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CHAPTER XIII

UNDULANT FEVER

In the introductory sections to this work we stated that military medical officers, profiting by experience acquired in warm climates, have contributed in no small degree to our knowledge of disease in the tropics and subtropics. Undulant fever, in its earlier restricted sphere as Malta or Mediterranean fever, is an instance of a disease whose elucidation is attributable almost solely to officers of the Medical Service of the British Army.

Knowledge of a low type of fever with remissions, occurring along the Mediterranean littoral, has been general for many centuries, since the time of Hippocrates (Topley and Wilson, *Principles of Bacteriology and Immunity*). Evidence of this is found in some of the synonyms of the last and present centuries—Malta fever, Mediterranean fever, Neapolitan fever, the Rock fever of Gibraltar, Cyprus fever, the New fever of Crete, and Danube fever. It was first brought prominently to the notice of the medical profession in and after 1854 when cases of a prolonged fever, differing in many essentials from typhoid fever, were observed among the troops engaged in the Crimean War. Many of the British sick and wounded were sent to Malta to recuperate and among them various febrile conditions were observed—malaria, dysentery, typhoid, typhus, cholera—and in addition an ill-defined unclassed type of fever which Marston (in the Army Medical Report of 1863) called *Mediterranean gastric remittent fever*; he himself was attacked by it. He noted the irregular type of fever, the muscle and joint pains, the gastro-intestinal symptoms and the long duration of illness, thirty to ninety days, and even more. His account was admirable as a clinical record and to it little has been added since and nothing has had to be taken away. He thought, as naturally did others, that infection had been acquired in Russia and brought by the patients to Malta, though he noted that there was a greater prevalence in the summer months, that in spite of the length of illness the prognosis as

regards recovery was good and that it was probably not contagious from sick to healthy.

In 1872 appeared the first account given by an Italian, Giulia, in *Gazetta di Medicina*, Naples, his article being entitled *Febri endemichi di Malta* and in the course of the next twelve to fifteen years several articles appeared from the pens of British and Italian writers; Aitken, Duffey, MacLean, Notter, Wood and Veale among the former, Baccelli, Borelli, Cantani, Tomaselli, Galassi, Frederici and de Renzi among the latter. Surgeon-Major Veale's account was published on cases seen by him at Netley in 1879 and in it he pointed out the distinctions between this fever and malaria. The British described it usually under the name Malta fever, the Italians as Febbre di Napoli (Borelli), Miliary fever of Palermo (Frederici) or typhoid fever.

Boileu in 1863 and Chartres in 1866 wrote on Malta fever, but the earliest French work dealing with it at any length which we have been able to trace is an article by Giuffre appearing in 1893 in Charcot and Bouchard's *Traité de Médecine*. For the next decade French writers contributed nothing of note, but in the earlier years of the present century several publications appeared of which the following are the chief: Brault in 1903, Ch. Nicolle in Tunisia in 1904, Gillot in 1905, Cochez and Lemaire the same year, and Soulie and Gardon. In 1903 Hayal in his *Thèse de Montpellier* published a valuable monograph with the title *Contribution à l'étude de la fièvre dite ondulante*. Between 1906 and 1914 many contributed to the literature on this subject, most of them army medical officers in Marseilles (Conor, Huon, Simond, Aubert, and Blanchard), Malta (Thibault, Brun, Vincent, Cillognon, and Schneider), Corsica (Du Bourguet), Montpellier (Vedel, Papon and Tartavez), Ajaccio (Defressine).

The studies of M. L. Hughes, made public in 1897, led him to conclude that the disease had been endemic in Malta and Gibraltar at least from the beginning of the nineteenth century.

Malta fever caused much absenteeism and sickness in the early years of its recognition, and in 1884, three years after Veale issued his account, David Bruce reported that between 600 and 700 soldiers and sailors were attacked every year and that the average length of stay in hospital was 120 days, so that this fever alone accounted for nearly 80,000 days' illness yearly in Malta. Two years later Bruce discovered the causative organism, isolating it from the spleen in fatal cases and he named it *Micrococcus melitensis*; later it was transferred to a separate genus *Brucella*,

so called in honour of its discoverer. Bruce by inoculating the organism he had isolated conveyed the disease to monkeys and again recovered it from them. F. Smith and D. Semple demonstrated by agglutination tests the existence of infection in soldiers sent home to England, invalided from the Punjab and Hong Kong and some of these had never served in Mediterranean stations. C. Birt and G. Lamb carried out agglutination tests in 1889 with the sera of patients in the Victoria Hospital, Netley, and obtained positive results with dilutions up to 1 in 700 in patients from India. They found that normal sera might agglutinate in low dilutions of 1 in 10 (experiments in America resulted in positives as high as 1 in 40 in normal subjects). Many patients in the Punjab and Bombay were diagnosed as suffering from undulant (Malta) fever because agglutination had been obtained in these low dilutions and we may mention in passing that for the same reason or (should we say ?) owing to the same mistake kala azar was thought at one time to be epidemic Malta fever. Afterwards, as is not unusual, the pendulum swung to the other extreme and doubt was thrown on the presence of 'Malta' fever in India at all.

To complete this part of the story we may anticipate the chronological sequence of events and say that in 1905 Lamb and Pai in India isolated the organism, as Bruce had done originally, from the spleens of eleven cases. It reacted with a known Malta fever serum in high dilution and also produced the disease when inoculated into monkeys.

Returning to Malta; measures directed towards prevention of infection by general cleanliness and attention to hygiene were found quite ineffectual; water-supplies were analysed and investigated, drainage rectified and improved, walls of dwellings and hospitals scraped, and dust and refuse removed, but the disease continued its ravages unabated and nearly every patient admitted to hospital contracted it.

In 1897 B. Bang reported the finding of an organism which was causative in contagious abortion in cattle, but it was not for more than twenty years after that the significance of this as regards undulant fever came to be recognized (see later).

In 1904 a Royal Society Commission was established at the request of the Admiralty and the War Office, with Bruce as president, and Bassett-Smith, Klein, Martin, Horrocks, Shaw, Johnstone and Zammit as members, to investigate the fever which was

causing so much sickness and invaliding in the Malta garrison. Their first object of study was to determine how the causative agent entered and how it left the body, and its action on experimental animals. In the following year the problem was solved, almost, one might say, by accident, when it was found that the goat was highly susceptible. The reverse had been thought to be the case because injection of cultures into these animals gave rise in them to no signs of ill-health and they were, in consequence, regarded as immune or refractory. Then Dr. Zammit, of the Malta Board of Health, examining in 1905 the blood of these animals, found that the serum agglutinated the organism, and he concluded that though it had caused no symptoms the organism must have lived and multiplied in the tissues—a condition now known as *inapparent infection*. The milk also of infected goats was proved to contain agglutinins. In the same year J. C. Kennedy discovered that the organism was excreted in the urine of these animals.

Further examination revealed the astonishing fact that nearly half (41 per cent.) of the 20,000 goats in Malta were infected and that some 10 per cent. were actually excreting the organism in their milk—hence another, later, synonym of the disease was Goat Fever. Monkeys fed with the milk contracted the disease just as they did when inoculated with the organism.

The results of the investigation carried out by the Commission in Malta were summed up by Bruce as follows:

1. Fifteen per cent. of 525 dock hands at Malta gave a positive serum reaction, thus proving the existence of ambulatory cases.

2. Nine out of twenty-two examined were excreting the organism in their urine and probably about 2 per cent. of the native population are thus excreting them and such constitute a possible danger.

3. Mules and dogs in Malta are infected as well as goats. About half the goats are infected and 10 per cent. excrete the organism in their milk.

4. The chief source of infection in man is goats' milk.

In consequence of this Maltese goat milk was struck out of the dietary of the garrison and the disease incidence at once began to fall. Among the general population who continued its use there was no corresponding drop—an excellent and instructive control test to the experiment on the garrison. As the knowledge and the application of it extended to the people the incidence among them fell also, but not to the same degree as they could

not be controlled in the same way as the troops or naval personnel. The following table shows very impressively the results of the application of this preventive measure.

Year.	Cases of Undulant Fever among		
	Navy.	Army.	Civilians.
1905 . . .	270	643	663
1906 . . .	145	163	822
1907 . . .	12	9	714
1908 . . .	6	5	502
1909 . . .	10	1	456
1910 . . .	3	1	318

The fall in incidence must not be ascribed entirely to this happy discovery for, as the Mediterranean Fever Commission Report 1905–07 shows, it had been falling prior to this. It was remarked that in Malta the officers and upper classes of the civilian population suffered more than the non-commissioned officers and men and the lower classes of the people, but the incidence per mille had fallen from 269·5 in 1859 to 91·2 in 1888. The civil population have continued to drink goats' milk even to the present day and until 1937 pasteurization had not been carried out, and even then quite inadequately, and among them the number of cases had not only remained high but of late has increased greatly. In 1926 there were nearly 600 cases; in 1934 some three times that number.

It was fortunate that cutting off goats' milk from the dietary of the naval and military personnel was followed by such a dramatic illustration of the value of this measure, for in the same year (1905) Johnstone carried out an epidemiological investigation and came to the conclusion that neither food nor drink played a part in causation or spread, nor did dust or personal contact; in the following year Davies arrived at the same conclusions as regards food and drink, but was of opinion that some cases could be accounted for by contact, either direct or indirect through the agency of mosquitoes, the latter theory having the support of Zammit.

Further and more intensive investigations were at once taken in hand and medical officers in India found cases to be far from rare in the Punjab, and W. C. H. Forbes found also that goats there were infected. The disease was shown to be widespread in North-west India and especially in places where the British

troops were stationed. C. Birt reported in 1906 that he had found Malta fever endemic in the Orange River Colony and that goats' milk was much used in the district. The presence of the disease in Rhodesia was observed after goats had been introduced and among children drinking unboiled milk the number attacked was four times as great as among those drinking boiled milk. In the *Journal of the Royal Army Medical Corps*, 1906, is an interesting account of an outbreak on a ship, due, it was believed, to the crew drinking the milk of goats brought on board at Malta.

Incidental mention may be made of Ross's view of the causation of the disease at Port Said in 1906. He attributed it to *Acartomyia zammitti*, a Culicide, the larva of which exists only in concentrated sea water. This recalls Zammit's theory of transmission of the infection by mosquitoes.

Evidence that animals other than goats are concerned in the spread of infection was accumulating for some years but the work of the Undulant Fever Centre of the Rockefeller Foundation established in the south of France did much to prove it. This showed, in 1930, that undulant fever was widespread in south-east France; though cattle are few there sheep and goats are common.

The disease was seen to attack mainly those engaged in rearing sheep and goats and the incidence was highest at the lambing season. Males were attacked twice or even three times as frequently as females. Further, it affected not merely those who drank milk or ate milk products; in fact, an even more potent cause appeared to be actual contact with the animals or their excreta. The report of the Foundation noted that " cows in close contact with sheep and goats might contract the infection, and excrete the organism in their milk for a long period, and human beings drinking the milk might fall ill with undulant fever." There was no little difficulty in assessing the prevalence accurately because, in the first place, many practitioners were still in ignorance of the disease and diagnosed patients as suffering from enteric fever, tuberculosis, rheumatism and so on. One patient had been recorded and diagnosed successively as malarial, then as suffering from enteric fever, then a streptococcal infection, next influenza, whereas all the time it was a case of undulant fever. Secondly, diagnosis can only be made with certainty by laboratory methods and many practitioners were not within reach of laboratory facilities or they failed to utilize them. Thirdly, in some countries, Great Britain among them, undulant fever

is not a notifiable disease, hence it is advisable to report all cases of prolonged fever of obscure origin or character, in order that bacteriological examination may be undertaken. Lastly, the organism, like *Mycobacterium tuberculosis*, may infect but remain latent and only in a certain (perhaps small) or, more correctly, uncertain proportion are conditions such that symptoms are set up rendering the disease clinically recognizable. It may also be that latent infection may lead to latent immunization—inapparent infection—so that undulant fever is not apparently so common as we would expect among veterinarians.

As the disease came to be studied more and more and investigations into the cause and nature of prolonged and obscure fevers were undertaken, and still more when the fever due to Bang's "*Bacillus abortus*" was shown to be a form of undulant fever (see below) the geographical distribution of the disease was seen to be very widespread. Thus, along the Mediterranean littoral it is present in Italy, Spain, Algiers, Tunis and in Portugal and France; also in Greece, Turkey, and Palestine; in Egypt and South Africa. P. D. Strachan in 1906 noted the existence of the disease in the Transvaal, the Orange River Colony and Cape Colony, but stated that up to that time the organism had not been cultivated from the blood or milk of South African goats. In the course of the next ten to fifteen years it had spread widely —at least, if it had existed in other districts previously it had not been recognized—and was reported from Cape Town, East London, Kimberley, Johannesburg, Pretoria and several country districts. It was then thought that infection had been introduced long before by Angora goats and more recently again by importation of Swiss goats. The disease was also present in the Sudan, Uganda, in South-west Africa and in Northern Nigeria. David Bruce, A. E. Hamerton, H. R. Bateman and F. P. Mackie in 1910 discovered its existence, under the local name Muhinyo, in Uganda. They saw fifty patients collected from the eastern shore of Lake Albert Edward and proved it to be undulant fever (then called Malta fever) by culture from the spleen and by agglutination of the serum; they found also that local goats were infected. Up to the time of this discovery by Bruce and his colleagues the condition had been variously diagnosed as beriberi, dengue and kala azar, although no Leishmania had been seen. Other countries where the infection was known to occur were Arabia, China, the Philippines; in India the Punjab and North-west Provinces were particularly affected, the United Provinces less, Bombay occasion-

ally, Madras and Bengal rarely except sailors from the Mediterranean. C. N. C. Wimberley drew attention in the *Indian Medical Gazette* of 1907 to the existence of Malta fever in Northern India, in Mian Mir, Rawal Pindi, Murree, Nowshera and Peshawar where goats' milk was commonly drunk by the natives. It was known also in the West Indies and in parts of America, notably Texas, Mexico and Peru and in the Mississippi Valley.

In 1921 Bevan reported that cases were occurring in Southern Rhodesia, though the patients had no communication, direct or indirect with goats (see below).

The connection of undulant fever with the United States is of great importance historically and merits more than the passing mention already accorded to it. The Bureau of Animal Industry, of the United States Department of Agriculture, had observed that the keeping and breeding of goats would be particularly suitable for the peasant classes who had immigrated from Italy, Spain, and Switzerland on several grounds ; the milk was cheaply furnished and compared very favourably with cows' milk, contained a high percentage of fats, was easily digested and by many was preferred to cows' milk for the sick and in the nursery ; lastly, many, perhaps the majority, could afford to keep a goat whereas a cow was beyond their means. Goats, though not in large numbers, had been reared and kept in parts of the United States for some time, particularly in the Southern and South-western States and those where Italian colonists were present in fair numbers.

Members of the Bureau, after visiting several districts in Europe decided on importing the Maltese goat because it was a prolific breeder and a good producer of milk. In Malta they were usually in relatively small herds, from four to thirty-five animals in charge of a single goatherd. They were driven along the streets and customers brought their pails or other receptacles and the animals were milked directly into them at the house-doors.

In 1905 G. F. Thompson, of the Bureau of Animal Industry, went to Malta to collect a herd for the United States. He selected sixty-five and with three goatherds left Malta on the 19th August, 1905. They were quarantined at Antwerp for five days and re-embarked for New York on the 7th September and arrived there on the 23rd of that month and were taken at once to the Bureau's quarantine station at Athenia, New Jersey.

During the voyage all on board drank of the milk and of a crew of twelve whose movements could be traced eight developed " Malta fever." Two others boiled the milk before drinking it, and

two did not like the milk and soon refused to take it. On the second stage of the voyage, after re-embarkation at Antwerp, the complement increased to sixty-four and the goats were giving less milk, so that each person had only a little.

Malta fever was not indigenous in the United States, but while the imported goats were on their way the preliminary findings of the Commission were made public and these tentative findings were brought by the Royal Society to the notice of the United States Secretary of Agriculture.

At the Athenia Quarantine Station there were then remaining forty-four of the imported goats and their sera were tested for indications of infection; eleven gave good reactions, nine were doubtful and twenty-four negative. On subsequent re-testing some of these last were found to have become positive; in other words there were signs that the infection was spreading in spite of isolation. Some were found to be excreting the organism in large numbers although the milk was to all appearances normal and by chemical standards good. A few of the animals were off their feed and suffered with diarrhœa, but these symptoms might have been due to one or other of several diseases to which goats are subject, and the majority, even though excreting the organism, seemed to be in good health.

One fact, the importance of which was not known till some years afterwards, was noticed, namely, that the infected goats did not conceive readily; some of those which did suffered from a septic metritis after parturition and the kids might become attacked with arthritis resulting perhaps in permanent deformity. So severely did the infection spread among the imported goats and their offspring that about a year after their arrival a decision was come to to destroy them all.

We have seen above that cases of disease clinically indistinguishable from Malta fever were from time to time reported where there was no history of the patients having drunk goats' milk or eaten of its products, nor of their having even been in contact with goats.

As already noted, in 1897 Bang in Norway reported the finding of an organism which seemed to be associated ætiologically with contagious abortion in cattle and this he named *Bacillus abortus*.

In 1914 another important and interesting line of investigation was opened up. J. E. Fraum described an organism from the pig which might set up a febrile disease in men who handled the carcases of such pigs. Four years later Alice Evans in America

noted the similarity between the *Bacillus* (or *Micrococcus*) *melitensis* of Bruce and the *B. abortus* of Bang, and both were put into a separate genus, *Brucella*. *Brucella melitensis* it was thought was the form which was infective for man and *Br. abortus* that infective for cattle.

The remark had been made many years before that abortion and, it was thought, a contagious abortion was common among goats of the Mediterranean littoral, and early in the present century bacteriologists at the Royal Veterinary College, London, had proved the existence of *Br. abortus* in goats in England and Northern Ireland. Bevan in 1921 had reported undulant fever in Rhodesia (see above) among persons who had had nothing to do with goats or their milk ; he noticed, however, that abortion was common among cattle there and that the organism responsible for this would set up in man a febrile disease resembling, in fact indistinguishable from, that due to *Br. melitensis*. Further study showed that *abortus* fever was also worldwide in distribution and occurred in the same localities as had been determined for Malta fever, *viz.* Italy, Sicily, Corsica, Spain, Greece, Algeria, Tunis, Palestine, Arabia, India, South Africa, China, South America and the United States.

In 1927 F. E. Robinson demonstrated that the behaviour as regards agglutination and absorption tests of strains of *Br. abortus* isolated from human cases of undulant fever in Rhodesia and strains supplied by F. Huddleson from America was indistinguishable one from the other.

The infection of pigs is far less common than that of man or cattle and, though probably first observed by Keefer in 1922, the causative organism was not determined for a considerable time (Topley and Wilson). It is chiefly restricted to the middle west States of North America and to Brazil and the Argentine, because it is almost confined to slaughterers and packers—in short, an occupational disease in man. Of those engaged in these occupations many harbour the infection in a latent form, as Hardy, Huddleson, Johnson and others have shown. In 1927 J. G. McAlpine and C. A. Stanetz by biochemical methods divided the group Brucella into the *abortus* strain of bovine origin, the *abortus suis* of porcine origin, and *melitensis*, the human strain ; but the issue is not so clear-cut as this. According to some authorities *abortus* infections in the United States are mostly by porcine and not bovine strains, but, according to others, cows may become infected with porcine strains of *Br. abortus.*

Before pasteurization was so widely adopted the presence of

Br. abortus in cows' milk was more common than is generally believed. Thus, according to E. C. Fleischner and K. F. Meyer, in 1917 practically all the certified milk in San Francisco was infected; E. C. Schroeder and W. E. Cotton in 1921 found 10 per cent. of seventy-seven samples of market milk and six out of thirty-one dairies infected in America; G. S. Wilson in 1926 from an examination of 488 samples at Manchester showed 5·7 per cent. of single milks and 8·8 per cent. of mixed milks to be positive, and in 1927 C. M. Carpenter and D. W. Baker found nine herds out of fifty infected in Ithaca, New York. More instances might be given, but these must suffice.

Researches carried out by bacteriologists in different countries have proved the natural occurrence of Brucellosis in goats (Bruce *et al.*), cattle (Bang), sheep (Dubois), swine (Fraum, Hayes, *et al.*), mules (Sergent), horses (Dubois), dogs (Kennedy), cats, rabbits, guinea-pigs (Aubert, Thibault), rats and mice. Fowls and ducks may also carry it (Fiorentini, Dubois). Only a few of the chief names have been given, the literature is too large to include all.

When speaking of the history of undulant fever we must not omit the introduction of the Brucellin test for purposes of diagnosis. In 1922 E. Burnet used the filtrate of a twenty-day-old broth culture of *Br. melitensis*, called by him *melitin*, as an intradermal allergic test, analogous to the tuberculin test. The corresponding filtrate of *Br. abortus* was known as *abortin*. The opsonocytiphagic test of Huddleson and his co-workers introduced in 1933 because of the difficulty of correctly interpreting the cutaneous reaction calls for no more than mention here, as evaluation of it has not yet been satisfactorily determined. Its name sufficiently indicates its nature.

Sir Weldon Dalrymple-Champneys, in a special Report on Public Health and Medical Subjects, issued by the Ministry of Health of Great Britain in 1929, sums up the position by stating that in Britain the disease is not very rare. Investigation has resulted in the discovery of unsuspected cases in the United States, in Canada, Denmark, Sweden, Holland, Switzerland and Poland, and it has extended rather rapidly in France and Northern Africa. In France the spread occurs chiefly through goats and sheep, little by the cow; in the United States by the cow and the pig, the latter particularly in the middle West; in Denmark and Sweden it is the cow that is the most important agent.

When goats' milk was believed to be the only source there was naturally no reason to expect that there was any considerable

number of cases in Great Britain, but with proof of a bovine origin the matter becomes more grave. Apart from cases in England in which the infection was of foreign acquisition, and laboratory infections which are not altogether rare, Dalrymple-Champneys noted fourteen cases by 1929 and Topley and Wilson record that of 3175 sera examined 101 agglutinated *Br. abortus* at 1 in 40 or higher and estimated that there were eleven cases per million of the population, or 0·001 per cent., while of those exposed more particularly to infection—slaughterers, veterinarians, milk and farm employees—the following were the relative percentages in different countries: *Slaughterers:* in Great Britain 13·1, Hungary 22·6, United States of America 13·7, the Argentine 10·8. *Veterinarians:* in Great Britain 20·6, France 25·0, Denmark 23·4, the Argentine 26·4, the United States 12·9. *Dairy and Farm employees:* in Germany 14·1, Hungary 15·9, New Zealand 16·4, the Argentine 11·8 per cent.

A short recapitulation will indicate how rapidly the disease has spread—allowing, of course, that increased knowledge of the possible presence of the disease and a more intensive search for it tend to exaggerate the significance of the figures themselves. In 1901 only two Departments in France, namely Languedoc and Provence, were known to be infected; by 1926 the disease was present in fifteen and, two years later, in seventeen Departments. In 1910 it was thought to be almost limited to the north coast of the Mediterranean, from Spain to Smyrna, on the east to Beirut and Jerusalem, on the south to Algiers and to Tunisian and Egyptian ports, and to the islands of Sicily, Malta, Cyprus, Corsica, Sardinia and the Balearic Isles. Since then it has been found in—we are loth to say 'has extended to'—Morocco, Tunisia inland, Tripoli, Egypt, Greece, Italy, Southern France, Spain and Portugal. Further, it has been reported from Sweden, Denmark, Holland, Switzerland, Germany, Austria, the Valley of the Danube, the Caucasus, Mauritania, Russia, Poland, the Blue Nile, Aden, Somaliland, the Sudan, Uganda, Rhodesia, South Africa, Northern Nigeria, South-west Africa, India, Ceylon, China, the Philippines, Fiji, the West Indies, Canada, the United States, Peru, Chile, Uruguay, Brazil and Venezuela.

As regards East Africa, Brucellosis has recently been found as the cause of cases of fever hitherto of obscure nature in seven stations in Tanganyika Territory and it is noteworthy that the organism isolated is not purely a *melitensis* or purely *abortus* type, but approaches the Rhodesian type and also *Br. melitensis*.