, in order to make comparison easy. This arrangement brings the subject, broadly, under four heads: I. Epidemiology. II. How does the *Micrococcus melitensis* leave the body? III. The Micrococcus outside the body. IV. How does the Micrococcus gain entrance to the body? But first a word in regard to the history of the investigation of this disease since 1904.

Historical.—The chief event of importance which has happened during the last two years is that a Committee has been formed by the Royal Society, at the request of the Colonial Office, Admiralty, and War Office, to take steps for the investigation of this fever. A Commission, consisting of Major W. H. Horrocks, R.A.M.C., Staff-Surgeon E. A. Shaw, R.N., Dr. T. Zammit, and Captain J. Crawford Kennedy, R.A.M.C., has been at work during the last two seasons, with the result that many interesting observations have been made. Dr. R. W. Johnstone, Local Government Board, went out to Malta during the summer of 1904 to work at the epidemiology of the fever, and Lieutenant-Colonel A. M. Davies, R.A.M.C, took up the same line of work in the summer of 1905. Fleet Surgeon P. W. Bassett-Smith, R.N., Staff-Surgeon R. T. Gilmour, R.N., and J. W. H. Eyre, have also sent in Reports.

I.—Epidemiology.

The keynote of this paper is prevention. What we have set out to do is to discover some fundamental fact in the mode of spread of Malta fever, which knowledge will enable us to lessen the numbers attacked in future. Under this heading of Epidemiology are therefore collected observations which may assist in this search, and help to point to the factor or factors concerned in the spread of the infection. If Malta fever is spread by contaminated dust, then the curve of rain-fall should show some connection. If by mosquitoes, the temperature-curve. If the spread is due to insanitary conditions, the study of the incidence among various classes of the community might be expected to throw light. If the infection is altogether due to an animal, such as the goat, then the fever should be absent where the goat is absent, and thus the Geographical Distribution might give some aid.

Geographical Distribution.—The most important addition to our knowledge of the distribution of this fever is contained in a paper by Lieutenant-Colonel C. Birt, R.A.M.C., on Mediterranean Fever in South Africa, in which he shows conclusively that Mediterranean fever is endemic in certain parts of the Orange River Colony. It has been the fashion of late to try to limit the geographical distribution of Malta fever to Malta itself. Especially has it been doubted if it is endemic in India. This doubt has now been set at rest by Lamb and Pais, who have isolated the *M. melitensis* from the spleens of a number of persons in the Punjab suspected to be suffering from Malta fever.

Distribution in Malta.—In the previous Editorials it was stated that Malta fever is as prevalent in the country villages as in the big cities. The same result is arrived at by Dr. Johnstone in his Report to the Royal Society, dated April, 1905. He says, that the very general distribution of Malta fever throughout the island is perhaps the most striking feature of this disease. It is by no means the localities closest to the harbours which suffer most severely. Hamrun, a somewhat squalid suburb, and the combined villages of Lia, Attard, and Balzan, show the heaviest incidence, while Valletta and the three fortified towns are amongst the least severely attacked. He divides Malta into three areas, and gives the rates of incidence per 10,000 for each area as follows:—

(1) Urban drained area	18·8
(2) Suburban undrained area	41·8
(3) Rural area	33·4

These figures are probably much smaller than they should be, on account of deficient notification. Johnstone concludes, that the distribution of Malta fever amongst the civil population goes to show that, outside certain paved and drained areas, aggregation of persons in one locality, and density of population upon area in a district, favour the spread of the disease. What factor this is due to he cannot say, although he has suspicions that excretal pollution of the hands and the food, or the dust of houses, may have something to say to the spread of infection.

Ambulatory Cases of Malta Fever.—Related to the distribution of this fever in Malta, is the question as to whether there is any danger to the community from unnotified ambulatory cases. If it were shown that a large number of Maltese are going about their ordinary work, showing no symptoms of Malta fever, but carrying the *M. melitensis* in their blood, and excreting it in their urine, it is possible that this, as in enteric, would constitute a danger. Shaw undertook the investigation of this. He examined 525 men working in the dockyard by the serum test, and seventy-nine of these responded. Twenty-two out of the seventy-nine responded in a marked manner, and these were examined as to their urine and blood containing the specific micro-organism. In nine out of the twenty-two the micrococcus was recovered from the urine, and in four from the blood. It is therefore possible that 10 to 15 per cent. of the native population are suffering from some mild form of the fever, or from the effects of an attack within the previous two or three years, and that 1 to 2 per cent. excrete the micrococcus in their urine, and are therefore a possible danger to the community.

Are other Animals besides Man Susceptible to Malta Fever? Attention was first directed to the goats, which are so numerous and so much a feature in every-day life in Malta, and which supply most of the milk used in the island. It is unnecessary to describe the various steps which led up to the important discovery that, roughly speaking, about 50 per cent. of the goats in Malta are affected by this disease, and that 10 per cent. are excreting the micrococcus in their milk.

This led to the examination of the cows in the island. Thirty-three were examined by Shaw by means of the serum agglutination test. Nine out of the thirty-three responded to the test. The milk of these nine was then examined for the presence of the micrococcus, and it was found in two.

Then the mules were suspected. Kennedy examined eighty-seven of these animals, and obtained a positive reaction in thirty-nine. The serum reaction was in every case rather low, only two reaching 1—40. He concludes that mules suffer in a mild way from Malta fever infection.

Lastly, the dogs were examined by Kennedy. One hundred and fourteen were tested, with a positive agglutination reaction in fifteen. These fifteen dogs were examined *post-mortem* and the micrococcus removed from the mesenteric glands of one.

It appears, then, that even the dog can harbour the virus of Malta fever, and as it is reported that there are some 40,000 in Malta and Gozo, it is possible that the dog may act to some small degree as a carrier of the disease.

In addition to these domestic animals the monkey takes the fever readily by either feeding or subcutaneous inoculation, and the common laboratory animals—the rabbit and guinea-pig—can also be artificially infected.

This micrococcus is therefore capable of living in and affecting many species of animals. The disease it sets up is most severe in man and next in the monkey; it does not appear to give rise to marked symptoms in the domestic animals.

Relation of Temperature and Rainfall to Malta Fever.—The following chart, given by Johnstone, shows the temperature, rainfall and number of cases amongst the civil population during the period 1894-1903.

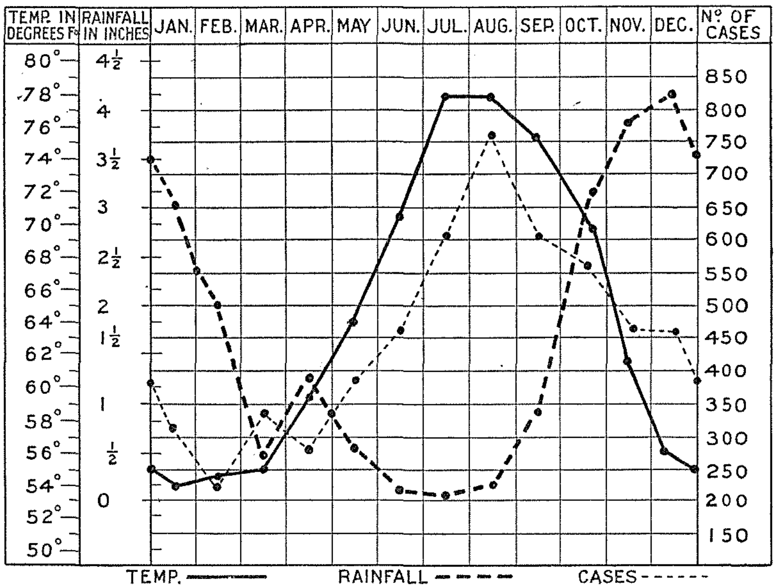

CHART 1.

Johnstone's chart may be compared with the next, which represents the number of cases admitted into the Station Hospital, Valletta, during fourteen years, with the temperature and rainfall as registered in Army Records.

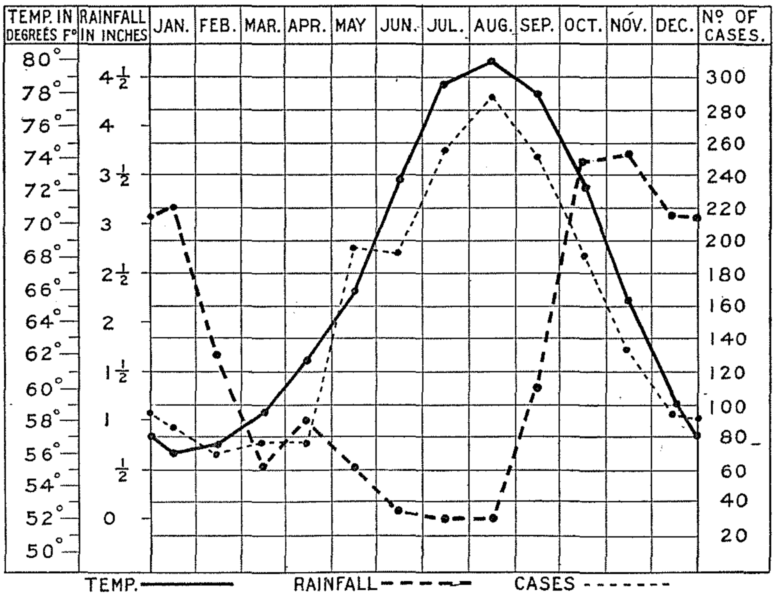

CHART 2.

Johnstone writes: "It will be at once seen that there is a very close correspondence between the curve representing the temperature, and that representing the number of cases. The rise of the latter curve follows that of the former at an interval of about one month, which would be approximately sufficient to allow for the incubation and notification if the incidence of fever were directly dependent upon the temperature of the air. The case-curve attains its maximum in July, but, unlike the temperature-curve, it at once commences to drop, so that it would appear that whatever connection the air temperature may have with case incidence, it does not remain so obvious after the former has attained its maximum. The curve representing rainfall is, in general, the inverse of that representing temperature. The case-curve commences to drop at the same time that the rainfall-curve commences to rise, allowing no interval for incubation and notification, so that the connection is not clear; nor does the steep rise of the rainfall-curve at the end of September produce a corresponding steep decline in the case-curve, as might have been expected, were the connection between the two intimate."

It also appears to us as if there must be some connection between Malta fever and temperature, but what it is is impossible at present to say. If there is, as is probably the case, more than one factor in the spread of the disease, dust or mosquitoes might account for the prevalence in the hot, dry months, and some other factor, such as goats' milk, for its persistence throughout the year.

Seasonal Incidence.—The following chart represents the number of cases of Malta fever admitted to the Station Hospital, Valletta, each month, for fourteen years :—

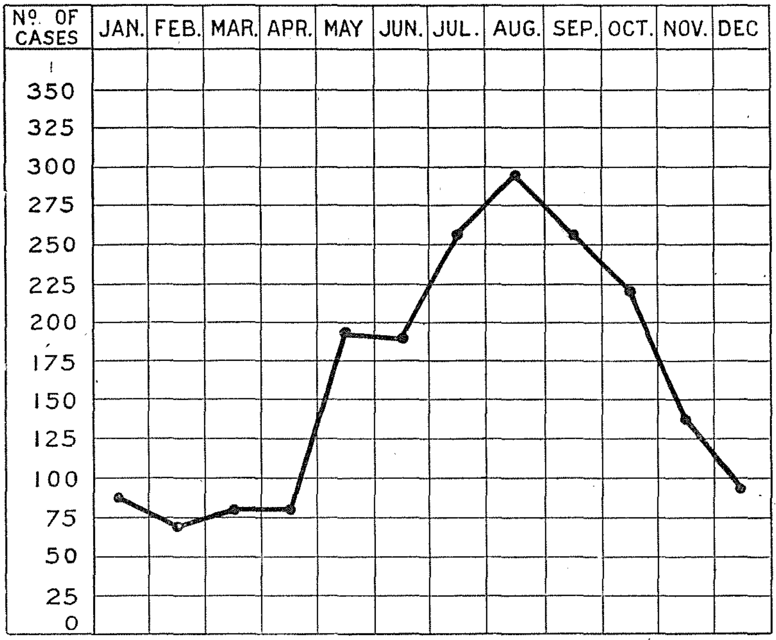

CHART 3.

The numbers are taken from papers by Hughes, Kennedy and the writer, and may be relied upon as being fairly correct.

Dr. Johnstone also gives a chart in his Report, showing the number of cases amongst the civil population during the period 1894-1903, which is also given. (See Chart 4.)

These charts are fairly alike, and from them may be learnt that the fewest number of cases of the fever occur in the cold months, that the curve begins to rise in May, and reaches its highest point in August, and that the greatest number of cases occur in July, August and September. One important point should be noted: that although there is a great increase in the prevalence of Malta fever during the hot months, yet many cases also occur in winter. In the one chart, the cases in January, February and March are about one-third as many as in July, August and September, and in the other about one-half. Now what interpretation can be put on these charts? If the disease is spread by contaminated dust, or by mosquitoes, one would expect to find the curve sink much further during the rainy, cold months of winter; if, on the other hand, goats' milk is chiefly to blame, then it is difficult to understand the difference of incidence in summer and winter. As mentioned above, two or more factors may come in to determine the curve of the seasonal prevalence. It is evident, however, that curves of temperature, rainfall and seasonal prevalence will not as yet give us the clue sought.

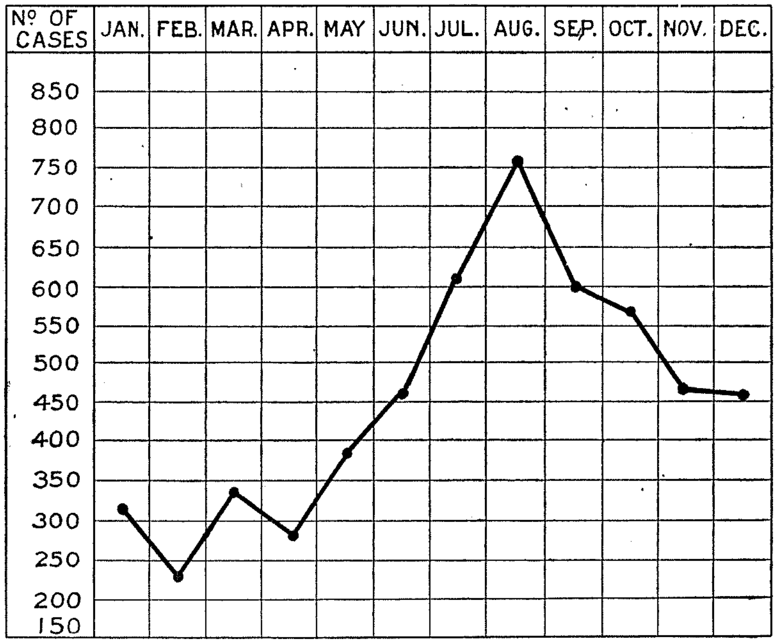

CHART 4.

Incubation Period.—It is most important that this should be known as accurately as possible. The work of the epidemiologist depends much on this knowledge, as it enables him to locate the sick at the time of infection. It has always seemed likely that given a correct incubation period, the careful collection of a few hundred cases, with the circumstances of their surroundings at the time of infection, should give the key to the mode of spread of this disease. Every case which occurs among our soldiers and sailors should certainly be subjected to the most careful study from this point of view, in order that a body of evidence may be collected to this end. Johnstone came to the conclusion that the incubation of Malta fever ranges about a period of fourteen days. Kennedy, in working at the incidence among patients in hospital, excluded all cases diagnosed Malta fever within twenty days after admission. Davies writes: "As we are at present ignorant of the path of infection in man, we must assume that incubation may be as short as about a week, and may be as long as about five weeks, according as the infection is by inoculation or by feeding. But considering the very much smaller doses of pathogenic material likely to be actually absorbed than those used experimentally in the laboratory, it seems probable that not less than a fortnight should be regarded as a minimum period, and that the maximum period should be extended to about six weeks at least."

From subcutaneous inoculation experiments on monkeys, it would appear that about five days elapse before signs of the disease appear. In feeding experiments, one monkey fed on infective material on two successive days, did not show any symptoms for thirty-two days: and Horrocks thinks from his experiments with infective goats' milk, that the incubation period may be long, and may even extend to two months.

The writer, in previous papers, stated that it is impossible to state definitely how long the period of incubation is, but that it probably ranges from a few days, say six, to twenty or thirty. The conclusion at the present time must be much the same—more observations, more experiments are wanted.

Does one attack of Malta Fever confer Immunity ?—In 1889, the writer stated that his experience led him to the general conclusion that, as in many other infective diseases, one attack of this fever does, as a rule, confer immunity.

The only experiment made by the Commission bearing on this matter is that which Shaw reports. Two monkeys which had recovered from an attack of Malta fever were further inoculated subcutaneously. No rise of temperature or other symptom of fever supervened.

Length of Service in Malta.—According to Johnstone, the heaviest incidence is upon men with less than one year's service. The incidence upon men with over two years' service is less than half that upon men with under two years' service. This, he considers is no doubt due to a large extent to the elimination of the more susceptible subjects.

Case Mortality.—In 1889, the writer put it at about 2 per cent. Hughes, in 1897, stated that during the six years he spent in Malta the mortality varied greatly from year to year, but averaged fairly constantly slightly over 2 per cent. of the cases attacked. Johnstone states that, in the Army, during the period 1897 to 1903, the case mortality was 3·2 per cent.; among the civil population 8·9 per cent. This high mortality among the civilians he considers is largely due to the fact that mild cases more often escape notification than severe ones.

II.—How does the *Micrococcus melitensis* Leave the Body?

The *M. melitensis* has never been found, up to the present time, outside the bodies of warm-blooded animals or blood-sucking insects, except under artificial conditions. We will, therefore, describe how it leaves the body before studying its behaviour outside. The distribution of the micrococcus in the body on *post-mortem* examination has been made by Kennedy. He found it in the spleen, liver, kidneys, lymphatic glands, salivary glands, blood and bile, but not in the intestines. He thinks the examination of the lymphatic glands to be most important, as they are often the only organs which contain it.

The various channels by which a micro-organism might be supposed to leave the body, are by such secretions as the tears, nasal mucus, saliva, bronchial secretion by expectoration, gastric by vomiting, sweat, milk, urine and fæces. Further, an important way of leaving the body may be by way of the blood, by the agency of biting insects. Several of these routes have been investigated by the members of the Commission.

Expired Air.—A great many experiments were made to try to discover the micrococcus in expired air. Patients in various stages of the disease were made to breathe through an apparatus containing sterile broth, and this broth was then plated out. Two monkeys were also injected with similar broth. In no single case was the microbe recovered.

Saliva, Expectoration, Sweat, and Scrapings of Skin.—Many experiments were made by Horrocks, Shaw and Kennedy on these lines, but in no case was the micrococcus found.

Fæces.—More than a thousand plates were examined by Horrocks without success. It is probable, however, that it does leave the body in this way in small numbers, as it has been found in the bile of man; and Eyre has found it all along the small and large intestines of experimental animals. It must surely be in small numbers in man, else it would have appeared on the plates, and therefore this source of infection is probably not an important one.

Urine.—This seems to be one of the main paths by which the micrococcus leaves the body. Horrocks isolated it thirty-nine times from thirteen cases of Mediterranean fever. He did not find it earlier than the fifteenth day, or later than the eighty-second day of disease. The average number per cubic centimetre was fifty-three (maximum 596, minimum 3). Kennedy examined sixty-one cases, and isolated it from the urine of thirty-three (54 per cent.). He examined 1,974 samples from these sixty-one cases, and recovered it 186 times (9·5 per cent.). The earliest day he recovered it was the twenty-first, and the latest the two hundred and forty-ninth. On two occasions he found the micrococci innumerable in the urine, The other cases gave an average of 139 per cubic centimetre (maximum 1,068, minimum 3).

The result of these experiments shows that the micrococcus is excreted in the urine of Malta fever cases from about the fifteenth day of disease until after convalescence is established. In one hundred samples of urine it will probably be present in ten. The number of micrococci present, except on rare occasions, is small. The urine, then, is the most important path we know of, except milk, by which the virus can leave the body. Infection by means of food, dust, &c., contaminated by Malta fever urine, must, therefore, receive careful consideration.

Milk.—This is, perhaps, from an etiological point of view, the most important route by which the micrococcus leaves the body. Observations up to the present have only been made on the milk of the lower animals, especially the goat and cow, but there can be little doubt that it is also excreted in human milk. It is not possible to give the number of micrococci per cubic centimetre in the milk, as this fluid was always centrifuged before being plated, but practically there were sufficient present to infect healthy monkeys when the milk was given by the mouth. This subject will be more fully dealt with in the section on infection by goats' milk.

Blood.—The presence of the micrococci in the peripheral blood has been investigated very fully by the Commission, as the subject is important from the point of view of infection by means of biting insects. Gilmour found it in 82 per cent., Zammit in 54 per cent., Shaw in 68 per cent. and Bassett-Smith in 59 per cent. of the cases examined.

The micrococci are never numerous in the blood. The smallest quantity of blood in which it was found by Shaw was 4 cubic millimetres, and Gilmour states that "the number per cubic centimetre is small, rarely reaching 100." The largest number found by him was 400 per cubic centimetre. These numbers may not be very accurate, but the broad fact remains that this micro-organism is never found in large numbers in the blood.

The question of infection by way of the blood, through the agency of mosquitoes, &c., requires careful consideration. This will be done in the section on how the micrococcus gains entrance to the body; suffice to point out here that the micrococci are so scarce in the peripheral blood, that it is difficult to imagine this disease being conveyed by mosquitoes or other biting insects. It must be borne in mind, however, that the latest teaching on the subject of plague would go to show that the spread of that disease is mainly by the rat-flea, and the plague bacilli are absent, or almost absent, from the blood of the rat, except during the last few hours of life.

III.—The Micrococcus Outside the Body.

The M. melitensis.—There is little to add to the description the writer has written in previous Editorials. In regard to the best culture medium for separating this micro-organism from others, and of recognising it when found, a word may be said. During the work of the last two years, Horrocks has found a medium, containing glucose, litmus, nutrose, and agar, and having an acid reaction of + 10 (Eyre's scale), to be the most satisfactory material for separating it from other bacteria. To recognise it, he writes: "A micro-organism which agglutinates with a specific animal serum in a high dilution, does not ferment glucose, renders milk alkaline without coagulation, may justly be regarded as the *M. melitensis*." [1]

Shaw tried to make out if there was any likelihood of being able to separate it from other species of bacteria by means of filtration. As this microbe is small, it was thought that a filter might be found which would let it pass through, while the bulk of the ordinary water bacteria were caught. Experiments were made with Chamberland filters, F, and with Berkefeld filters, N, V, and W, but in no case did it pass through. The experiment, therefore,

[1] *Vide* Horrocks' Reports reprinted in the Royal Army Medical Corps Journal, vol. v.

failed, and it does not appear likely that this method will succeed in the future.

Duration of Life in Water.—The following table gives the result of the several experiences.

Sterilised.

	Number of experiments	Minimum number of days	Maximum number of days	Average number of days
Tap-water	12	6	50	32
Sea-water	6	13	34	23
Unsterilised.				
Tap-water	6	7	73	42
Sea-water	2	0	46	23
Tank-water	2	10	12	11

From this it can be seen that it can retain its vitality in various waters, sterile and non-sterile, for considerable periods of time, but there is no proof that any multiplication takes place; it seems rather to die out gradually, and the length of time it is recovered depends a good deal on the number put into the water at first. Up to the present, it has never been found in water under natural conditions.

Although it appears to be possible that infection may be carried by means of drinking water to which the micrococcus has gained entrance, still there is no proof that this has ever occurred, or does occur, or is an important factor in the spread of this disease. The old speculation in regard to the part played by the harbour water may now be abandoned.

Duration of Life in Urine from Mediterranean Fever Cases.—In view of the fact, as shown above, that the micrococcus is frequently excreted in urine from Mediterranean fever cases, it seemed important to find out how long it retained its vitality in this medium. The point was approached in various ways. Bassett-Smith sterilised various Mediterranean fever urines, and artificially inoculated them. He found it retained its vitality on an average for twenty-two days (minimum 9, maximum 41). Kennedy, working with naturally-infected urines, found that it could be recovered on an average for eight days (minimum 1, maximum 16).

Duration of Life in a Dry Condition in Sterilised Materials:—

Method used	Number of experiments	Minimum number of days	Maximum number of days	Average number of days
Dried on cover-slips ..	2	15	16	15·5
On flannel, serge, &c. ..	7	7	80	28
In sterile dust, sand, limestone, &c.	19	3	91	31

Duration of Life in natural non-sterile Street Dust which has been artificially inoculated with an Emulsion of the Micrococci from a Culture.—Horrocks made several experiments in this direction, with the result that living micrococci were recovered for twenty-eight days. When he tried the experiment with ordinary non-sterile manured garden soil, he was only able to recover it for five days.

These experiments are, of course, laboratory experiments, in which large quantities of the cocci are added to the dust or soil. It is difficult to picture such gross contamination of the soil under natural conditions. This leads us to the next question.

Duration of Life in non-sterile Street Dust which has been wet with Mediterranean Fever Urine.—The most usual way in which the dust or soil becomes contaminated is probably by the urine of men or animals suffering from Mediterranean fever. Horrocks, therefore, tried to recover the micrococcus from street dust which he had artificially contaminated with a urine known to be rich in these organisms, but in no instance did he succeed, not even when he first sterilised the dust. Of course, this is no argument that it is really killed off, it only proved that it cannot be recovered on account of the overwhelming numbers of other micro-organisms which appear in the urine-contaminated dust. It may be that it is still alive and capable of doing mischief.

Conclusions.—On the whole, these experiments show that the *M. melitensis* is a fairly resistant organism, and that it can live in a moist or dry state outside the body for long periods of time. But we have seen that in the majority of cases there are comparatively few micrococci excreted in the urine, so that gross contamination of the dust can seldom or never occur. Again, when we consider the bactericidal action of the sun, and the enormous dilution the *M. melitensis* must undergo when the dust is raised in clouds into the air, it is difficult to believe that this fever can be spread to any extent through the dust or soil. We may therefore conclude this section by stating that, outside the body, the *M. melitensis* shows no signs of leading a saprophytic life—it does not thrive and multiply—but, on the other hand, it is proved to be a resistant organism which can retain its vitality for long periods under varied conditions.

IV.—How does the Micrococcus gain Entrance to the Body?

It is on finding the correct answer to this question that the success of prevention probably hangs. Does the virus enter by way of the alimentary canal, by the lungs, through mucous membranes or through the skin? Is it conveyed from the sick to the healthy by means of food, water, milk, dust, or by biting insects? The difficulty in dealing with human infectious diseases is to find a suitable animal to experiment with, man not being available. Fortunately, in Malta fever we have the monkey, which is also susceptible to the disease. How far one can reason from the behaviour of the monkey to the virus to what happens in man, is difficult to say, but it may be assumed that there is a practical degree of similarity.

In trying to find out some method of prevention it is evident that the important thing to strive for is the narrowing down of the paths of infection. In yellow fever, as long as it was believed that it could be spread by contact, fomites, food, water, &c., nothing could be done. The moment the mode of infection was narrowed down to a particular species of mosquito the problem of prevention was simple. In the same way with Malta fever, if it can be spread by contact, contamination of food, water, by the inhalation of dust, sewer air, &c., it will be impossible to do more than recommend the ordinary established rules of hygiene. But on the other hand, if the mode of spread could be narrowed down to such a vehicle as milk, or a mosquito, something rapid and dramatic in the way of prevention might be attempted.

By Contact?—The only experiments which have been made in order to prove this have been made with monkeys. In 1904 two monkeys took the fever naturally. They were both living close to affected monkeys, and it was supposed, and probably rightly so, that they had taken the disease from their neighbours. This was repeated as an experiment on three occasions, with a positive result in two. Experiments made in which the contact was limited, that is to say, in which infection by urine or mosquitoes was excluded, never succeeded.

It was therefore concluded that the monkeys probably took the disease by having their food contaminated with the urine of their neighbours, or it might possibly be by eating ecto-parasites containing blood, and that, therefore, contact resolved itself into a feeding experiment.

As the chance of man having his food contaminated in this way is very remote, it is probable that very few cases of Mediterranean fever arise in this manner. At the same time, this mode of infection cannot be absolutely excluded, and the high incidence, according to Johnstone, among those who nurse Malta fever cases may possibly be due to insufficient care in the handling of the micrococci-containing urine of the patients. But the fact that no case of Mediterranean fever has ever been known to occur at Netley or Haslar among the patients, sisters or orderlies, is sufficient proof that, in practice, contact as a factor in the causation may be almost put out of court.

By Dust Contaminated with Micrococcus melitensis?—In view of the fact that this organism can retain vitality for a long time in a dry condition, it was thought probable that the infection might be conveyed from the sick to the healthy by means of dust. Dust contaminated with urine from Mediterranean fever cases might be blown into the atmosphere and so be inhaled or swallowed. In order to put this to the test various experiments were made. At first, artificially contaminated dust was used. The dust was sterilised, then made wet with an emulsion of the organisms from agar cultures, and finally dried.

Horrocks relates two experiments, in one of which this dust was blown about the cage, and in the other blown directly into the nose and throat. Both were successful.

Shaw also describes two experiments of blowing contaminated dust about an air-tight box containing the monkeys, but both were unsuccessful. In three experiments by him in which the dust was blown into the nostrils, one remained negative, and two gave a positive result. Of four experiments in which he frequently dropped dust into the conjunctival sac, two remained negative, two became infected.

From these experiments it may be concluded that *artificially* contaminated dust may convey Malta fever to healthy animals. This is no proof, however, that this ever occurs in Nature. Artificially contaminated dust contains myriads of the specific micrococci. Dust in Nature can contain but few, seeing how sparse they are in the urine as a rule. The dust blowing about under natural conditions must rapidly dilute the micrococci to an extraordinary extent, so that we can only picture a micrococcus here and there in a great quantity of dust. But the conditions occurring in Nature can be more closely imitated if the dust is contaminated with Malta fever urine instead of from a culture.

By Dust Artificially Contaminated with the Urine of Malta Fever Patients?—A urine known to contain the micrococci was chosen to contaminate the dust. After drying, the infective dust was blown into the nostrils and added to the food of monkeys. Four experiments are reported by Horrocks, lasting from twelve days to two months, but in no case did infection occur. It is difficult to understand why this experiment did not succeed. The dust was infected by a urine containing exceptionally large numbers of the micrococci, and immediately dried. It was evidently added in fairly large quantities to the food, as three out of the four animals suffered from severe vomiting and diarrhœa. Shaw also reports that he experimented on four monkeys in the same way, but did not succeed in conveying the infection in a single case.

These experiments are much more severe than anything we can imagine occurring in Nature, and tend to throw doubt on dust being an important factor in the spread of Mediterranean fever. It must be mentioned here, however, that Horrocks states that he succeeded in infecting two goats by adding this dust to their food.

By Dust Collected from Suspicious Places?—This is, of course, the crucial experiment as far as infection by dust is concerned. Judging from the non-success of the last series of experiments with urine-contaminated dust, it was little likely that this experiment would succeed. It was, however, necessary to make the attempt. Dust was collected from fever wards, from places where cases had occurred, from goats' sheds, where affected goats were milked, from around urinals, &c., and blown about the cages and food of monkeys, or injected subcutaneously. Up to the present these attempts have failed. At the same time, it must be admitted that but few experiments have been made. Horrocks only experimented on seven monkeys, and it takes many experiments to prove a negative.

What then does the evidence which has been collected in regard to the spread of Malta fever by means of dust amount to? When one considers the numbers of ambulatory and convalescent cases which must frequently be excreting this organism in their urine, one is led to think that this must constitute a danger of spreading the disease. At the same time it must be borne in mind that there is no absolute proof that this is so; the micrococcus has never been recovered from urine-contaminated places, or from the dust of such places; nor has the disease been set up in any animal by artificial inoculation with material from such places. Theoretically, there seems to be danger from the scattering broadcast of such a virulent and resistant microbe, but it is possible that not a single case of infection occurs in this way. As sound practice, however, any sanitary measures which could be devised to prevent the fouling of the soil by Malta fever urine would be steps in the right direction.

The conclusion to be drawn from these experiments on the conveyance of Malta fever by means of dust is, that up to the present, there is no absolute proof that dust, as it occurs under natural conditions, ever conveys the disease from the sick to the healthy.

By way of the Alimentary Canal?—It has been repeatedly demonstrated by experiment that a small quantity of a culture applied to a scratch, or injected under the skin, will give rise to Malta fever in man and monkeys. Also that dust or fluids containing the micrococci, if applied to the unbroken conjunctiva, nasal passages, pharynx, interior of the larynx and trachea of monkeys, will set up this fever.

In a previous Editorial the writer stated that experiment was against the micrococci gaining access to the body by water or food. This idea was based on reports by Wright and Zammit, in which they stated that they had failed to induce the disease by feeding experiments. The evidence now available is given in the following table.

This question of the micrococcus gaining entrance by way of the alimentary canal is one of the most important with which we have to deal. It is most essential that it should be known without any shadow of doubt whether or not a man can take this fever by swallowing the micrococci in his food or drink. It would also be well to know if this mode of infection takes place readily, or whether many micrococci are wanted, and some particular state of the digestive organs. Now a careful study of the table below must convince anyone that Malta fever can be conveyed to monkeys by feeding experiments, and if to monkeys, then probably to man. Especially suggestive are the experiments on monkeys numbered 4, 5, and 99, with milk from affected goats. When an animal is fed day after day on an artificially contaminated food containing myriads of micrococci the result may be misleading, just as in the case of dust experiments. But with ordinary milk taken from goats in the street, the natural conditions are exactly followed and there seems little room for fallacy.

Species of animal	Mode of infection M. = *M. melitensis*	Probable time which elapsed before infection took place in days	Result. + Infection – No infection	Remarks
Monkey 39	Feeding on potato containing M.	30	+	Recovered the M. from spleen (Horrocks).
,, 40	Do. do.	31	+	Had serum reaction, 1 in 100 (Horrocks).
,, 66	Accidental feeding ..	..	+	Probably by feeding (Horrocks).
,, 72	Milk + M.; stomach tube	..	+	(Horrocks).
,, 113	Dust + Mediterranean fever urine. Dried	..	–	Do.
,, 114	Do. do.	..	–	Do.
,, 119	Dust + Mediterranean fever urine. Moist	..	+	M. recovered (Horrocks).
,, 124	Potato + M. from spleen	..	+	Agglutination, 1 in 1,000 (Shaw).
,, 125	Do. do.	..	+	Agglutination, 1 in 800 (Shaw).
,, 126	Potato + M. from urine	..	+	Agglutination, 1 in 80 (Shaw).
,, 127	Do. do.	..	+	Agglutination, 1 in 800 (Shaw).
,, 2	Milk from affected goat	..	+	M. recovered (Horrocks and Kennedy).
,, 4	Do. do.	..	+	Do. do. do.
,, 5	Do. do.	..	+	Do. do. do.
,, 99	Do. do.	..	+	Do. do. do.
,, 6	Culture from milk ..	..	+	Do. do. do.
,, 7	Do. do.	..	+	Do. do. do.
,, 8	Do. do.	..	+	Do. do. do.
,, 9	Do. do.	..	+	Do. do. do.
,, 19	Do. do.	18	+	Blood reacts. Experiment continuing (Horrocks and Kennedy).
,, 19*a*	Do. do.	32	+	M. recovered (Horrocks and Kennedy).
Kid 9	Milk from affected goat	..	–	Blood reacted, 1 in 10. Experiment still going on (Horrocks and Kennedy).
,, 19*a*	Mother's milk ..	..	–	Agglutination, 1 in 50 (Horrocks and Kennedy).
Goat 12	Culture from milk ..	..	+	Blood reacts, 1 in 40. Experiment still going on (Horrocks and Kennedy).
,, 13	Mediterranean fever urine and dust	..	+	M. recovered from milk (Horrocks and Kennedy).
,, 14	Do. do.	..	+	Agglutination, 1 in 20 (Horrocks and Kennedy).
,, 4	Milk + culture ..	..	+	Recovered from milk (Horrocks and Kennedy).

By Means of Goats' Milk ?—This is probably the most important question in the whole subject of the etiology of Mediterranean fever. When the astonishing discovery was first made that goats could be affected by Malta fever and act as a reservoir of the virus, and that they were frequently excreting it in their milk, it was hoped that the main source of infection had been discovered. Whether this is so or not still remains to be proved. What are the facts?

About one thousand goats taken from all parts of the country have been examined by the Commission. The goats were examined in the first instance, for a serum, or milk reaction to the micrococcus, and then the milk of those which gave a reaction was directly examined by plate cultivation for the presence of the micro-organism. Shortly, it may be stated that as the result of this examination it is shown that, broadly speaking, some 50 per cent. of the goats in Malta respond to the agglutination reaction, and that 10 per cent. are actually excreting the *M. melitensis* in their milk. This excretion may continue for three months without any symptoms of disease in the goat, or change in the appearance of the milk. The mode of distributing the milk in Malta adds to the danger. Herds of goats constantly perambulate the streets of the towns and villages. When milk is wanted the housewife beckons to the nearest herd-boy, who drags up a goat to the door and milks directly into a dish provided by the consumer.

But is it proved that the drinking of infected goats' milk by man will give rise to the disease? To this question, of course, there can be no direct answer; but there is, as already mentioned, abundant proof that monkeys fed on naturally infected goats' milk take the disease after a time, and therefore there can be little doubt that the same thing occurs in man. It cannot be said that the monkeys take the disease readily or rapidly when fed on infected milk. Horrocks gives four experiments, in each of which infection took place, but only after twenty-four, thirty-three, seventy and seventy days respectively. It seems to be even more difficult to infect goats. Experiments made by Horrocks and Kennedy, in which a goat and four kids were fed on infected milk, showed no signs of infection after four months.

As bearing on the possible infection of man by goats' milk, Sir Charles Metcalfe informed the writer that the introduction of Maltese goats into Rhodesia was followed by an outbreak of Mediterranean fever. Again, the case of the s.s. "Joshua Nicholson" can be cited. In 1905 this steamer shipped sixty-five goats at Malta for export to the United States of America. The milk was drunk by the captain and many of the crew, with the result that an epidemic of Mediterranean fever broke out on board the vessel. Dr. Strachan, of Phillippolis, in the Orange River Colony, who discovered that Malta fever was endemic in some parts of that

Colony, thinks it probable that the infection has been spread by goats' milk, which is largely used in these districts. In India also, Captain Forster, I.M.S., isolated the micrococcus from the milk of goats supplying the 14th Sikhs at Ferozapore, among whom cases of Malta fever had occurred. Lastly, Davies found that the children in Malta who drank unboiled milk suffered four times as much as those who drank boiled milk.

Taking all these cases into consideration, there can be little doubt that Malta fever is conveyed to man by means of goats' milk.

By Mosquitoes or other Biting Insects?—This is a theory which has been brought forward again and again of late years. Horrocks and Kennedy, in their last Report, go so far as to say that it is extremely probable that human beings are infected by the bites of infected mosquitoes. Let us see what evidence there is for this. The species found in Malta appear to be *Culex pipiens*, *Culex fatigans*, *Culex spathipalpis*, *Stegomyia fasciata*, and *Acartomyia zammitii*. Theobald thought that probably *A. zammitii* would be found to be the carrier, but as this species only breeds in the salt-pans along the coast, it is difficult to believe that it is the carrier of a disease which is as common in the inland towns and villages as on the sea-coast.

Zammit brought forward a case in which he claimed to have infected a monkey by feeding *S. fasciata* on it after they had fed on a Malta fever patient. He allowed two of these mosquitoes to bite the monkey forty-eight hours after feeding on the man, and ten days later the monkey was again bitten by one of the same mosquitoes. Thirteen days after the first feeding experiment the monkey had a rise of temperature, and shortly afterwards its blood reacted. There is no apparent fallacy in this experiment, as the monkey was well removed from any infected monkeys, or other known source of infection. Horrocks and Kennedy also relate how the laboratory assistant at the lazaretto was bitten by a *C. pipiens*, which was at once killed and found on examination to contain *M. melitensis*. The assistant fell sick of Malta fever eleven days later. On January 29th, 1906, a telegram was received from Captain Kennedy, announcing that he had been successful in transferring the disease to a monkey by means of the mosquito. It is evidently a monkey mentioned in a letter as having been bitten by mosquitoes caught in the nets and wards of the Malta fever patients. It began to react slightly some ten days after the last biting, and had not been in contact with anything likely to infect it. These are the only experiments, up to the present, which can be called successful, and it is doubtful if any of them are quite free from fallacy. In 1905, this mode of infection was taken up seriously. Horrocks and Kennedy examined the blood found in the stomachs of 896 mosquitoes caught in hospitals, barracks, &c., and recovered the micrococcus from four of them (three *C. pipiens* and one *S. fasciata*). The number of colonies appearing on the plates from the three *C. pipiens* were thirty-four, six and eleven, respectively. Taking 5 cubic millimetres as the ordinary amount of blood sucked in by a mosquito, it would appear that some multiplication of the micro-organism had taken place in the interior of the insects, since never more than one or two micrococci have been found in that quantity of blood by direct examination. Shaw found it once in 4 cubic millimetres. and Gilmour once in 3 cubic millimetres.

In spite of this possible, but very improbable, multiplication of the micro-organisms in the blood contained in the stomach of the mosquito, it is still difficult to understand their transference to a healthy person. It is evidently true that something of the kind occurs in plague, and if it is true that the rat-flea can convey plague bacilli from sick to healthy animals, there is no easily apparent argument why the mosquito should not do the same for the Malta fever micro-organism. But the crucial proof of this transference of Mediterranean fever by the mosquito would be by directly doing it repeatedly by experiment. Horrocks made in all ten experiments with goats and monkeys to try to settle this point, at first on a large scale with a mixture of Culex, Stegomyia, and Acartomyia, and afterwards with the separate species. Shaw also attempted to infect a monkey in this way during a period of two months, and Zammit repeated his former experiment twice. Up to the present, all these experiments have been negative.

It must therefore be concluded that there is, at present, not sufficient proof that Malta fever is conveyed from the sick to the healthy by mosquitoes, but that a case is made out for more experimental work in this direction.

Criticisms and Suggestions.

Epidemiology.

(1) Although it is to be regretted that nothing very definite has been made out as to the mode of infection in Malta fever by the epidemiological study of the disease, yet it is believed that by the continuation of this work, especially by the careful study of

each individual case and its surroundings as soon as it occurs, information will be gained which may in time throw some light on the little-known etiology of this fever.

(2) The question of the evacuation and disinfection of barrack-rooms in which cases occur ought to receive attention.

(3) A more complete isolation of the sick, convalescent and ambulatory cases might also be considered.

(4) In regard to the various animals susceptible to Malta fever, cats, rats and mice might be added to the list.

(5) The incubation period of this fever is important and requires further experiment and observation.

How the Micrococcus Leaves the body.

(6) It may be accepted that the main paths of exit are the milk, urine and perhaps fæces; the others are negligible. The question of the excretion in human milk may be important.

(7) It is suggested that the micrococci may not be so numerous in goats' milk in winter as in summer, and so account to some extent for the seasonal prevalence.

The Micrococcus Outside the Body.

(8) It seems to be sufficiently proved that this micro-organism can retain its vitality and virulence for long periods outside the body.

(9) If there is any conceivable likelihood of the micrococcus being found in external Nature, in air or dust, this search might be persevered in. Up to the present it has been found outside the body of warm-blooded animals in milk, urine, and the blood contained in the stomach of the mosquito.

How The Micrococcus Gains Entrance to the Body.

(10) The experiments made with monkeys sufficiently prove that Malta fever may be conveyed from the sick to the healthy by intimate contact without the aid of mosquitoes. How the infection is carried is not strictly made out. It may be by way of the urine and contaminated food, and this appears probable enough; and it is also suggested it may be by eating ectoparasites containing the micrococci. Also, in view of the fact that plague bacilli can be carried by the rat-flea, it is further suggested that in intimate contact the flea or louse may play a part.

(11) In regard to dust experiments, it is proved that dust

artificially contaminated by laboratory cultures can carry infection. It is not proved that this takes place under natural conditions.

(12) It is sufficiently proved that Malta fever can be conveyed to animals by way of the alimentary canal. It is suggested that infection by way of the rectal mucous membrane be made the subject of an experiment.

(13) It seems to be proved that Malta fever may be conveyed to man by means of infected goats' milk. This important subject should be followed up in every possible direction. The suggestion that villages served by infected herds suffer more than those served by "clean" herds seems capable of expansion. The question of butter and cheese as carriers of infection ought to be strictly enquired into, as a quantity of local cheese may be consumed by the soldier, and especially in sergeants' Messes.

(14) In regard to biting insects, there is at present no sufficient proof that Malta fever is carried by mosquitoes, but that a case has been made out for more experimental work in this direction.

(15) The two most important lines of work now seem to be the conveyance of infection by biting insects, such as mosquitoes, fleas, ticks, &c., and by goats' milk, or other articles of diet into which milk enters.