

The Milroy Lectures

ON

MELITENSIS SEPTICÆMIA

(MALTA OR MEDITERRANEAN FEVER).

Delivered before the Royal College of Physicians of London on March 5th, 10th, and 12th, 1908,

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LECTURE II.¹

Delivered on March 10th.

SYMPTOMATOLOGY.

[AFTER describing the micrococcus *Melitensis* and detailing its bacteriological attributes and the effects produced in the lower animals by inoculating living cultivations of the organism, the lecturer proceeded to describe the clinical symptoms of the disease as met with in man.]

The monograph of Hughes deals so exhaustively with the clinical pictures observed in the many varying types of micrococcus *Melitensis* septicæmia as it occurs in endemic areas when naturally acquired that I am relieved of the necessity of doing more than briefly indicating the main features of the disease. Of the clinical appearances of Malta fever the most important, and indeed the only one that aspires to constancy, is the repeated alternation of pyrexial attacks with periods of normal or nearly normal temperature, and in this respect compares closely with enterica followed by many relapses. The character and duration of the pyrexia often vary considerably throughout the course of the disease, so that whilst in many cases the fever is of the remittent type, in others it is intermittent; in some it is continuously high and in a few continuously low; at almost any stage of the disease one type of pyrexia may give place to another. According to the severity of the symptoms cases of Malta fever are often grouped under the headings of acute, subacute, and chronic, but such distinctions are purely arbitrary.

The onset and progress of cases of Malta fever present different features with almost every individual attacked, and consequently render diagnosis from such diseases as enteric fever, acute rheumatism, tuberculosis, malaria, and septicæmia due to other bacteria difficult in the early stages. Some cases are extremely acute from the onset and are initiated in the previously healthy by rigors accompanied by a temperature of 38·5°, 40°, or 41·5° C., severe headache often limited to the back of the eyeball, indefinite pains about the trunk and limbs—particularly in the back—and general malaise. In such a case the face is flushed, the dorsum of the tongue is thickly coated with white fur but pink and moist at the sides and tip, or more rarely dry, brown, glazed, and cracked, and the breath is offensive. Diarrhœa is not infrequently present during the first few days of the attack but soon gives place to constipation. The pulse is strong and increased in frequency, though not usually in proportion to the temperature. The urine is diminished in amount, high in colour, and contains large quantities of uric acid and urates. This type of fever sometimes passes into the "typhoid" state and death results from cardiac failure or, more rarely, hyperpyrexia supervenes. Sometimes a crisis occurs and recovery takes place, but usually the temperature gradually falls to or near normal and the case assumes the subacute type.

The subacute form, on the other hand, is often slow and gradual in onset. For some days slight headache, thirst, constipation, and gastric disturbances, pains in the back, neck, and limbs, usually described as "rheumatic," accompanied by insomnia, mental anxiety, and general depression, combine to produce a marked but at the same time indefinite feeling of ill-health. Next follows a steady and gradually increasing rise of evening temperature with morning remission until 39·5° to 41·5° C. is reached, followed by a similar and almost equally gradual fall until the morning temperature

becomes practically normal. The remissions of temperature are almost invariably accompanied by profuse perspirations. The duration of the initial pyrexial attack varies in different cases from one to five weeks, then after an apyrexial interval lasting from five to ten days or a fortnight, during which the temperature remains at or about normal, a relapse sets in, similar in all respects to the first attack but often distinctly shorter and less severe. This sequence of events is repeated again and again, the duration of the disease varying from six weeks to six or nine months. I have seen several cases where the duration of the disease has exceeded two years and one where the fever had existed with typical pyrexial attacks at irregular intervals for three years.

Finally, mention must be made of the ambulatory type of case described by Shaw in which symptoms are entirely absent or are limited to a few days' fever (37·5° C.) and the only proof of the existence of the disease is the presence of agglutinins in the blood and occasionally of the micrococcus *Melitensis* itself also; while in the urine (although normal in appearance) the specific organism is often present in enormous numbers (22,000 per cubic centimetre) and in a highly virulent condition. Marston, it should be noted, was also familiar with this ambulatory type of case, for he says "..... upon the other [hand] so mild may the symptoms appear that the patient may never be confined to bed and be all the while supposed to be labouring under a peculiar form of dyspepsia."

The more prominent clinical symptoms throughout the course of the disease, grouped under their respective systems, may be very briefly dismissed.

Tegumentary system.—When the temperature is high the skin is hot and dry, but while the temperature is falling night sweats are frequent and profuse and the perspiration then has a readily perceptible and peculiar odour, which can hardly be described but which is easily recognised by those familiar with the disease. In long protracted cases the nails become brittle, break easily, and show transverse grooves corresponding roughly to pyrexial attacks. The hair, too, becomes dry and brittle and distinctly lighter in colour, or even grey. Towards the termination of the disease, or during convalescence, an extensive falling out of the hair takes place which is usually, but not invariably, followed by a complete renewal. Subcutaneous hæmorrhages of a purpuric rather than petechial type are seen in acute severe cases and are usually of ominous import. During convalescence desquamation occurs, usually extensive, sometimes limited to the hands and feet, and although the flakes are sometimes large more usually they are small and fine like bran.

Alimentary system.—The dorsum of the tongue is furred and white, the edges and tip are pink and moist, and the breath is offensive. The fauces and tonsils are often more or less congested; occasionally and in consequence the submaxillary and cervical glands are enlarged and tender. Constipation is usually present, although in severe and acute cases, also when the height of a pyrexial wave is reached, diarrhœa, with light-yellow pea-soupy motions, may be present. At the onset of an attack the appetite is poor and capricious, but provided due attention is paid to the condition of the bowels is good throughout the illness, solid food being readily digested even during the pyrexial periods. The liver is often enlarged. The spleen, except in very few cases, is slightly but distinctly enlarged and can readily be palpated, as its edge is well below the costal margin, while the organ itself is tender and soft during the height of the pyrexia, but firmer during the apyrexial intervals.

Nervous system.—The micrococcus *Melitensis* and its products appear to have a selective influence upon the nerve tissue, more particularly peripheral, but also central, and neuritis in some form or position is noted in quite 50 per cent. of the cases. The neuritis, usually of the sciatic, less frequently of the circumflex and peroneal nerves, commences suddenly and severely; the acute symptoms pass off rapidly—usually within from 24 to 48 hours—leaving a subacute or chronic affection of the nerve which may continue long after the convalescence has otherwise been established, particularly liable to exacerbations in response to alterations in atmospheric conditions. Cutaneous and deep reflexes are usually increased and areas of hyperæsthesia, especially over affected nerves, are far from rare, while in severe cases control over the sphincters may be abolished. In the long-continued attacks headache, insomnia, nervous prostration, and mental incapacity are common sequelæ and point to the effect of the disease on the central nervous system.

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Respiratory system.—This is usually unaffected. Pulmonary congestion secondary to the cardiac disturbance is sometimes met with. Pneumonia, generally due to secondary infection with the pneumococcus, also occurs. Occasionally a pneumonia primarily due to the micrococcus is noted, as in such cases where Fiorentini has recorded the presence of the micrococcus in the sputum. Pneumonia, followed by empyema where the pus from the pleural cavity contained no organism other than the micrococcus *Melitensis*, has also been observed.

Circulatory system.—Cardiac irregularity—palpitation—from trifling cause, is probably the result of implication of the vaso-motor nervous system, but may also be due to direct irritation of the cardiac muscle by the micrococcus and its products present in the circulating blood. The rate of the heart's action is somewhat, but usually not markedly, increased. Anæmia is a fairly constant and persistent feature. The red cells may fall as low as 2,800,000 per cubic millimetre; the hæmoglobin becomes reduced in amount but out of proportion to the fall in red cells, so that the *index globulaire* falls also; although there is sometimes a true leucopenia the white cells are relatively and sometimes absolutely increased, the increase being almost entirely confined to the non-granular leucocytes—the lymphocytes and hyaline cells.

Articular system.—Effusions into joints, particularly those of the shoulder, knee, and ankle, often occur in the course of the disease and the specific micrococcus has been isolated from the fluid (Gilmour, Kennedy). The costosternal and costochondral articulations are also frequently affected and these joints sometimes suppurate when the only micro-organism to be detected in the pus is the micrococcus *Melitensis*. But the "rheumatism" so frequently noted in Malta fever is in the majority of cases neuritis pure and simple. Effusion into tendon sheaths at the wrist and ankle is also sometimes noticed.

Urinary system.—The kidneys are generally unaffected, although occasionally acute nephritis is associated with the height of the early pyrexial attacks, when the urine is scanty, high coloured, loaded with uric acid and urates, and sometimes albumin is present, though generally not more than "traces" are found. During the apyrexial periods and in the very chronic cases the urine is generally normal.

Generative system.—The sexual system shares in the general nervous irritability and priapism is common, often, it is said, leading to masturbation. Orchitis and epididymitis are not uncommon metastases but are usually mild in character. Catarrhal vaginitis is sometimes observed. Dysmenorrhœa is often noticed during the incubation period and sometimes during the attack of the disease, but amenorrhœa is more frequent, not only during the pyrexia but also during the apyrexial periods; thus of 12 functionally active female patients in one ward, suffering from micrococcus *Melitensis* septicæmia, amenorrhœa was present in five, dysmenorrhœa in one, and in the remainder the catamenia were unaltered. Menorrhagia is more rarely observed; often the menstrual function is uninfluenced by the disease. Pregnancy frequently synchronises with an attack of Malta fever and its course is unaffected, although lactation is frequently curtailed. According to Schoull, loss of virility sometimes followed protracted cases, but the majority of observers agree that neither impotence nor sterility in either sex is noted during, or resultant upon, an attack of the fever.

Complications.—Hyperpyrexia and cardiac failure are the only direct complications of a serious nature. Pyogenic foci due to micrococcus *Melitensis*, although not unknown (Eyre and Fawcett), are by no means common, but the small furuncles which so frequently occur in the sweat-sodden skin are usually due to staphylococcal activity. With the generous assistance of many of my friends, including Staff-Surgeon G. E. Duncan, Staff-Surgeon H. O. Whiteside, and Mr. Gerald Sichel, who together have contributed more than half the total, I have analysed the clinical symptoms of 1000 cases of *Melitensis* septicæmia and have arranged them in tabular form. The temperature curve in every case has been assigned to one or other of the four types, but with regard to other features of the disease every case has supplied one or more symptoms, but no symptom has been included which has not been noted in at least five cases in the series. One's recollection of some particular cases suggests that the occurrence of many symptoms is underestimated; for instance, under the heading of "critical sweats" only such cases have been included where the sweating was so profuse as to necessitate "changing" the patient more than once in the course of the night.

Analysis of Clinical Symptoms in 1000 Cases of *Melitensis* Septicæmia.

	Per cent.
Pyrexia.	
Continuous	26
Intermittent	14
Remittent	58
Hyperpyrexia	2
Tegumentary System.	
Subcutaneous hæmorrhage (purpuric spots)	2
Critical sweats	31
Loss of hair	1
Change in colour of hair	1
Circulatory System.	
Anæmia—clayey-coloured complexion	30
Edema of extremities	2
Epistaxis	6
Pericarditis	0.5
Endocarditis	5.0
Hæmic murmurs	5.0
Painful pulsation of large arteries	3.5
Palpitation	2.0
Nervous System.	
Exaggerated reflexes	4
Hyperæsthesia	6
Headache	54
Insomnia	9
Delirium	6
Impairment of memory	2
Peripheral neuritis	52
Neuritis of special nerves	42
Intercostal neuralgia	14
Paralysis	1
Alimentary System.	
Constipation	32
Diarrhœa	8
Vomiting	9
Anorexia	13
Respiratory System.	
Pleurisy	2
Pneumonia	3
Broncho-pneumonia	2
Bronchitis	12
Urinary System.	
Retention of urine	1
Hæmaturia	0.5
Albuminuria	8
Metastasis.	
Abscess formation	5
Epididymitis and orchitis (25 per cent. bilateral)	8
Parotitis	1
Arthritis and tenosynovitis	21
Visceral changes.	
Hypertrophy of spleen	51
" " liver	8

MORBID ANATOMY.

It has already been remarked that the case mortality of Malta fever is extremely low. The records for the last seven years, during which the diagnosis of the disease has been universally based upon the serum reaction, show that the navy had 1705 cases with 30 deaths and the army in Malta 1947 cases with 55 deaths, an average case mortality of 2.3 per cent., or if we include the civil administration with its 4627 cases with 489 deaths we get a combined case mortality of 6.9 per cent. Under these conditions facilities for post-mortem observations are limited. The pathological appearances presented by cases of Malta fever may be summarised thus:—

Heart.—This is usually normal in appearance. Sometimes the cardiac muscle is pale, soft, and flaccid. Rarely it undergoes some slight fatty degeneration. Micrococcus *Melitensis* can be isolated from the heart's blood, though sometimes only in small numbers. Some alteration appears to take place in the walls of blood-vessels, which makes for ease of passage of red discs evidenced during life by ready bruising for trivial injuries, and often recalled post mortem by localised extravasations of blood at various points in the subperitoneal connective tissue. Possibly this is due to irritation of the vaso-motor system by micrococcus *Melitensis* toxins.

Pericardial fluid.—This is often increased in amount, clear or blood-stained; it usually contains micrococcus *Melitensis*.

Lungs.—These often show oedema and congestion of the bases and occasionally small patches of broncho-pneumonia.

Pleuritic fluid.—This is sometimes present in large quantities, but apparently the result of passive effusion rather than of acute inflammation. The presence of micrococcus *Melitensis* has not been recorded in this situation.

Alimentary canal.—Small areas of localised congestion are commonly found throughout the intestinal canal limited to the mucous membrane and the submucosa, occasionally

associated with very limited extravasation of red blood cells. Marston lays stress on this feature, which led him to apply the name gastric remittent fever of the Mediterranean to the disease. In very chronic cases, especially in those associated with diarrhoea, the mucous epithelium may undergo superficial necrosis resulting in surface denudation of small areas. Bruce, indeed, records one case in which he found definite ulceration of the colon. Cultivations prepared from the contents or with scrapings from the walls of the duodenum, jejunum, ileum, and colon usually fail to demonstrate the micrococcus *Melitensis* by reason of the numerous intestinal saprophytes present with it in these situations.

Liver.—Sudan III. shows the presence of very little fat in the liver and chiefly at the periphery of the acini. The organ is congested, slightly hypertrophied, and increased in weight (from 1415 to 2730 grammes), resembling an early cardiac liver. Micrococcus *Melitensis* is present in cultivations from hepatic tissue. The gall-bladder is usually distended, the bile often containing micrococcus *Melitensis* in fair numbers.

Spleen.—This is always hypertrophied, the size and weight varying somewhat in proportion to the acuteness of the attack (averaging from 57 grammes in very acute cases to 250 grammes in those of long duration, and spleens have been recorded weighing 594, 684, and 810 grammes), from dark red to black in colour, often showing numerous bright-red hæmorrhagic points and usually soft and friable. Micrococcus *Melitensis* is readily isolated from this organ.

Kidney.—This is sometimes congested but usually shows no abnormal appearances. Occasionally the kidney is hypertrophied and pale, resembling the large white kidney of chronic Bright's disease. Micrococcus *Melitensis* is usually but not invariably present in this organ.

Urine.—This is normal in appearance and composition. Only rarely is albumin present; micrococcus *Melitensis* is often present, especially in those cases of long duration.

Mesenteric glands.—These are often enlarged—sometimes from 10 to 12 millimetres in diameter—spherical with injected capsule and semi-fluid purulent contents. Such glands often yield a pure culture of micrococcus *Melitensis*. In many cases, however, the mesenteric glands are normal in appearance and prove to be sterile.

Bone marrow.—Marrow from the long bones and also from the ribs, although normal in appearance, usually contains micrococcus *Melitensis*—often in considerable numbers.

Brain and cerebro-spinal fluid.—The cerebro-spinal fluid is often increased in quantity; in cases exhibiting meningeal symptoms markedly so, leading to flattening of the cortical convolutions. Ordinarily the brain and cerebro-spinal fluid appear normal. Micrococcus *Melitensis* does not appear to be present in the fluid.

[Dr. Eyre next proceeded to describe the morbid histology of the different organs, the chief changes being a great increase of lymphoid tissue in the spleen and in the bone marrow a marked increase in nucleated red cells and lymphoid cells—that is, giant cells, mononuclear cells, and lymphocytes, with a considerable diminution in the granular cells—i.e., myelocytes and polymorphonuclear leucocytes—the whole forming a typical lympho-erythroblastic bone marrow in marked contrast to the leucoblastic marrow associated with pneumococcal infections. He said further that one point on which all Italian observers were agreed as being the most striking feature of sections, not only of spleen but also of liver and kidney, was the presence of the numerous cells which they termed globuliferous cells, derived from the endothelium lining blood sinuses and containing in their interior from one to 15 or 20 red blood discs. In the spleen of a case examined by Carbone he said they were absolutely innumerable; those containing a few blood cells only were rare, those containing from eight to ten were common, and some were seen containing very many more. Dr. Eyre continued:]

DIAGNOSIS.

In the early stages of the disease the diagnosis from, say, malaria, enteric fever, miliary tuberculosis, acute rheumatism or septicæmia due to some other micro-organism by clinical symptoms alone is well-nigh impossible. Consequently the diagnosis of Malta fever is based upon (1) the agglutination reaction, that is to say, the agglomeration of the individual cocci present in a laboratory cultivation of the specific micrococcus by certain specific anti-bodies—agglutinins—present in the blood serum of the patient; (2) the isolation of the micrococcus *Melitensis* from the blood of the peripheral circulation; (3) the isolation of the micrococcus

Melitensis from the splenic pulp; or (4) the isolation of the micrococcus *Melitensis* from the excreta (urine and fæces).

Agglutination Reaction.

Since the "serum reaction" test of Gruber and Durham was applied to the diagnosis of micrococcus *Melitensis* septicæmia by Wright in 1897 this method has been extensively employed; and it has been shown that the specific agglutinin may be present in the blood of patients suffering from the disease, from the fifth day onwards (Aldridge, Bassett-Smith, and Gilmour); exceptionally it is present on the first day; sometimes its appearance is delayed until weeks after the disease is well established. Usually it is present in large amount, giving to the serum a titre of 1 in 100 or 1 in 1000 even during the first week of the disease, whilst subsequently sera reacting in much higher dilutions even up to 1 in 500,000 have been observed. Moreover, it must be noted that the agglutinins persist in the blood long after recovery and the serum may react in dilutions of 1 in 50 and 1 in 100 for from three to seven or even ten years after an attack of the fever. Finally, sera from healthy individuals and from patients suffering from diseases other than *Melitensis* septicæmia never yield a complete reaction when tested in dilutions of 1 in 10 (Birt and Lamb), or a partial reaction when tested in dilution of 1 in 20.

The reaction may be observed macroscopically in the test-tube or in capillary pipettes, or microscopically in the hanging drop.

1. Where the supply of serum is adequate the test is best carried out by emulsifying one loopful (two milligrammes) of living agar culture in each of several small test-tubes each containing one cubic centimetre of the various dilutions of serum respectively and subsequently observing in which dilutions, if any, the delicate flocculi of agglutinated cocci form.

2. According to Wright the test is better carried out by aspirating (by means of a small rubber cap) small quantities of an emulsion of living cocci and of diluted serum into a capillary or sedimentation tube made from a piece of glass tubing, sealing the end in the Bunsen flame, and allowing the pipette to stand at the room temperature for 24 hours. At the end of this time it is compared with a control preparation consisting of equal parts of emulsion and salt solution or diluted normal serum. The mixture in the control pipette will still be opalescent and turbid, whilst that in the pipette containing specific serum will be perfectly clear as to the upper part and containing small pellets of agglomerated cocci at the lower extremity of the column. The test can also be carried out with the aid of watery suspension of dead micrococci but under these conditions it is distinctly less satisfactory.

3. Microscopically the addition of specific serum to an emulsion causes the micrococci to cease vibrating and to collect into large and small masses similar to, but much more tightly packed than, those noted in a similar preparation of specific serum and typhoid bacilli.

For the purpose of establishing the diagnosis I personally require a positive reaction in a dilution of 1 in 30 to 1 in 50, preferably the latter, within half an hour if microscopical examination of the hanging-drop preparation is relied upon or within three hours if the test-tube (macroscopical) is employed, or within 24 hours if the capillary pipette is used. Certain precautions must be observed in carrying out the test. The serum should be clear and free from red blood discs. The culture of micrococcus *Melitensis* used in the test should be one recently isolated from the human body (or recently passed through a laboratory animal) and grown on agar of + 8 or + 10 reaction and incubated at 37° C. for not longer than two or three days—a 24 hours old culture giving the most reliable results. If an emulsion is prepared for the sedimentation test, sterile distilled water, not salt solution, should be used for the purpose. A control consisting of equal quantities of emulsion and normal serum, or even normal saline solution, should invariably be employed for purposes of comparison. Old cultures, or cultures of the micrococcus many generations removed from the animal body, are prone to agglutinate automatically in the presence of normal serum, or normal saline solution, or even when simply suspended in distilled water. Most important of all, the observer must recollect that the so-called "pro-agglutinoid" zones are more common in micrococcus *Melitensis* septicæmia than, for example, in enteric—that is to say, a serum will yield a good reaction when tested against micrococcus

Melitensis in, for example, dilutions of 1 in 30, 1 in 40, 1 in 60, 1 in 80, but will fail completely to clump the cocci in dilutions of 1 in 50 or will react in dilutions from 1 in 50 upwards to 1 in 500 and fail to react in lower dilutions such as 1 in 10 and 1 in 20. The first case of the disease I personally diagnosed during a recent stay in Malta was one in which this phenomenon was well marked. Microscopically and with a 30-minute time limit a complete reaction was obtained in 1 in 50, 1 in 75, and 1 in 100. An incomplete one was observed in the 1 in 30 dilution and no trace whatever of clumping could be detected in the low dilutions of 1 in 10 and 1 in 20. The same dilutions put up simultaneously in sedimentation tubes when examined after 24 hours completely confirmed the microscopical results. Another good example of this phenomenon was afforded in another case where serum dilutions of 1 in 10, 1 in 20, 1 in 50, and 1 in 100 failed to produce any agglutination of the micrococci, while a 1 in 200 dilution caused instant agglutination, and within five minutes the clumps were sufficiently large and compact to be readily recognised by the naked eye. At the present moment there is no really satisfactory explanation of this phenomenon. Dryer has shown experimentally that the preliminary heating of emulsions of bacteria may so alter the agglutinable substance that "zones of inhibition" appear. On the other hand, Eisenberg and Volk note that sera which have been similarly heated (to 65° or 70° C.) likewise exhibit similar zones of inhibited agglutination which they explain by the assumption that part of the agglutinin has been converted by the heat into agglutinoid, which has a greater affinity for the agglutinable substance of the bacteria than has agglutinin. Dryer, however, from his experiments with heated emulsions refuses to accept this explanation, but all that he has to offer in exchange is that, in part at least, the phenomenon may be due to the "slowing of the velocity of the agglutination reaction." No matter what the explanation, it becomes obvious that it is essential to prepare and observe a series of dilutions in performing the test for diagnostic purposes.

Splenic Puncture.

As in Melitensis septicæmia the specific micrococcus is constantly present in the spleen its detection in this situation and its isolation therefrom afford the most certain method of diagnosis. Post mortem, of course, no especial difficulty is encountered. Intra vitam the procedure is simple enough and if carefully performed the risk incurred is not very great. In the vast majority of the cases of micrococcus Melitensis septicæmia the spleen is enlarged, perhaps only slightly, but still distinctly, and is readily palpable. Usually it is painless. Exceptions occur at the height of a pyrexial attack. After careful sterilisation of the skin over the enlarged spleen a sterile exploring needle of some 2 millimetres calibre (with syringe attached) is thrust into the centre of the organ and a small quantity of blood and soft pulp is drawn into the syringe, then transferred to the surface of a previously prepared agar plate, over which it is spread by means of a sterile L-shaped aluminium or glass rod, which is then further employed to prepare two or three other similar agar plates in series with the first. The entire set of cultures are incubated at 37° C. for from three to seven days, by the end of which time the micrococcus, if present, will certainly have developed colonies.

Blood Examination.

The specific micrococcus has been shown by various observers (Gilmour, Shaw, Smith) to be present in the peripheral blood in numbers varying from 1 per 5 cubic centimetres to 400 per 1 cubic centimetre as early as the second and as late as the 300th day of the disease, just as Durham had previously noted in the case of experimental laboratory infections in guinea-pigs and rabbits. The general results are shown in the following table:—

Cases examined.	Micro-coccus recovered from—	Maximum number of cocci recorded per cubic centimetre.	Minimum number of cocci recorded per cubic centimetre.	Observer.
16	8	—	—	—
45	38	400	Less than 1	Gilmour.
103	69	256	"	Shaw.
49	27	200	2	Zammit.
24	16	—	—	{ Bassett Smith.

The above shows 158 successful cultivations out of a total of 235 examined, or a percentage of 65·4. The number of cocci present, however, varied from 1 per 5 cubic centimetres to 400 per 1 cubic centimetre, so that it was often necessary to work with fairly large quantities of blood in order to secure cultivations of the organism; in some instances the agglutinating power of the patient's serum, which varied from 1 in 20 to 1 in 3000 in the different cases from which the micrococcus was recovered, was suggested as a factor probably having some bearing upon the relatively large amount of blood required in order to demonstrate the presence of the coccus.

A critical examination of the results obtained by Gilmour and Shaw leads one to the conclusion that the successful isolation of the micrococcus from the peripheral blood depends mainly upon factors other than agglutination or phagocytosis. Consequently for purposes of diagnosis I consider that the blood should be collected late in the day, when the patient's temperature certainly stands at a higher level than during the forenoon, and at or near the height of a pyrexial attack. Thus working on these lines and by employing the technique usually adopted in England—that is, by using a solution of citrate of sodium to prevent alteration in the freshly drawn blood—I was able to demonstrate the micro-organism in the peripheral blood (drawn from the median basilic or median cephalic vein) in much larger numbers in the three acute early cases which I examined (as will be seen from the table below). Consequently the culti-

Isolation of the Micrococcus Melitensis from the Peripheral Blood.

Patient.	Day of disease.	Time of collection.	Temperature.	Agglutination value of serum.	Number of cocci per cubic centimetre of blood.
K.	7	7 P.M.	105° F.	1 in 2000	At least 1900
F.	38	7 P.M.	103°	1 in 200	10,000
K.	46	7.30 P.M.	103°	in 200	1000

vation of blood taken from a vein of the arm (median cephalic or median basilic) under strict antiseptic precautions holds out a fair prospect of success in the isolation of the specific coccus. The method to be adopted is to withdraw five cubic centimetres of blood into a sterile syringe already containing a few drops of 10 per cent. sodium citrate solution, transfer the citrated blood to a test-tube or small flask containing 45 cubic centimetres of nutrient broth, and incubate at 37° C. From the third to the tenth day of incubation an agar slope-tube must be inseminated from the broth culture and itself incubated for from three to seven days before a negative result can be recorded. The identity of the resulting growth must of course be confirmed by the ordinary bacteriological methods.

Urine.

From about the fifteenth day of the disease in chronic cases and towards the end of an attack in more acute cases, and onwards during convalescence, many patients pass the specific cocci in varying numbers in the apparently normal urine, so that surface plate cultures prepared from the centrifuged deposit of a catheter specimen of the urine suffices for the isolation of micrococcus Melitensis. In many instances the number of cocci present in the urine is so great that centrifugalisation is unnecessary and the surface planting on plate cultures of a drop of the urine itself will yield a vigorous growth of the coccus. Two ambulatory cases (workmen in the Royal naval dockyard, Malta) which were transferred by Staff-Surgeon Shaw to me for further observation, excreted the coccus for months in numbers varying from 440 to 30,000 or more per cubic centimetre, and in order to obtain countable plates it was necessary to dilute the urine, not to concentrate its bacterial content by centrifugalisation. If, on the other hand, it is feared the number of cocci present in the urine is small the prospect of the successful isolation of the coccus is heightened if some specific agglutinating serum is added to the urine previously to centrifugalisation.

Fæces.

In the course of some experiments upon acute micrococcus Melitensis infections in the guinea-pig I was able to demonstrate the presence of the organism in the gall-bladder and intestinal canal and tracing it down from the duodenum to

the rectum finally isolate it from the fæces. The number of observations in this direction that I have been able to make in human patients is limited to eight. Seven of these were cases of the chronic type and the motions were firm and formed, and plating experiments failed to demonstrate the presence of the micrococcus. In one fatal case (of one and a half months' duration) the colon was found post mortem to be filled with light-coloured semi-fluid fæces and the plate cultivations yielded a very mixed growth of a large variety of bacteria, including the micrococcus Melitensis. By emulsifying some of the growth in saline solution, precipitating the micrococci by the addition of a powerful agglutinating serum, and again plating the sedimented micrococci I was able to obtain it in pure culture.

PROGNOSIS.

The prognosis of Malta fever, so far as life is concerned, is good. The mortality of the disease as recorded in army and navy statistics reaches not more than 2 per cent. of the case incidence; but indications upon which to base a prognosis as to the duration of an attack are usually conspicuous by their absence. Speaking generally, an attack commencing with acute symptoms, one or two sharp pyrexial attacks accompanied by high agglutination reaction and a gradual increase in the amount of specific agglutinins in the blood, will be of shorter duration than one when the pyrexia is slight and the agglutinating reaction low or gradually diminishing in intensity. On working out the duration of a large number of cases of Melitensis septicæmia under treatment in naval and military hospitals, together with many others seen in civil life (including those still suffering from various sequelæ after their discharge from the services), one may safely say that not more than 10 per cent. are convalescent in a shorter period than one month from the onset of symptoms. In 50 per cent. the disease extends over two months, in 25 per cent. to three months, and in fully 15 per cent. a duration of three months is exceeded.

Second attacks.—As an apyrexial period of very extended duration may still be followed by a relapse, and as the diagnosis prior to 1900 or 1901 was usually made upon clinical grounds only, any dogmatic statement on the subject of second attacks of Melitensis septicæmia would be distinctly premature. Moreover, the opinions of naval and military surgeons elicited by my inquiries are diametrically opposed. The former consider that an attack confers little or no subsequent protection; the latter are inclined to believe that considerable, if not absolute, immunity is conferred by one attack of the disease. Personally, I believe one attack does confer a certain slight amount of immunity—an opinion which derives some support from the fact that records of authenticated second attacks are very rare. That second attacks do occur I am convinced from my own personal experience. In 1903 I suffered from a sharp attack of the septicæmia, lasting in all about three months, resulting from accidental inoculation in the laboratory. During the next two and a half years I remained in perfect health, my agglutination reaction gradually fell to 1 in 50, and I was passed as a first-class life by a life insurance office. Shortly after my arrival in Malta in 1906 I took a perhaps too active part in the cleansing of the Mediterranean Fever Commission's laboratory (as I had found that the accumulated dust of the room contained the micrococcus Melitensis), and shortly after the agglutination reaction of my serum sank and I found that I was more or less out of sorts—headaches and occasional evening temperature of 100° F. which might merely have been the result of the associated constipation but which culminated in sudden effusion into both ankle-joints, necessitating several days in bed. The effusion gradually subsided and a sea trip to Naples and back restored matters to the previous state of occasional headache and occasional pyrexia and night sweats for another month, when acute pyrexia of 104·5° F. ushered in a severe relapse and it was not until some six months later that convalescence was fully established.

TREATMENT.

Drugs.—Of drug treatment of Melitensis septicæmia *per se* there is none. Osler puts the matter so concisely that I cannot do better than quote the few lines in which he disposes of the subject. "Hydrotherapy, either the bath or the cold pack, should be used every third hour when the temperature is above 103° F. Otherwise the treatment is symptomatic. No drugs appear to have any special influence on the fever. A change of climate seems to promote convalescence."

IMMUNITY AND SERUM TREATMENT.

Prophylactic vaccination.—In experimental animals, such as the rabbit and guinea-pig, long-continued treatment by injections of "killed" cultures of micrococcus Melitensis provokes the formation and maintenance of a high agglutinating power in the blood, but such inoculations not only fail to protect the animal against the fatal consequence of a subsequent injection of virulent living culture but in some cases appear to render the animal more susceptible. The one observation in this direction recorded in man has a similar bearing. After several preliminary vaccinations with dead cultures of micrococcus Melitensis a small quantity of living culture injected subcutaneously into the arm was followed after 15 days by a typical attack of the fever (Birt and Lamb). The probable value of preventive vaccination has not, therefore, the experimental support that is available in the case of other diseases. Nevertheless, during the summer of 1906 I carried out a series of vaccinations with dead cultures amongst the attendants in the naval and military hospitals of Malta which, it was hoped, would afford further information on this point.

Dose.—The initial dose varied slightly in individual cases, but was either two, three, or four hundred millions of cocci. Subsequent doses were regulated by the response of the individual to inoculation, as judged by the movements of the curve representing the agglutinin-titre of the serum, but were usually 400,000,000 cocci. In many of the cases two inoculations were given at suitable intervals.

Sequelæ of inoculations.—But few words are necessary as to the local and constitutional effects following the introduction of the dead bodies of micrococcus Melitensis into the subcutaneous tissue of the normal human subject, as observed in these 51 men.

Local appearances.—The introduction of such a small quantity of fluid into the subcutaneous tissue produced no immediate effect other than a slightly marked prominence of the skin at the seat of inoculation. Usually the emulsion was completely absorbed within a few hours and on the morning following the inoculation no local alteration was discernible. In three of the orderlies of the Royal Army Medical Corps the first inoculation was followed by a very distinct, hard, tender lump at the seat of inoculation, the skin over the swelling being red and slightly cedematous. Some tenderness of the inguinal and axillary glands was present so long as the lumps remained tender, but this passed off rapidly when the swelling had disappeared. In all three cases the swelling subsided without interference, the duration of a visible tumour being limited to two or three days respectively in the first two cases. In the third the lump, which was on the right side, remained visible and tender for seven days and was probably due to the fact that the subject—an ardent cricketer—was on bowling for practically the whole of the afternoon following inoculation. Inoculations subsequent to the first failed to cause any discomfort. The inguinal glands in many were slightly tender for the 24 hours following an injection, but not longer.

Constitutional symptoms.—Beyond slight headache and feeling of malaise, associated with a rise of temperature to 98·6° or 99°, complained of by a few on the day following inoculation, no constitutional symptoms were observed. Two of the controls, however, who had been injected with normal saline solution complained of severe headache and showed temperatures of 99·6° and 99·8° respectively on the day following the injection. It will thus be seen that none of the disquieting results recorded by Lieutenant L. Bousfield, R.A.M.C.,² were noted in this series of inoculations. That they do occur, however, was well shown in the case of one of the members of the working party who was inoculated by Lieutenant-Colonel W. B. Leishman, R.A.M.C., immediately prior to leaving England. Marked enlargement, accompanied by tenderness on pressure of the superficial lymphatic glands, was observed within 24 hours of inoculation, together with some headache and malaise. The seat of inoculation was occupied by a raised, hard, and tender lump, which gradually became soft and boggy to the touch, and the skin over it acquired a dusky-red colour. As there was every evidence of pointing, the tumour was incised on the eleventh day and some thin serous pus, which proved sterile, was evacuated; and no higher dilution of the blood serum than 1 in 10 would give a positive agglutination

² Bousfield: Some Remarks on Protective Inoculation against Malta Fever. Journal of the Royal Army Medical Corps, vol. vii., 1905, pp. 179-182.

reaction. Later on an injection of the same brew of vaccine that was used in the series of prophylactic vaccinations now under consideration was introduced into the opposite flank. This was followed by a precisely similar train of events, although on this occasion the symptoms were distinctly less severe; the agglutination response on this occasion rose to 1 in 40.

The subjects.—*Naval.*—Of the staff of the Naval Hospital at Bighi 43 men were available for observation in this connexion, of whom 23 were vaccinated (seven on one occasion only and 16 on two occasions) and 20 were reserved as controls. From the 23 vaccinated men, however, two must be deducted, for the danger that must always exist in carrying out a series of vaccinations within the endemic area was here encountered and two of the men were vaccinated—each with a dose of 200,000,000 cocci—during the incubation period of the naturally acquired disease. This leaves 21 inoculated men and 20 controls who were under observation from April 27th to August 30th, 1906. During this period one of the controls contracted the disease, but no cases occurred amongst the vaccinated men.

Military.—The strength of the Valetta detachment of the Royal Army Medical Corps at the commencement of the experiment comprised 84 men, of whom 12 had already suffered from an attack of "Malta fever" and four were then in hospital. This left a balance of 68 available for the purposes of observation. Of these 30 volunteered for inoculation; the remaining 38 served as controls. The fallacies involved in such a division have already been threshed out in connexion with prophylactic inoculations of typhoid vaccine, and need not be further enlarged upon here. Suffice to say, that of the inoculated men 15 received one injection only and 15 received two injections; and during the four months from April 26th to August 30th, 1906, two cases occurred amongst the non-vaccinated controls and none in the vaccinated men. At the beginning of September, however, after I left Malta, two cases occurred in the vaccinated men. The first, a lance-corporal, an assistant in the Commission Laboratory at Valetta, who had been injected twice with a dose of 400,000,000 cocci on each occasion and whose serum value had reached 1 in 50, suffered a typical attack, and the second, a private, who had been inoculated once only with a similar dose and whose serum had a value of 1 in 30. In this series of inoculations it was noted that the response of the individual as judged by the movements of the agglutination value of the serum varied within wide limits from a positive reaction in a dilution of 1 in 200 to a negative reaction in a dilution of 1 in 5 as a result of the first injection. A further point was the very distinct fall in the titre of the serum that has taken place by the end of the four months, in one case from 1 in 200 to 1 in 10, showing that the individual response to vaccination, so far as relates to the production of antibodies of the agglutinin group, at any rate, is limited to a comparatively short period, and apparently indicates that a further inoculation is necessary at the end of about three months after the first or second. The immunity of the inoculated men during a period of four months from any attack of Melitensis septicaemia, though possibly due in part to the elimination of the "goat's milk" factor, also indicates to my mind that prophylactic inoculations have a distinct value.

Anti-serum.—In 1895 Wright infected goats and in 1896 a horse was inoculated with *Micrococcus melitensis* in the attempt to produce an anti-serum, and about 50 cases seem to have been treated with the serum from the horse (Aldridge, Fitzgerald, and Ewart), but the published cases do not offer any very convincing evidence of the value of such serum. In connexion with the use of serum a word of warning is necessary, as in the immunisation of both goat and horse I have noted that after the injection of living cultures the cocci are present in the blood from four to six weeks, and if the animal is bled during this period living cocci can be demonstrated in the serum by inoculating some 10 to 20 cubic centimetres subcutaneously into the guinea-pig. In the case of a horse which had been treated for a period of 11 months, with first dead and subsequently living cultures of *micrococcus Melitensis*, 0.1 cubic centimetre of the serum (which had an agglutinating value of 1 in 1500) was found to protect when injected simultaneously into the cerebral tissue of the guinea-pig against some ten lethal doses, but even 10 or 20 cubic centimetres of serum injected subcutaneously failed to protect against an identical dose of the virus injected into the brain.

The action of the serum was also tested upon monkeys

previously injected subcutaneously with 0.1 loopful of cultivation of *micrococcus Melitensis* emulsified in one cubic centimetre of normal saline solution. Eight days later, when signs of successful infection—rise of temperature, appearance of agglutinins in blood, &c.—were apparent, two were set aside for observation as controls; three others each received three cubic centimetres of horse serum subcutaneously daily for eight days and a fourth received three cubic centimetres of horse serum injected directly into the external saphenous vein daily for a similar period. The result was by no means encouraging, for while one of the monkeys showed a comparatively even temperature and an absence of marked pyrexia that might be attributed to the action of the serum, the charts of the remaining three serum-treated monkeys showed no mark differences, so far as concerns the range and duration of pyrexia, from those of the two controls, while throughout the course of the experiment simple visual observation of the infected animals was insufficient to enable one to distinguish between those treated with serum and the controls. Whilst in Malta I was only able to obtain permission to administer serum to one human case, but beyond steadying the pulse and bringing it down from 108 to 96 per minute, a result which, in my own opinion, might equally well have been achieved by a simple injection of normal saline solution, no further effect could be detected.

A Clinical Lecture

ON

CONGENITAL DISLOCATION OF THE HIP AND ITS TREATMENT.

Delivered at the Hospital for Sick Children, Great Ormond-street, on Dec. 12th, 1907,

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LADIES AND GENTLEMEN,—I do not think I need apologise for making congenital dislocation of the hip the subject of my lecture to-day, as the frequency of its occurrence warrants us in paying considerable attention to its pathology and treatment. The work of Paci, Hoffa, Lorenz, and others has given us a sound knowledge of the morbid anatomy of the deformity and enabled us to treat it with considerable success. Let me first remind you of some facts relating to its occurrence before passing on to its pathological anatomy, a knowledge of which is essential if our treatment is to be scientific and successful.

Congenital dislocation of the hip is far commoner in females than males; Young has collected figures from various sources and gives 3113 cases, with 456, or 14 per cent. in males, and 2657, or 86 per cent. in females—i.e., about one male to six females. Two-thirds of the cases in this series were unilateral and one-third bilateral. When unilateral the left hip is slightly more frequently affected than the right. Young gives 637 right and 799 left.

The etiology of this deformity need not detain us for long. We may admit at once that the cause is unknown. That heredity sometimes plays a part is shown by the numerous instances reported of the deformity occurring in more than one member of a family. Dupuytren mentions the case of a girl who had eight relatives similarly affected. As to the preponderance of females over males affected, the former are said to be more prone to deformities of all kinds. Heusner and Marcwald found that the capsule of the hip-joint was more lax in female than in male fetuses. That arrest or defect of development is the essential factor in the majority of cases, whether traumatism in utero or at birth plays a part or not, is, I think, proved by the frequency with which imperfect development of the pelvis and often of all the bones of the leg accompanies the dislocation, to which further reference will be made later.

PATHOLOGICAL ANATOMY.

The condition of the joint will be found to vary according to the age of the case; the older the child the greater the alteration found in all the structures composing the joint.