

JRAMC 1905: 5 :

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August issue

EXPERIMENTS ON THE TRANSMISSION OF MEDITERRANEAN FEVER.

BY EDWARD H. ROSS AND G. MURRAY LEVICK.

Surgeons, Royal Navy.

IN the *British Medical Journal* of April 1st, 1905, we published a preliminary report on some experiments made by us, in the hope of discovering the nature of the transmission of Malta fever.

We have since repeated those experiments and have confirmed their results; but we have, in some instances, employed slight modifications of the original experiments in an attempt to imitate natural methods. Some new experiments have also been performed.

EXPERIMENT I.—TRANSMISSION BY DIRECT CONTACT, FOMITES, &c.

Modification.—A nightshirt, which had been worn by a Malta fever patient with high fever for four days previously, was slept in by the non-immune C and the non-immune B on successive nights. Another nightshirt, worn by the patient for two days, was slept in by the non-immune E, and the following two nights by the non-immune F. None of them contracted Malta fever.

EXPERIMENT II.—TRANSMISSION BY INFECTED DUST.

Modification.—The urine of a Malta fever patient was mixed with some dust. This was dried, partly in the sun, partly in the shade, then kept for thirty days; this dust was then sniffed up the nostrils, as in the former experiment, by the non-immunes A, B, C, D. They all remained well.

In one of our earliest experiments, the effect of the inhalation of a culture of the *Micrococcus melitensis* was tried. We then realised, however, that the result of this would be quite inconclusive, owing to the fact that this disease can be transmitted by cultural inoculation, and that the difficulty of excluding the possibility of abrasions in the air-passages was insurmountable. Experiments with artificial concentrated cultures, therefore, have not been repeated.

EXPERIMENT III.—TRANSMISSION BY INFECTED WATER, MILK.

Modification.—Six ounces of urine obtained from a Malta fever patient was allowed to stand for two hours; it was then mixed with four gallons of drinking water, and again allowed to stand for twenty-four hours; eight ounces of this mixture were then added

to twenty-four ounces of pure goat's milk, and this kept for eight hours. Eight ounces of the thus prepared milk were then drunk by the non-immunes A, B, C, D, simultaneously. None of them contracted Malta fever. From the specimen of urine employed in this experiment, the *Micrococcus melitensis* was separated amongst other organisms.

EXPERIMENT IV.—TRANSMISSIONS BY MOSQUITOES.

Stegomyia fasciata (Fabricius).—Our experiments with this species of mosquito have not, up to the present time, been repeated.

Culex pipiens (Linnæus).—One female *Culex pipiens* was fed on the blood of a Malta fever patient, whose temperature during that night reached 103·2° F. This mosquito was then allowed to bite the non-immune A on the third night, and the non-immune D on the fourth night after. It was then conveyed to Crete, and there allowed to bite the non-immune B on the tenth, seventeenth, eighteenth, twentieth, and twenty-first nights after infection. Another *Culex pipiens*, infected from another case of Malta fever, was allowed to bite the non-immune A on the third, fifth, seventh, ninth, and twelfth nights after; and the non-immune D on the eleventh and fourteenth nights after infection.

Culex fatigans.—Another mosquito, which was subsequently considered, owing to its peculiar wing-venation, to be *Culex fatigans* (Wiedemann), was allowed to bite the non-immune B every second night up to the fourteenth night after infection. Malta fever was not conveyed to these non-immunes by these mosquitoes.

Theobaldia spathepalpis (Rondani).—We have tried, on numerous occasions, to make this species of mosquito suck blood, but without success. We have tried both the fresh and the sea-water-bred insects, but have always failed, and none of the numerous individuals of this species caught by us have ever contained blood. This experience agrees with the statements of Ficalbi and Grabham, quoted by Mr. Theobald in his "Monograph of the Culicidæ." We therefore think ourselves justified in regarding this mosquito as a non-blood-sucking insect.

EXPERIMENT V.—TRANSMISSION BY FLEAS.

Pulex irritans.—A female flea was allowed to bite a Malta fever patient, whose temperature at the time registered 105° F. This flea then bit the non-immunes A, B, C, D, successively every day, from three hours after its infection until the sixteenth day after, when it died. Malta fever was not contracted by any of the non-immunes.

EXPERIMENT VI.—TRANSMISSION BY BED-BUGS.

Cimex lectularia.—A bed-bug of unknown sex was fed on the arm of a patient suffering from Malta fever with a temperature of 104° F.; it was then made to bite the non-immune B on the fourth, eighth, eighteenth, and twenty-sixth days after, the non-immune F on the thirty-fourth, and the non-immune E on the thirty-ninth day after infection. All of us who have volunteered for this work continue well up to the present time, nor have any of us had any illness of a serious nature during the past few years. The temperatures of the patients employed in these experiments have been noted, because it is supposed by some that the micrococcus is present in greater numbers in the peripheral blood during high fever.

TABLE SHOWING NUMBER OF NON-IMMUNES EMPLOYED IN EACH EXPERIMENT.

Transmission by	Number of Non-Immunes
Direct contact, fomites	3
Repetition	3
Modification	4
Infected dust... ..	2
Modification	4
Infected water, milk	2
Modification	4
<i>Stegomyia fasciata</i>	2
Repetition	2
<i>Culex pipiens</i>	3
Repetition	2
<i>Culex fatigans</i>	1
Fleas	4
Bed-bugs	3

Every one of these experiments has been performed faithfully and without partiality or confusion, but we would now state that we are strongly of the opinion that Mediterranean fever is insect-borne. This opinion is based on, firstly, the results of these experiments—for we have not yet exhausted the blood-sucking insects found in the Mediterranean—and, secondly, the due consideration of many epidemiological factors. Thus, in support of this theory of the insect-borne nature of this disease, the following cases may be cited:—

CASE 1.—Mr. H. N., a gentleman of independent means, living near London, and who had not been out of England for nearly three years, and whose health had always been good, paid a visit on October 5th or 6th, 1904, to the United States battleship "Olympia," which had arrived at Gravesend from the Mediterranean. He spent

two hours on board between noon and 2 p.m. During that time he was bitten on the wrist by an insect, and was informed that there were several mosquitoes on board. The bite gave rise to a considerable amount of irritation and swelling which did not go down for some days. He returned to his home, and on October 12th or 13th he began to feel ill. He was found to be suffering from fever which was variously diagnosed at first, but ultimately was considered to be Malta fever by his medical attendant, who had seen other cases. The patient's blood was therefore sent to the Clinical Research Association in order that a serum reaction might be performed. The Association reported that a marked reaction had occurred. Positive reactions were also obtained with blood sent to the Lister Institute, and by Professor A. E. Wright, who obtained a reaction with a dilution of 1 in 1,000. The fever continued for more than two months, but the patient has now completely recovered. The incubation period of this case, therefore, was from seven to nine days. Enquiries have been instituted to find out if there were any other cases of this disease on board the "Olympia" about that time. We are very much indebted to Dr. Sandford Smith, of Eltham, who sent us the particulars of this decisive case.

CASE 2.—On August 29th, 1904, at 11 a.m., when the Mediterranean Fleet was at Vourlah Bay in Asia Minor, Captain C. and Lieutenant K., officers of one of H.M. cruisers, left their own ship to pay a visit to one of the neighbouring battleships, amongst the officers and crew of which a series of cases of Malta fever had occurred, and had been treated on board. They did not, however, go near the men's quarters, but remained for half an hour in one of the after cabins. While there Captain C. was bitten on the wrist by a mosquito, Lieutenant K. was not. The former complained of the bite on their return to his own ship, which left the fleet the next day. On September 7th Captain C. was taken ill, and was sent to hospital on September 12th suffering from Malta fever. On board his own ship, which had only been on the station for six weeks, no cases of Malta fever had previously been contracted, nor did any other cases occur on board for several months. The incubation period of this case was therefore eight to ten days.

CASE 3.—Mr. G. dined with Mr. and Mrs. H. in their house near a hospital in Malta, on January 26th, 1905. During the evening both Mrs. H. and Mr. G. complained of having been bitten by an insect, one on the neck, and the other on the arm; but Mr. H. was not so bitten. The next day Mr. G. left for England. On February 3rd both Mrs. H. and Mr. G. were taken ill, the former in Malta and

the latter on the voyage home. The incubation period in both instances was eight days. All these facts are strongly in favour of the transmission of Malta fever by biting insects. We therefore think that there is reason for the following suggestion:—

SUGGESTION.

That as numbers of the patients admitted to the naval, military, and civil hospitals of Malta for surgical or other affections, as well as the medical and nursing staffs, often contract Malta fever—ten cases occurred among the patients in one of these hospitals during one week in June, 1905—even when the fever cases are isolated in special wards,¹ we suggest that all the wards and rooms in these establishments be at once rendered mosquito-proof.

Then statistics prepared now of the cases which have contracted the disease while in hospital, allowing for an incubation period of ten days, could be compared under the new conditions with similar statistics obtained, say, three years hence.

This could be regarded as an experiment upon a large scale; it could be carried out with but little trouble; the expense would be trifling, and the increased comfort acquired by the patients would alone make it worth while.

We hope ultimately to obtain sufficient evidence to warrant the institution of an anti-mosquito campaign in the places where Mediterranean fever abounds, but we would point out that so far as Malta and Gibraltar with their existing naval and military garrisons are concerned, myriads of larval mosquitoes could be destroyed now by the expenditure of a few gallons of paraffin oil.

THE PROBABLE INSECT.

We have collected and experimented with nearly all the common species of biting insect found in the several places of the Mediterranean we have been to, and but one common species of mosquito remains to be tried. This is *Acartomyia zammitii*.

This mosquito is peculiar, for its eggs are laid and its larval stages can only be passed in warm, concentrated sea-water.

The eggs of this species are laid separately like those of the stegomyiæ, not in rafts like those of the culices. The larvæ also resemble those of *Stegomyia fasciata*, inasmuch as the breathing position is at an acute angle to the surface of the water, not perpendicular like *Culex pipiens*; but the imagines resemble the culices both in their general appearance, and the head, scales, &c.

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The breeding grounds of this mosquito are the "salt-pans" and shallow pools on the rocks of the sea-coast in the vicinity of towns. We have found individuals of this species in Malta in the winter, and in houses some distance inland.

We have attempted to repeat our experiments with this insect, but so far have only succeeded in making them bite for eight days after their emergence from the pupa; we think that probably twelve, if not more days, must elapse after its infection before it can re-infect, as is the case with yellow fever, and also that there is some definite period during which the conveying insect must bite the patient in order to transmit the disease, for they then apparently deem it necessary to return to the edge of the sea in order to lay their eggs. If they are supplied with suitable water when kept in captivity, our experience is that they die after laying their eggs; this cannot be the case under natural conditions, however, for this mosquito has been observed on board a ship which had not been anchored near the shore for more than two months, so that it had apparently in this case utilised the sea-water which collects about the decks for the periodical laying of eggs.

We have found this gnat in Malta, Gibraltar, Beirut in Syria, and at Marmarice in Asia Minor, and in all these places Malta fever is supposed to be endemic.² We have not found it at Corfu, or at Platea in Greece, but these places were only visited in the winter. Although stray females of this species are to be found in the towns in the cold weather, the larvæ are not found in the "salt pans" until April. Their advent during this month is coincident with the sudden increase of the incidence of Malta fever which occurs regularly every year. There are breeding pools of this mosquito in close proximity to the naval, military, and civil hospitals of Valletta, Malta, in which the disease is always prevalent, and we have found them near several of the barracks and houses where epidemics have occurred. They may also sometimes be found in the puddles of sea-water used for the manufacture of mortar when building operations are in progress.

If these observations are borne in mind by those who have any experience of the habits of mosquitoes, and the fact remembered that these insects will not leave the house or room in which there is a plentiful supply of food except periodically to lay their eggs, after which they will again return—if the descriptions of such epidemics as those of the Essex Regiment, St. Elmo Barracks,³ and at the Florian Barracks,⁴ Malta, are considered, the probability of Mediterranean fever being conveyed by these insects will at once become apparent.

Acartomyia zammitii, Theobald, bites by day, by lamplight, or by night, and its bite is often very irritating; in the summer it bites regularly every day, but in the winter the digestive periods are much prolonged.

Should it be ascertained that it is this mosquito which transmits Malta fever, then its extermination should prove a comparatively easy matter owing to its peculiar breeding propensities; but the systematic co-operation of the naval, military, and municipal authorities would be required.

In conclusion, we would reiterate the opinion that a war against the biting insects in places where this disease is prevalent, will ultimately result in its prevention.

We wish to take this opportunity of thanking Dr. Thenu Zammit, Government Bacteriologist of Malta, for his help and suggestions. He has done much of the bacteriological work which we have purposely avoided.

REFERENCES.

- ¹ Kennedy. JOURNAL OF THE ROYAL ARMY MEDICAL CORPS, May, 1905.
- ² "Reports of the Health of the Navy for the past Ten Years."
- ³ Johnstone. "Reports of the Commission of the Royal Society for the Investigation of Mediterranean Fever," Part II, pp. 50, 51.
- ⁴ Glen Allen. JOURNAL OF THE ROYAL ARMY MEDICAL CORPS, June, 1904.

NOTE.

The following is a description of the epidemic of Malta fever which occurred on board the battleship which was visited by Captain C. and Lieutenant K. on August 29th, 1904.

Ship left Malta July 17th, 1904. She was not anchored near the shore after that date.

Name	Date of being taken ill
Mr. W.	July 26th
Mr. M.	" 28th
Mr. S.	" "
Mr. Sc.	" "
Mr. Mr.	Aug. 1st
Mr. R. ? Enteric	" 3rd
B.	" 5th
Mr. H.	" 11th *
L.	" 27th *
M.	Sept. 2nd
G.	" 5th
D.	" 12th
Capt. C.	" "

* The gaps between these cases can be explained by the fact that there were several immunes on board, who may have been bitten on the intervening days, or the mosquitoes may have bitten an already infected patient in his cabin.

End of series of cases of Malta fever; Captain C. was taken ill on the same day as the last case. It is noteworthy that he stated that he thought that he had killed the mosquito which had bitten him, but was not sure.

It would seem, therefore, that all these cases had been caused by one mosquito.

NOTE BY ASSISTANT-SURGEON WALLACE B. SMITH, U.S. NAVY.

Your letter and inquiries of May 4th, 1905, in regard to a case of Malta fever, probably originating from exposure to mosquitoes, &c., on board the "Olympia," while at Gravesend, have been referred to me by the Commanding Officer, and I take great pleasure in giving you the following data, collected partly from memory and the Medical Journal of the ship:—

"(1) We were at Gibraltar from August 22nd until September 3rd, 1904, just prior to going north, and later to England, arriving at Gravesend on September 24th.

"(2) At no time either before or after touching at Gibraltar or Gravesend, has there been any sickness on this ship which resembled Malta fever in the least.

"(3) Whether or not mosquitoes or other insects were on board during this period in question I cannot positively state. If they were, they were in such small numbers as to escape notice and remark of both officers and men."
