The extinction of Malta fever : (a lesson in the use of animal experiment) / by David Bruce.

Research Defence Society

The Extinction of Malta Fever

(A Lesson in the use of Animal Experiment)

By

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RESEARCH DEFENCE SOCIETY.

SIR,

A Society has been formed, with the name of the Research Defence Society, to make known the facts as to experiments on animals in this country; the immense importance to the welfare of mankind of such experiments; and the great saving of human life and health directly attributable to them.

The great advance that has been made during the last quarter of a century in our knowledge of the functions of the body, and of the causes of disease, would have been impossible without a combination of experiment and observation.

The use of antiseptics, and the modern treatment of wounds, is the direct outcome of the experiments of Pasteur and Lister. Pasteur's discovery of the microbial cause of puerperal fever has in itself enormously reduced the deaths of women in child-birth.

The nature of tuberculosis is now known, and its incidence has materially diminished.

We owe the invention of diphtheria anti-toxin entirely to experiments on animals.

The causes of plague, cholera, typhoid, Mediterranean fever, and sleeping sickness, have been discovered solely by the experimental method.

Not only have a large number of drugs been placed at our disposal, but accurate knowledge has replaced the empirical use of many of those previously known.

The evidence before the Royal Commission has shown that these experiments are conducted with proper care; the small amount of pain or discomfort inflicted is insignificant compared with the great gain to knowledge and the direct advantage to humanity.

While acknowledging in general the utility of the experimental method, efforts have been made by a section of the public to throw discredit on all experiments involving the use of animals. The Research Defence Society will therefore endeavour to make it clear that medical and other scientific men who employ these methods are not less humane than the rest of their countrymen, who daily, though perhaps unconsciously, profit by them.

The Society proposes to give information to all enquirers, to publish *précis*, articles, and leaflets, to make arrangements for lectures, to send speakers, if required, to debates, and to assist all who desire to examine the arguments on behalf of experiments on animals. It hopes to establish branches in our chief cities, and thus to be in touch with all parts of the kingdom: and to be at the service of municipal bodies, Hospitals, and other public institutions.

THE

EXTINCTION OF MALTA FEVER

Introduction.

This short pamphlet has been written at the request of the Research Defence Society, to assist in bringing to the mind of the public the necessity of animal experiment in the investigation of human diseases. In it will be described the various steps in the study of Malta fever which led up to the discovery of its mode of spread, and so to its prevention and extinction. It will be shown that the success of this work depended altogether on experiments on animals. Without them the Malta garrison would still be groaning under the incubus of this fever. This island, situated as it is in the middle of the sunny Mediterranean, should be the healthiest of places. On the contrary, it was one of the most unhealthy of foreign stations, and was feared alike by officers and men. Now all this has been changed. The naval and military hospitals in Malta are almost empty, and the island has become, as it was meant to be, the healthiest of garrisons. This has been done by the experimental method, and by the experimental method alone, without which there cannot be any true or safe advance in our knowledge of human diseases.

Historical.

This fever has been studied in various ways for the last quarter of a century, but it was not until 1904 that the Government, alarmed by the great wastage in men, took the question up, and asked the Royal Society to undertake a thorough investigation of the matter. This the Royal Society agreed to do, and early in the summer of the same year sent out to Malta a Commission for this purpose. The work was carried on for three years before the discovery was made which led to the extinction of the fever.

It seems a pity that this research was not undertaken twenty years earlier, as during this time some 14,000 or 15,000 soldiers and sailors have suffered from the disease.

Description of Malta Fever.

At the outset it will be necessary to give a short description of this fever.

Malta fever is no trivial complaint, but is a severe and dangerous disease, which lasts a long time, and is accompanied by a good deal of pain. Our soldiers remain under treatment in hospital with it on an average for 120 days, and it is by no means uncommon for a patient to suffer almost continually from it for two or even more years. During the whole course of his illness the patient is apt to suffer from severe rheumatic pains in the joints, and neuralgia in various nerves, and this, combined with the long-continued fever, brings about a condition of extreme emaciation and weakness, from which recovery is slow.

In order to show to what a degree of emaciation a few weeks of this fever may bring a man, the photograph of a soldier who has been suffering from it is here reproduced (Fig. 1).

Incidence of Malta Fever in the Garrison.

Among the soldiers, who number about 7,000, there have been on an average 312 admissions to hospital every year from Malta fever alone, and among the sailors about the same number. This means that 624 soldiers and sailors have been treated in hospital 120

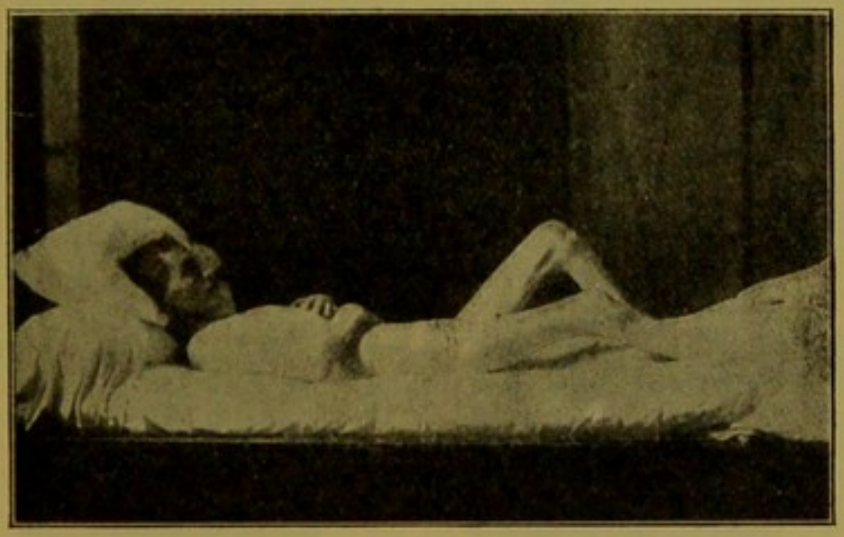


Fig. 1.

days each, which makes about 75,000 days of illness per annum.

The accompanying diagrams (Fig. 2) show the number of admissions to hospital for Malta fever among the soldiers. The first diagram gives the average for seven years (1899 to 1905), and it will be seen, for example, that on an average 18 men were admitted to hospital each January and 45 each August. The average number of admissions for these years is 315. But this represents a low average, as some of these

years were occupied by the South African war, when most of the regiments were away on active service, their places being taken by the so-called Garrison Regiments, composed of old seasoned soldiers. The second diagram shows the number of admissions to hospital among the soldiers for one year (1905). This reaches the startling number of 643, the best part of a regiment, incapacitated by this fever alone. During

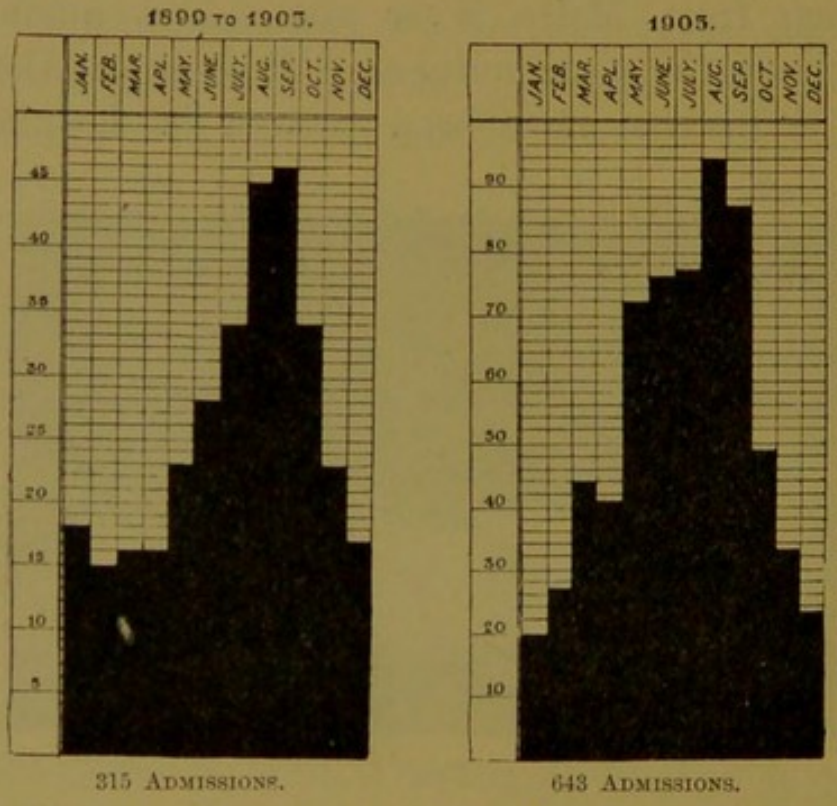


Fig. 2.—Charts of Incidence in 1899–1905 and 1905.

the same year as many as 403 officers and men were invalided to England as the result of Malta fever.

No wonder, then, that our soldiers looked on Malta as a place to be avoided.

Study of Malta Fever from the Epidemiological Point of View.

Before this fever was studied by the modern experi-

mental methods, many years had been spent in trying to arrive at a knowledge of its causation by the old statistical methods. Doubtless a good deal of light may often be thrown on the natural history of a disease by these means, but in this case they completely failed to solve the problem. The epidemiologist asks himself in what parts of the world the disease is found; under what conditions of climate; whether any connection can be made out between it and the temperature or rainfall; whether age or sex renders a person more liable; whether occupation or social position has any bearing on it; whether a difference in sanitary conditions has any effect, as, for example, Do people living in small villages without any proper system of water-supply suffer more than those living in towns supplied with pure water and a modern drainage system? Of course, all these questions can be answered without having recourse to animal experiment.

In a short paper such as this, it is clearly impossible to enter in detail into this side of the subject, but a few facts, some of which greatly puzzled the old workers, may be stated.

Geographical Distribution.—For example, it is interesting to know that Malta fever is not confined to Malta, but occurs in most parts of the world.

Climatic Conditions.—Then, again, in regard to the effect of climate. Malta is extremely hot and dusty in the summer, and correspondingly cold and wet in winter. But, although the number of cases of Malta fever do show an increase in summer, yet it is a disease which is prevalent all the year round, one-third as many cases occurring in the coldest and rainiest months as in the hottest and dustiest.

Another fact of importance is, that if we study the occurrence of Malta fever in individual years, we are struck by its irregularity, a number of cases appearing in December or February or other of the cold and rainy months.

Social Position.—Another curious fact in regard to this disease is, that the better the social position of a person the more risk is there of catching this fever.

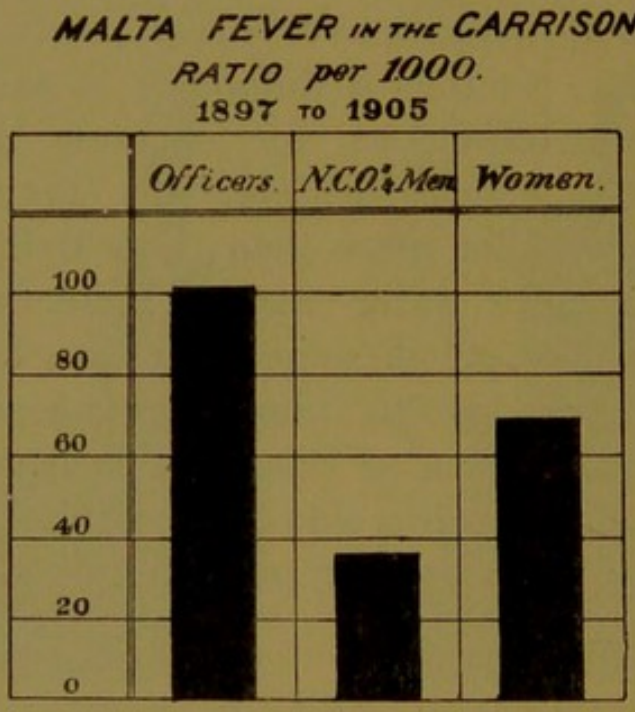
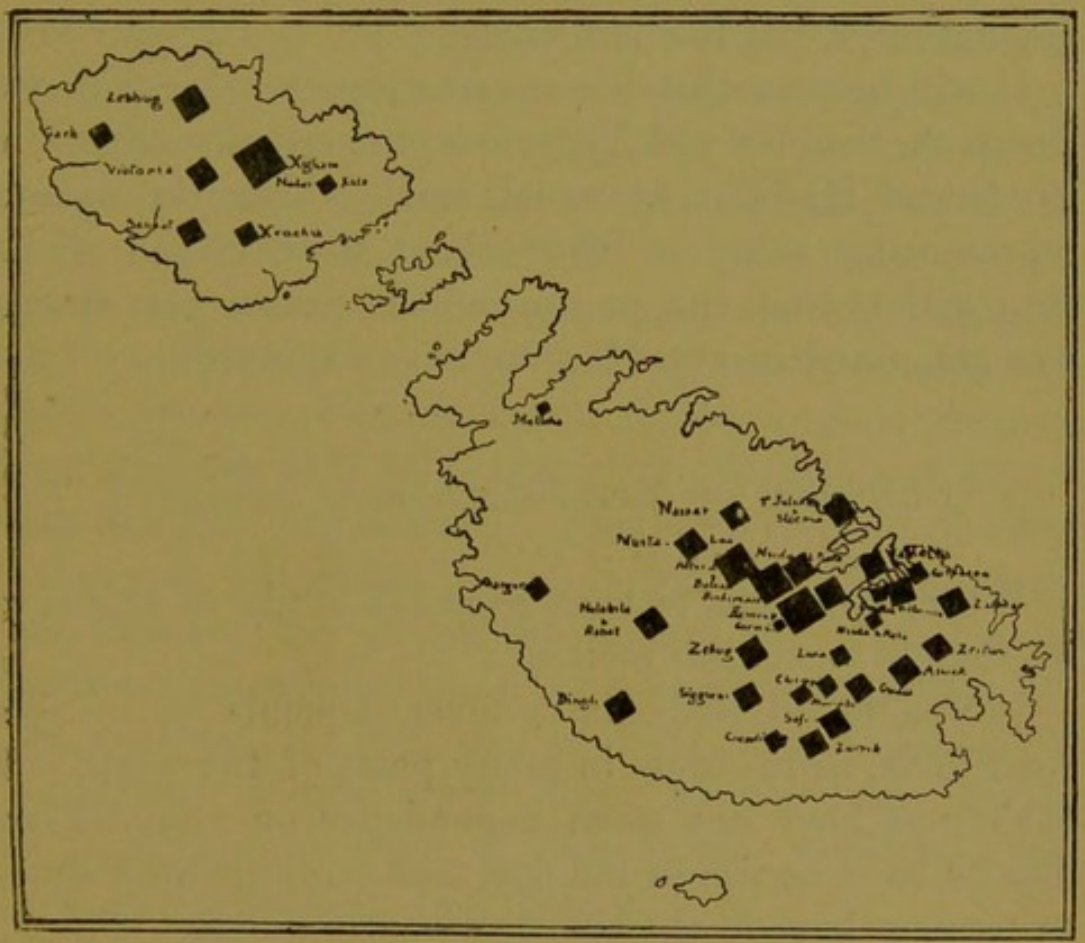


FIG. 3.—Incidence in Officers, Men and Women, for 1897–1905.

Officers and their wives and children, living in large, airy and clean houses, suffer more frequently than the rank and file in their more crowded barrack rooms. In fact, the chance of a naval or military officer taking this fever was more than three times as great as in the case of the non-commissioned officers and men.

The above diagram (Fig. 3) shows the incidence of the disease, from 1897 to 1905, among officers, N.C.O.'s and men, and women.

Distribution of Malta Fever among the Civil Population.—Another important fact is the distribution of Malta fever among the civil population. Until recently, it was supposed that it was mainly restricted to the inhabitants of the cities surrounding the Grand Harbour. This was in the days when the theory was held that the poison which causes this fever was found in



Map of Malta and Gozo, showing the Distribution of Malta Fever in the various Towns and Villages of the two Islands.

FIG. 4.—Incidence among the Civil Population.

the air. As the Grand Harbour at that time was in a very dirty condition, the drainage of Valletta and the three cities falling into it, there was excuse for this belief.

Malta fever is now known to occur in every part of the island, and, in fact, the general distribution of this

disease in Malta is very striking. It is not the cities round the Harbour which are struck most heavily, some of the inland towns and villages showing a much higher fever-rate.

This is illustrated by Fig. 4, where the number of cases are represented by different sized squares. The larger the square the larger the number of cases of Malta fever, reckoned, of course, in proportion to the population of the town or village.

It will be seen that the squares representing Valletta, Cospicua, Senglea and Vittoriosa, the cities surrounding the Grand Harbour, are much smaller than the squares representing some of the inland towns; and so the supposition that the poison which causes this disease was generated in the Harbour was exploded.

Summary of Epidemiological Evidence.

What, then, was learned from the study of this fever by the old statistical method?

It was found that Malta fever depends on no local conditions, as it occurs in many parts of the world. It could not have any great dependence on climatic conditions, as it occurs in the cool and rainy months almost as frequently as in the hot, dusty and rainless. Poverty and insanitary surroundings do not predispose; in fact, the well-to-do classes were shown to be more liable to take the fever than the poor. It has no connection with water supply or systems of drainage, as it breaks out as frequently in the smallest country village as in the large cities.

What, then, is the cause of this fever? The epidemiologists could give no answer to this question. They were sure the fever could not be traced to water,

or any food-stuff and so on, or any kind of dwelling, so they remained satisfied in thinking the disease was caused by some air-borne poison.

Study of Malta Fever by the Experimental Method.

Discovery of the Parasite.—Let us therefore approach this problem from the modern experimental side. The first step to be taken is to discover if any parasite or micro-organism is associated with this fever. To do this we examine the blood and the tissues of the various organs, both microscopically and by means of culture on various media, to find out if anything can be seen or grown. The blood and various organs are also inoculated into different animals to ascertain if any of them will take the disease. This is to try and discover if there is anything in the blood or organs which when injected into a healthy animal will give rise to symptoms resembling the fever under investigation.

In this way, as long ago as 1887, it was discovered by an Army medical officer that a minute living organism, to which the name of *Micrococcus melitensis* was given, is the cause of this disease.

Description of Micrococcus melitensis.—There is not much to be said about this micro-organism, except that it is very minute, only becoming visible under a magnification of 1,000 diameters.

But it is very important at the outset of an investigation such as this to be quite sure that the parasite found in the tissues is really the cause of the disease, and is not there by accident. If the history of malaria, yellow fever, sleeping sickness, and many other diseases

is studied, it is surprising to find how often scientific men were misled by finding organisms which they thought to be the cause of the disease, but which, on further knowledge, were found to have nothing whatever to do with it. This is especially true in the investigation of diseases to which human beings alone are susceptible. Happily, in the case of Malta fever, one of the lower animals, the monkey, is also susceptible, and so it could be made quite certain by animal experiment that this micrococcus is the true cause of the disease. Monkeys injected under the skin with this organism develop symptoms similar to those of Malta fever in man, and if they die or are killed their blood and organs are found to be swarming with the *Micrococcus melitensis.*

Without this animal experimentation it is often quite impossible to know whether a particular micro-organism is or is not the real cause of a disease.

Characteristics of the Micrococcus melitensis.

Behaviour Outside the Body.—Now, having found the micro-organism, it is necessary to study its characteristics.

It is found to survive outside the body for some time. For example, it can retain its vitality and virulence in a dry condition in dust or on clothing for at least two or three months. It can also live in a moist condition, in water—tap-water or sea-water—for a somewhat shorter period. This power of retaining vitality and virulence is proved by the injection of the various substances under the skin of susceptible animals, and the setting up of the disease. One important thing noted was, that the *Micrococcus melitensis* does not increase outside the

body, it merely survives for some time, and then dies off; and that, if exposed to direct sunlight, it disappears in a few hours.

Many attempts were made to discover it outside the body, under natural conditions. As the generally accepted theory was that it was conveyed in air, naturally the air of fever wards or of places where cases had occurred was examined with great care. Here, again, animal experimentation comes in. When a parasite is too small and featureless to be recognised by the microscope, or so mixed up with other organisms as to render its recognition by cultivation improbable, then the injection of the mixed material into an animal will often show its presence by setting up the disease. It is in this way that the germ of consumption is found in milk. The suspected milk is injected into guinea-pigs, and if this disease is set up, then the milk is condemned. Up to the present time, no other way has been discovered of testing milk for this germ of consumption.

So in the search for the germ of Malta fever in the air of fever wards, or of drains or sewers, a large quantity of the air was drawn by a suitable apparatus through water, and this water was afterwards tested on animals. If the animal showed symptoms of Malta fever, then the air contained the *Micrococcus melitensis*; if not, then the air was free from this micro-organism. In the same way it was looked-for in the dust of suspected places, and in the water of the Harbour, but with no success. It was evidently a parasite which depended on some warm-blooded animal for its continued existence.

Thus, then, the first important step in the discovery of the way to rid our garrison in Malta of this fever had been taken. The cause of the disease was known and could be recognised without difficulty when met

with, so that now an attempt could be made to find out where human beings got it from.

The next steps in the investigation were to find out how this micrococcus leaves and how it gains entrance to the body.

How does the Micrococcus melitensis Leave the Body?

In regard to this, it is conceivable that it might leave the body by way of the expired air, in the saliva, in mucus from the lungs, as in consumption, in the secretion of the skin, as in scarlet fever, in the renal secretion, or by way of the intestinal tract. Or it might leave the body by way of the blood, by the agency of mosquitoes or other biting flies. Many inoculation experiments on animals were made along all these lines, and it was decided that this micro-organism leaves the body principally in the renal secretion, and in the blood taken out of the body by blood-sucking insects.

The result, therefore, of this experimental work was to give rise to the belief that the disease was conveyed from the sick to the healthy either by personal contact, or by inhalation of infected dust, or, lastly, by the agency of mosquitoes.

How does the Micrococcus melitensis Gain Entrance to the Body?

The investigation of these various modes of infection was therefore undertaken.

Let us first consider infection by contact. Experiments were made by placing monkeys, one affected by Malta fever, the other healthy, in more or less intimate contact, and it was found that if the monkeys lived

together in the same cage infection did take place. If, on the other hand, the monkeys were kept in the same cage, but separated by a wire screen, so that, although they could touch each other, contamination of the healthy monkey's food by the sick monkey could not happen, then infection did not take place.

In regard to this question of conveyance by contact, there is one argument against it which has always seemed to me unanswerable, and that is, that thousands of cases of Malta fever have been invalided home to England, and treated in our naval and military hospitals without, so far as I am aware, a single case of the fever arising among the patients, orderlies, or nursing sisters.

It was therefore concluded that mere contact with Malta fever patients is not the mode of infection.

Then the question of infection by contaminated dust was taken up.

By Dust Contaminated by the Micrococcus melitensis.—For some time it was considered highly probable that this would prove to be the common method of infection. The fact that the micrococcus withstands drying for a long time, the dusty nature of Malta, and the probability that gross contamination of the surface of the soil takes place by infected discharges, rendered this view likely.

Experiments were made to put the theory to the test. Dust was artifically contaminated with the micrococci of Malta fever and blown about a room in which monkeys were confined, or blown into their nostrils or throat. Several of these experiments were successful. It was therefore proved that dust *artificially* contaminated with *Micrococcus melitensis* could give rise to the disease.

This, however, was no proof that this mode of infection occurs in Nature. The artificially-contaminated dust contained myriads of micrococci. Under natural conditions, they could seldom be numerous, and the powerful Maltese sunlight would tend to kill them off rapidly. The dust blown about by the wind must also dilute the micrococci to an enormous extent, so that it is only possible to conceive of a micrococcus here and there in a vast quantity of dust. Experiments were therefore made with dust naturally contaminated, in order more closely to resemble natural conditions. Dust contaminated in this way, and also that collected from suspicious places and blown about the cages, sprinkled on food, or injected under the skin of the experimental animals, always gave negative results.

The conclusion was therefore again come to that conveyance of the infective germ to human beings by means of contaminated dust could only rarely, if ever, take place.

By Mosquitoes or other Biting Flies.—As already mentioned, the theory has been strongly advanced that Malta fever, like yellow fever and plague, might be conveyed by blood-sucking insects. The fact that the micrococci are almost always found in the blood drawn from the skin gave some colour to this belief. This point was therefore fully investigated and numerous animal experiments made with the different species of mosquitoes found in Malta, and also with other blood-sucking insects.

The results, again, were all negative, and it was therefore decided that Malta fever is not conveyed by contact, by contaminated dust, or by mosquitoes.

What, then, could be the mode of spread ?

By Way of the Alimentary Canal.—It had long been known that the smallest quantity of the micrococci introduced under the skin or applied to a scratch would give rise to the disease in man or monkeys, but some work by previous observers had led to the belief that infection did not take place by way of the mouth in food or drink. They had fed monkeys on milk, in which they had mixed the micrococci, and asserted that in no case did infection take place. This observation kept the Commission at first from making feeding experiments. As infection, however, did not appear to take place by contact, by the inhalation of infected dust, or by mosquitoes, it was clearly necessary to repeat these feeding experiments.

Feeding Experiments.

The table on the next page shows the result of some of these feeding experiments, and it will be seen that it is abundantly proved that Malta fever can be conveyed to healthy animals by way of the alimentary canal. Even a single drink of a fluid containing but a few of the par ticular micrococci almost certainly gives rise to the disease.

From the result of all these experiments, then, it seemed most probable that the poison of Malta fever gains an entrance to the body by way of the mouth, and therefore by some infected food or drink.

This led to an examination of food-stuffs, and among these the milk of the goat is one of the most important in the island.

TABLE. (Fig. 5.)

Species of Animal.	Mode of Infection. M. = M. melitensis.	Probable time which elapsed before infection took place. In days.	Result. + Infection. − No infection.
Monkey.	Feeding on potato containing M.	30	+
,,	,, ,, ,,	31	+
,,	Accidental feeding	,,	+
,,	Milk and M.	,,	+
,,	Dust and Malta fever urine. Dried	,,	−
,,	,, ,, ,,	,,	−
,,	Dust and Malta fever urine. Moist	,,	+
,,	Potato and M.	,,	+
,,	,, ,,	,,	+
,,	,, ,,	,,	+
,,	,, ,,	,,	+
,,	Milk and M.	,,	+
,,	,, ,,	,,	+
,,	,, ,,	,,	+
,,	,, ,,	,,	+
,,	Culture of Malta fever	,,	+
,,	,, ,, ,,	,,	+
,,	,, ,, ,,	,,	+
,,	,, ,, ,,	,,	+
,,	,, ,, ,,	18	+
,,	,, ,, ,,	32	+
Kid.	Milk	,,	−
,,	Goats' milk	,,	−
Goat.	Culture from milk	,,	+
,,	Malta fever urine and dust	,,	+
,,	,, ,, ,,	,,	+
,,	Milk and culture	,,	+

Infection by Means of Goats' Milk.

The goat is very much in evidence in Malta, and supplies practically all the milk used. There is, it is said, one goat to every ten of the population, so that, as there are 200,000 inhabitants, there must be about 20,000 goats. Flocks of them wander about the streets from morning till night, and are milked as required at the customers' doors (Fig. 6).

It must be confessed there seemed little hope that an examination of these animals would yield any result. The goats appeared perfectly healthy, and they have the reputation of being little susceptible to human disease of any kind.

To put the matter to the test, however, several goats were inoculated with the micrococcus, and the result watched. There was no rise of temperature and no sign of ill-health in any way, but in a week or two the blood was found to show signs of being infected by Malta fever.

Fig. 6.—Milking Goat.

This raised suspicion, and a small herd of apparently healthy goats was then procured and their blood examined to see if they were all healthy. Several of them were found not to be beyond suspicion, and this led to the examination and the discovery of the *Micrococcus melitensis*, not only in their blood, but also in the milk of the milch goats.

The Poison of Malta Fever in Goats' Milk.

Some thousands of goats in Malta were then examined, and the astounding discovery was made that

quite half of them were affected by Malta fever, and that actually 10 per cent. of them were secreting and excreting the poison in their milk.

Monkeys fed on milk from an affected goat, even for one day, almost invariably took the disease.

S.S. "Joshua Nicholson."

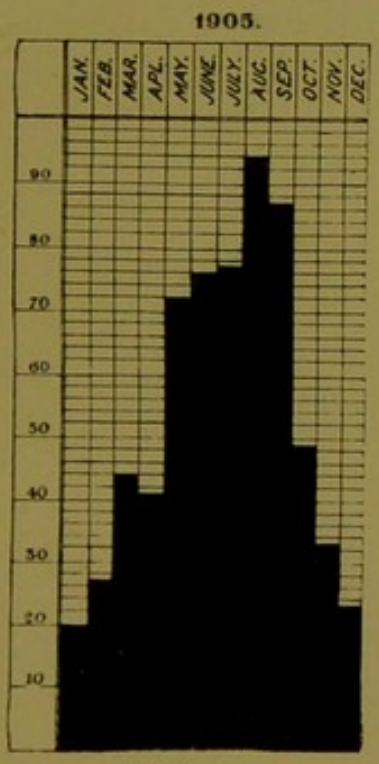
At this time, curiously enough, an important experiment on the drinking of goats' milk by human beings took place accidentally. Shortly, the story is as follows: In 1905 the s.s. *Joshua Nicholson* shipped sixty-five goats at Malta for export to America. The milk was drunk in large quantities by the captain and the crew, with the result that practically everyone who drank the milk was struck down by Malta fever. Sixty of the goats (five having died) on arrival in America were examined, and thirty-two found to be affected, while the deadly *Micrococcus melitensis* was isolated from the milk of several of them. This epidemic of Malta fever on board the s.s. *Joshua Nicholson* therefore clinched the fact, that the goats of Malta act as a reservoir of the poison of Malta fever, and that human beings are infected by drinking the milk of these animals.

Here, then, at last was discovered a mode of infection which explained the curious features of Malta fever—the irregular seasonal prevalence, the number of cases which occur during the winter months, when there are no mosquitoes and little dust. It is true there are more cases in summer than in winter, but this may be explained by the fact that more milk is used at that time of the year for fruit, in ice-creams, etc. It also explains the fact that officers are more liable

than the men, as the former consume more milk than the latter. It also explains the liability of hospital patients, milk entering so largely into a hospital dietary.

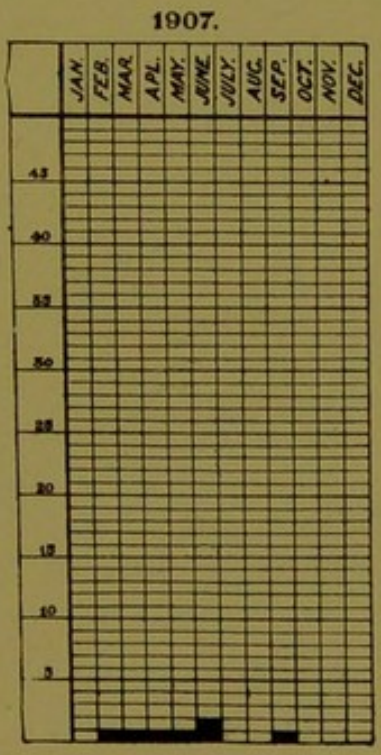
Result of Measures directed against the Use of Goats' Milk.

As soon as goats' milk was discovered to be the



643 Cases.

Fig. 7.



7 Cases.

Fig. 8.

Incidence of Malta Fever in Malta during 1905 and 1907.

source of infection, preventive measures were begun. The result is very striking, as is shown in the diagrams (Figs. 7 and 8), which give the number of cases of Malta fever among the soldiers in the garrison before and after the preventive measures came into force.

Fig. 7 represents the incidence of Malta fever in

1905 among the soldiers before the preventive measures were put into force, while Fig. 8 shows the number of cases of this fever which have occurred among the soldiers in Malta since goats' milk has been banished from their dietary.

In conclusion, I have no hesitation in asserting that this happy result, this blotting out every year of 75,000 days of illness, this extinction of Malta fever from our garrison in Malta, could never have been accomplished without the aid of animal experiment.

R. CLAY AND SONS, LTD., BREAD ST. HILL, E.C., AND BUNGAY, SUFFOLK.