

NOTE ON THE ENDEMIC FEVER OF THE MEDITERRANEAN

BY

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IN the countries bordering the Mediterranean Sea south of latitude 46° N. (isotherm 55° F.), an endemic fever prevails, to which neither satisfactory name nor a place in the official nomenclature of diseases has yet been given. In the navy this disease is returned as "remittent fever," though it has no connection with fevers of malarial origin. In the army it is returned, together with all cases of slight and indefinite pyrexia, as "simple continued fever," in spite of its many and obvious distinguishing characters. A certain slight resemblance to enteric and malarial fevers has been used as an excuse for calling it by many hybrid and unscientific names, such as pseudo-tifo, adeno-tifo, typho-malarial fever, &c. Various other names have been given to it, none of which can be said to be satisfactory, such as *febris complicata*, *febris sudoralis*, pythogenic septicæmia, and such local names as Gibraltar fever, Rock fever, Malta fever,

Mediterranean fever. In this paper I follow the example of others, and call it "Mediterranean fever," with a hope that a more suitable name may be soon adopted.

The specific nature of Mediterranean fever is proved by its long and indefinite duration, irregular course, tendency to relapse, and peculiar symptoms; by the absence of intestinal ulceration, and by the constant presence in certain tissues of a definite species of micro-organism capable of producing by inoculation a similar form of pyrexia in monkeys.

The fever prevails mostly in the large seaports, but is also to be met with in inland villages, even at high altitudes. During the early part of the present century it appears to have existed both in Malta and Gibraltar, but to have been returned under such symptomatic headings as rheumatism, bronchial catarrh, lobular pneumonia, climatic cachexia, &c. The first accurate description published was that by Dr. Marston in 1861, written while serving as an army surgeon in Malta.¹ He was followed by Chartres (1865), Boileau (1866),² Oswald Wood, Notter,³ and Donaldson⁴ in 1876, also army surgeons serving in Malta. In 1879 Prof. Veale,⁵ and in 1885 Prof. Maclean⁶ published valuable reports dealing with cases invalided to Netley from the Mediterranean. In 1887 Surgeon-Major Bruce published his discovery of a causal micro-organism, and later on other papers;⁷ while

¹ 'Army Medical Department: Statistical, Sanitary, and Medical Reports,' iii, 1861 (published in 1863), p. 486.

² *Ibid.*, 1865 (published in 1867), p. 527; 1866 (published in 1868), p. 478.

³ 'Edinb. Med. Journ.' xxii, 1876-7, pp. 40, 289.

⁴ 'Army Medical Department: Statistical, Sanitary, and Medical Reports' for 1876 (published in 1879), p. 238.

⁵ *Ibid.*, 1879 (published in 1881), p. 260.

⁶ 'Practitioner,' xxxiv, 1885, p. 78; and 'Brit. Med. Journ.,' 1875, vol. ii, p. 224.

⁷ 'Practitioner,' xxxix, 1887, p. 161; and xl, 1888, p. 241; 'Annales de l'Institut Pasteur,' vii, 1893, p. 289; articles in Davidson's 'Hygiene and Diseases of Warm Climates,' p. 265, 1893, and Quain's 'Dict. of Med.,' vol. ii, p. 10, etc.

Surgeon-Captain Moffat in 1889 dealt with its occurrence in Gibraltar.¹

Since that date I myself and others have endeavoured to carry on these investigations.² In Italy and Sicily, Borrelli (1872), Tomasi (1874), Cantani (1878), Rummo (1881), Galassi (1883), Capossi (1885), Federici (1885), Tomaselli (1886), Guiffre and Silva (1893), and many others have published papers;³ as have also Carageoriades of Cyprus (1891), and Typhaldos of Greece. These and others have met with the fever as an endemic disease in Middle and Lower Italy, Sicily, Constantinople, Crete, Greece, Smyrna, Cyprus, Malta, Gibraltar, Tunis, Algiers, &c.; while Drs. Hutchinson Miles, Pasquale, and Rho⁴ would lead us to believe that the same fever exists on the borders of the Red Sea. As in India and elsewhere there still exist forms of remittent fever of long duration and irregular course, neither enteric nor malarial in nature, it would be unwise to lay down any geographical limits to its prevalence in the limited state of our present knowledge.⁵

Symptomatology.

So variable are the symptoms, and so uncertain is the duration of this fever, that it is impossible to give a description to which all cases can be referred. Putting aside those short (abortive?) and indefinite cases of fever lasting from seven to twenty-one days, which are more severe than simple ardent fever, and unlike enteric fever,

¹ 'Army Medical Department: Statistical, Sanitary, and Medical Reports,' xxxi, 1889 (published in 1891), p. 403.

² 'Lancet,' ii, 1892, p. 1265; 'Annales de l'Institut Pasteur,' vii, 1893, p. 628.

³ 'Trattato di Medicina' di Charcot, Bouchard, and Brissaud, 22a del., vol. i.

⁴ 'Lancet,' i, 1892, p. 1359; 'Sperimentale,' anno xlvi, p. 545, etc.

⁵ The writer hopes shortly to publish a complete bibliography of this fever.

we meet with three varieties, to which all cases of this Mediterranean fever seem to approximate clinically. The following descriptions are based on notes of over a thousand cases which I have had the opportunity of seeing in Malta during five years of constant hospital practice.

1. *Malignant or fatal type.*—(a) The patient, often a strong muscular man, is admitted to hospital suffering from severe pyrexia, stated to be of only one or two days' standing. He complains of severe headache, "pains all over him," distaste for food, possibly nausea, and even vomiting. His face is flushed, his tongue thickly coated with whitish-grey or yellow fur, pink at the tip and edges, moist, swollen and indented by the teeth laterally. The temperature is 104° — 105° F. There is epigastric, splenic, and perhaps hepatic tenderness on pressure, while the area of splenic dulness is increased. Diarrhoea may be present, when it is usually due to involvement of the large gut. If left to take its course, after four or five days of constantly high pyrexia, signs of basal pneumonic congestion, with bronchial râles all over the chest, appear, and these may pass into lobular consolidation. The pulse remains strong and the mind clear. The urine is decreased in amount, dark in colour, and loaded with lithates; diarrhoea, if present, becomes profuse and frequent, the stools being usually brown in colour, very offensive, but variable in consistency. After a varying number of days the pulse begins to flag and become intermittent, the breathing laboured, and obstinate vomiting may be present. The tongue becomes brown, the teeth are covered with sordes, and other symptoms of the so-called "typhoid state" set in; the respirations are shallow and fast; delirium supervenes and passes into coma; the fæces are passed involuntarily; the temperature rises, the heart gives way, and the patient dies of hyperpyrexia. At death the temperature is, as a rule, about 110° F., but may continue to rise, so that a temperature of 112° — 115° F. has been registered shortly after in the internal organs. Rapidly fatal cases are rare in

these days of improved treatment. In a few cases there is a temporary fall to normal with great exhaustion, for a few hours before death from hyperpyrexia; while other delicate individuals appear to die of the direct toxic effects of the virus, at a temperature well below hyperpyrexia.

(b) In some cases the patient passes safely through the primary attack, the pyrexia abates at the end of two or three weeks for a few days, followed by a gradual rise and relapse, in the course of which similar fatal symptoms may supervene.

(c) In cases which prove fatal at a later stage in the disease (70th to 150th day) death is usually due to sudden cardiac failure, to debility and exhaustion, or to the super-vention of phthisis or some other intercurrent disease.

Of twenty-nine fatal cases, death occurred in 13·7 per cent. during the first week in hospital, in 18·3 per cent. during the second week, in 25 per cent. during the third week; in 57 per cent. during the first month, 22·6 per cent. during the second month, 9 per cent. during the third month, 4·5 per cent. during the fourth month, 2·2 per cent. during the sixth month.

2. *Undulatory type*.—These cases are marked by intermittent waves of remittent pyrexia of variable length, marking the pyrexial intensity, separated from one another by periods of temporary abatement or absence of symptoms. In typical uncomplicated cases, confined to bed, there is usually a premonitory stage of low spirits, sleeplessness, anorexia with dyspeptic symptoms, and each evening headache and slight pyrexia. The temperature next rises gradually, remitting each morning about half the amount of the previous evening rise. With this are combined slight headache, pains in the back and limbs, moist, furred, swollen tongue, a bad taste in the mouth, epigastric tenderness, and constipation. Most patients, however, do not at first report themselves sick, but, imagining that they have "a bilious attack" or "liver," take aperient pills, and attempt to work the

illness off by hard exercise. The result is that all the symptoms become exaggerated, and on admission the temperature is high, and the headache severe. The temperature having reached 103° — 105° F. in the evening, accompanied by some bronchial catarrh or hypostatic pneumonic congestion in proportion to the severity of the case, after a variable period gradually falls to normal or thereabouts in the morning; and though it may be slightly higher in the evening, the patient feels better and wants to get up, while the primary wave may be said to be over. After a day or two, however, the temperature again begins to rise, and a relapse ensues, similar to the primary attack, but usually less prolonged and less severe. This subsides, but is followed by other relapses forming the undulatory temperature charts so characteristic of this fever. Such pyrexia is nearly always accompanied by obstinate constipation, though diarrhoea may occur temporarily in very severe cases, more especially during the primary attack. Each daily remission of temperature is accompanied by profuse sweating. Anæmia and muscular wasting are progressive and often extreme. At any stage, but usually late in the attack or during convalescence, symptoms of localised interstitial neuritis may occur, leading to obstinate sciatica, intercostal neuralgia, &c., or to symptoms referable to irritation of the peripheral sensory nerves or of the nerves of special sense. In many cases effusion into one or more joints may suddenly occur, of a transitory and metastatic nature, but causing extreme tension and pain; or painful orchitis may appear. Finally the patient is reduced to an emaciated, anæmic, bedridden condition; subject to attacks of bronchial catarrh, lobular pneumonia, cardiac palpitation, rheumatic or neuralgic complications on the slightest exposure to chill, change in the weather, or excitement. Disappointed at each relapse, his whole expression is the picture of despondent apathy, his only wish to get away to England. His emaciated appearance, his profuse night sweats, often

intermittent pyrexia and cough, remind one forcibly of the late stages of phthisis. Gradually, however, towards the end of the second or third month, his temperature becomes normal or subnormal in the morning, and but slightly above normal in the evening; next the evening rise ceases, giving place usually to a day or two of subnormal temperature, after which convalescence is established. The strength now slowly returns, the cheeks fill out, and the patient gets up for an increasing period every day. After a few weeks, if not invalided home, he is sent to a sanitarium, or perhaps to duty, but for months after is liable to attacks of neuralgic pain, to swollen joints or testicles, combined with slight pyrexia. Final recovery cannot be said to take place for many months, and until the anæmia has disappeared and the mucous membranes have regained their complete functions; when once, however, completely free from the disease, it does not recur like paludism.

The average duration of pyrexial symptoms is sixty to seventy days, but cases have been known to last thrice as long. The average stay in hospital is over ninety days, and convalescence has been prolonged to a year or more in certain cases.

3. *Intermittent type*.—In these cases the temperature intermits daily, and being of a non-paroxysmal nature, they resemble hectic fever cases. If, however, the temperature be accurately taken, so as to register the daily maximum and minimum, these are found to form waves of pyrexial intensity similar to those previously described, the daily remittance being exaggerated into an intermittence. These cases are, as a general rule, shorter than the undulatory ones, complications being milder in character when present. Constipation, night sweats, and progressive anæmia accompany the pyrexia, while arthritic effusion may occur. The patient is usually less despondent, the absence of marked undulations does away with the disappointment felt at each relapse, the patient's daily remark being that he is "just the same." In many

cases non-paroxysmal pyrexia and profuse night sweats are the only symptoms present, and the patient, if allowed, wishes to get up and eat solid food each morning, but suffers from slight malaise in the afternoon. Such cases go on steadily in spite of all the drugs in the pharmacopœia, and though an indiscretion may bring on serious symptoms, they seem to cease spontaneously, or at the commencement of some new line of treatment which, however, fails to stop other and similar cases.

Between the undulatory and intermittent types we meet with every variety of curve that can be said to approximate to the above individual descriptions, or to a mixture of both; but there is always a tendency to the formation of waves of pyrexial intensity if the curve is accurately registered.

Special symptoms.—In severe cases the face may be cyanosed, but in long cases towards the end of an attack the face becomes of a dull clay colour, the skin tightly drawn over the skull, with an expression of listless resignation to an uncertain fate. There is no exanthem, but sudamina are not uncommon during and after the third week, especially when the skin is not properly attended to. Prickly heat (which may become pustular) is an annoying complication of hot weather, while in the spring and autumn boils may occur. Subcutaneous hæmorrhages, combined with scorbutic symptoms, are of rare occurrence. About the fourth week desquamation takes place, being most noticeable on the soles of the feet, where the skin peels off in large flakes. Towards the end of long attacks the hair falls out extensively, but is gradually replaced by new growth during convalescence. As in enteric fever, there is a certain amount of cutaneous bronzing, but nothing approaching the pigmentation of paludism. A distinctive and disagreeable odour is present in nearly all cases, being most especially marked at post-mortem examinations. The profuse diaphoresis following the fall of temperature when intermittence is present is most characteristic, and gives rise to the name "febris sudo-

ralis." The sweat rolls off the patient's face in large drops, soaking through the pillow; while at the same time it soaks through his flannel suit, the sheets, and even the blankets, occurring usually about one or two o'clock in the morning; this lasts an hour or more, necessitating two or three changes of clothing.

Pyrexia is the chief and often sole symptom present, and although, speaking generally, there is a relationship between the temperature curve and the other symptoms present, yet the pyrexial severity is not always an indication of the urgency of the symptoms or of the prognosis in any given case. Its height in a large number of cases seems to depend upon the capacity of the individual to nervous excitability.

The chief characteristic of the pyrexia of this fever when compared with that of others, is the variability which exists in its amount and duration in different cases. The daily curve may vary between a continuously high temperature and an intermittent one. One point, however, is common to all cases, in that the daily maximum and minimum temperatures tend to form waves of intensity of varying character and duration. These waves in individual cases have a tendency to resemble their primary wave, though they usually decrease in length and severity as the cases progress.

The typical wave in uncomplicated cases confined to bed rises like the ideal curve of enteric fever, and subsides in an equally regular manner (see Charts II and VII). Generally speaking, however, all sorts of variations occur (see Charts I, IV, VII, and XII), even to a sudden fall from a continuously high temperature to normal. The latter fall is not uncommon as a temporary abatement (see Chart X), but has only occurred three times in the writer's experience as a sudden permanent recovery by crisis. Not infrequently permanent cessation of pyrexia is immediately preceded by a burst of unusual severity (see Chart V), while convalescence is almost always preceded by a period of subnormal temperature

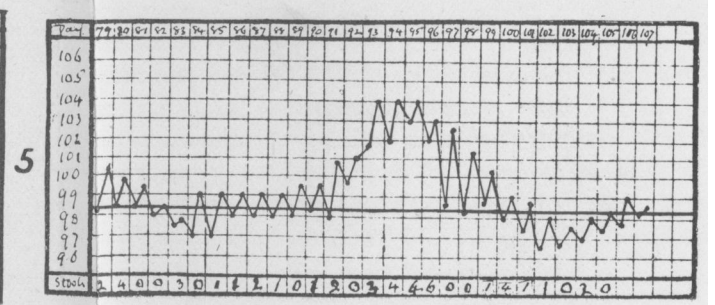
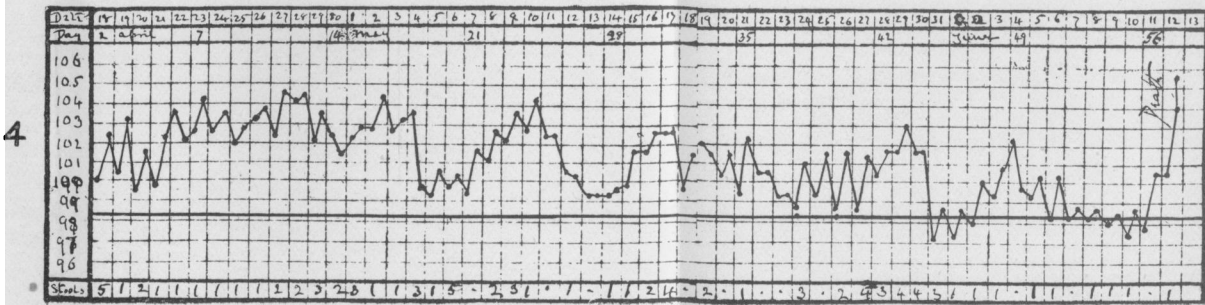
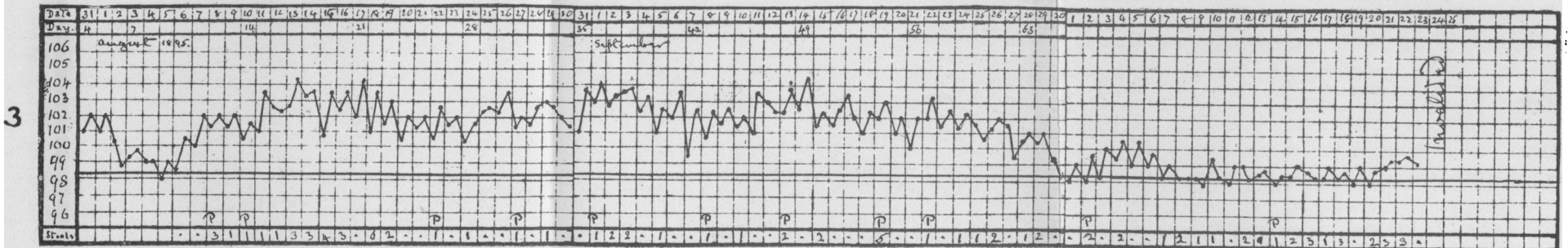
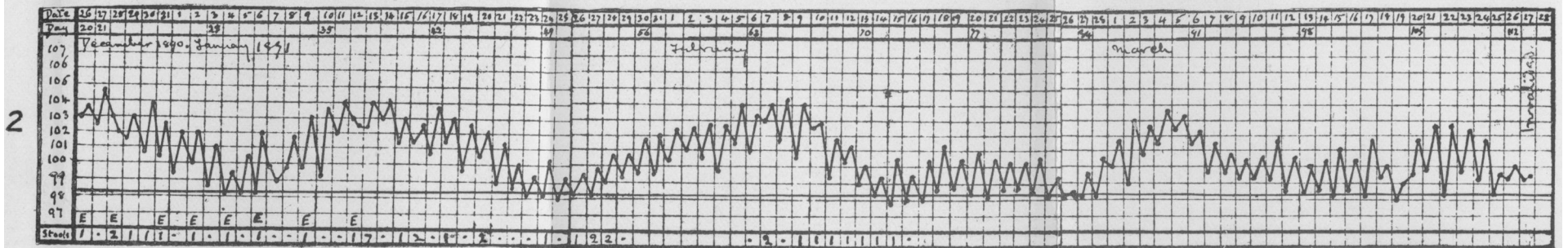
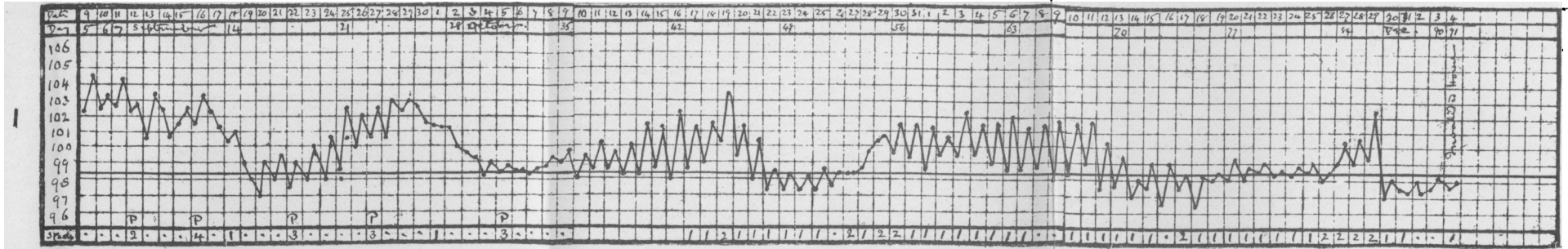
lasting from one to three or more days (see Charts I, V, and VII). The average length of 300 well-defined waves was about ten days, the primary wave being usually longer (eighteen to twenty-three days), or it may even last almost the whole pyrexial period (see Chart III, where it lasts fifty-four days). The durations of these 300 waves, occurring in ninety-five undulatory cases, were—

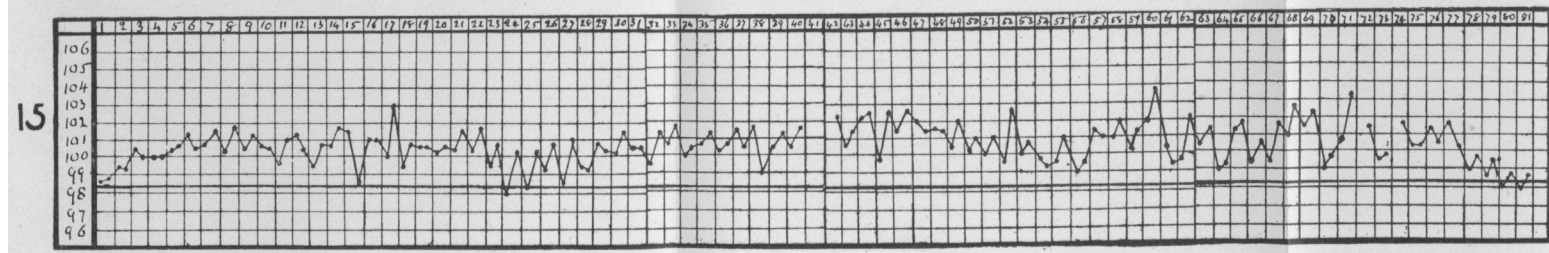
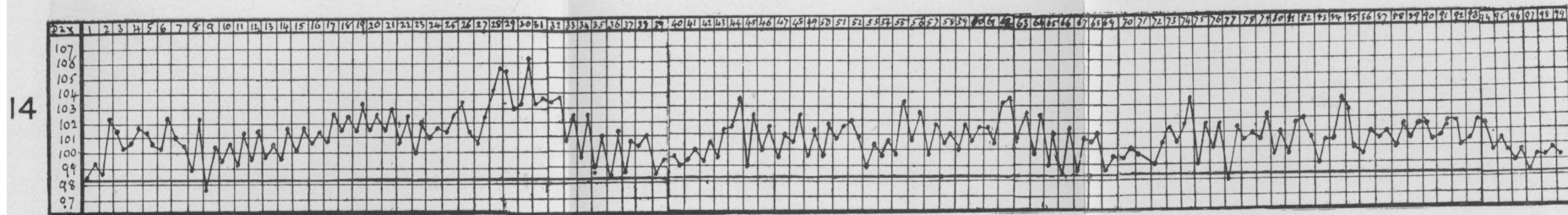
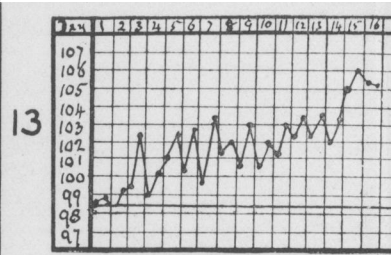
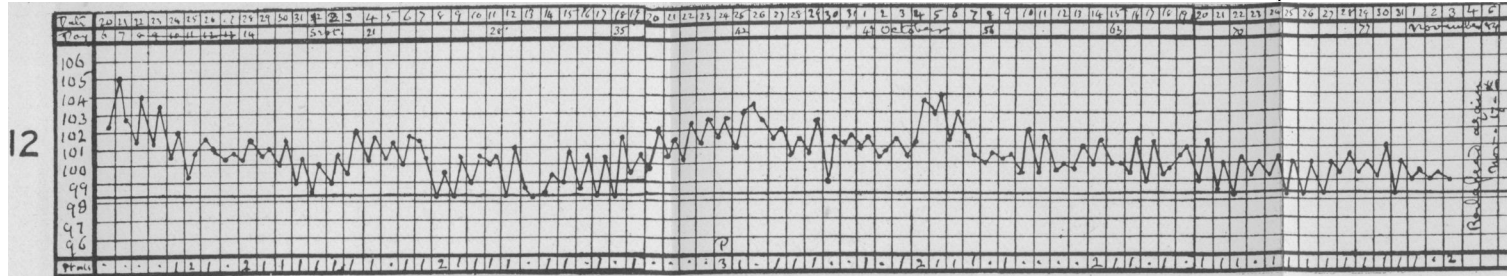
One week and under	70
Two weeks	97
Three „	60
Four „	23
Five „	42
Six „	3
Seven „	3
Eight „	2
	300

The average number of waves in an attack was three (one to seven). The interval between waves is marked by a period of apyrexia, without other morbid condition, lasting from one to ten or even more days (average three to four), or simply by a comparative abatement of pyrexial and other symptoms of variable duration and degree.

The daily temperature curve is usually remittent in character, the morning temperature being one or two degrees lower than in the evening, without actually touching normal except during the intervals between waves of pyrexia. It may, however, assume in different cases any type between intermittence and a continually high temperature, or pass from one type to another in the same attack (see Chart VII).

In intermittent cases (Chart VI) the temperature is usually at or near normal during the morning visit (8 a.m.), and begins to rise steadily a little before 11 a.m. to a maximum between 2 and 3 p.m. From this it gradually falls to halfway about 6 p.m., and reaches normal again about 10 or 11 p.m. or later, after which





profuse diaphoresis occurs. Occasionally slight supernumerary rises of temperature are added to this curve, a common one being just after the evening visit and bed-making. This curve is accentuated by mental emotion or excitement, by exertion, injudicious dietary or medicine, excessive constipation or the reverse, by the damp enervating sirocco wind, or by the appearance of any localised special symptom. The relief of constipation or the cessation of a sirocco wind often proves an excellent antipyretic. These maximum and minimum may be postponed, so that in a few extreme cases the morning temperature becomes the high one, and the afternoon the reverse. This daily curve is non-paroxysmal, resembling more the hectic fever of phthisis than the paroxysms of ague, the daily rise being associated with a feeling of chilliness and malaise only, rigor being absent except in a few cases of specially nervous temperament.

From the above mild type, the daily temperature curve may increase in duration so as to postpone the fall well into the night, and the diaphoresis to the early morning, while at the same time the morning rise is anticipated. In more severe cases one curve appears to run into and overlap the next, until with less and less remittance the temperature comes to be continuously high, the daily variation being less than one degree, a condition leading to danger from sudden hyperpyrexia.

The pulse is usually firm and slow at first (80—90), even out of proportion to the number of the respirations, and the amount of pyrexia present. In malignant cases, where there is lung stasis, it is rapid, and becomes small, thready, and then intermittent before the overburdened heart gives out entirely. In long-continued cases it often becomes constantly increased in rate (110—120). In such cases cardiac irritability is of common occurrence, giving rise to attacks of palpitation on the slightest exertion, or even under the influence of some trifling emotion. Hæmic murmurs are met with during convalescence. Organic cardiac disease is said to arise in some cases, but I

have only met with it in four instances (fatal on the 19th, 62nd, 111th, and 150th days), and in these the condition might have existed previously. In the first two cases the immediate cause of death was pericardial effusion (similar in onset to the characteristic arthritic effusions). Swelling and œdema of the ankles after standing is common during convalescence. The writer has only once met with phlegmasia dolens following an attack of this fever. The blood has been microscopically examined by Dr. Thin and numerous other observers, and culture experiments have been made, but no organisms have been found present. The spleen can nearly always be made out on percussion and palpation, and occasionally is considerably enlarged. During the first acute stage it is tender to pressure, and may be painful. The specific micro-organism has been isolated from the spleen during life. Epistaxis occasionally occurs early in an attack; intestinal hæmorrhage is limited to spots of fresh blood in the stools in cases where the lower bowel is affected.

About the beginning of the third week, or earlier in severe cases, bronchial râles may be heard on auscultation in nearly 95 per cent. of cases. In acute cases basal congestion of the lungs is a most common symptom. In severe cases, and especially in those who have previously suffered from pleurisy, pneumonia, or have organic heart lesions, this is apt to pass on to double lobular pneumonia of varying amount, most marked, as a rule, on the right side. A nervous cough unaccompanied by expectoration is occasionally present; while in mild intermittent cases emaciation and night sweats may be combined with bronchial râles and crepitations, and give rise to a wrong diagnosis of phthisis. Pleuritic effusion without suppuration is not uncommon, and often leaves permanent adhesions behind.

The tongue is usually thickly coated with whitish-yellow fur on the dorsum, pink at the tip and edges, moist, swollen, flabby, and indented laterally by the teeth. In very severe cases only does it tend to become dry and

brown. Occasionally it becomes red, glazed, raw, and with the epithelium denuded in patches. There is usually foulness of breath, tenderness on pressure in the epigastric region, nausea, and occasionally vomiting, with other signs of gastric derangement. In non-malignant cases constipation is the rule; in my experience constipation has been marked in 81 per cent., diarrhoea in 4 per cent., both conditions in 3 per cent., and a normal condition in 12 per cent. of such cases. In fatal cases, owing to the frequent involvement of the lower bowel, diarrhoea has been present in some 50 per cent. of those that were noted. The condition of the tongue is a valuable indication of the suitability of the diet given, and of the permanency of any amelioration of symptoms. A fall in the temperature rarely proves permanent if the tongue remains coated.

Albuminuria is rare even in fatal cases, though a form of large white kidney has been met with in very prolonged cases.

The action of the virus on the nervous system may be regarded as one of the special characteristics of the fever, of which indeed many of the symptoms already mentioned may be more or less the result. Severe headache with shifting pains in the back and limbs is rarely absent in the initial stages. Later on constant or repeated attacks of facial or occipital neuralgia may be present. In a large number of cases, generally late in the attack, or even during convalescence when pyrexia has ceased, other nerves may be affected, and obstinate lumbago, intercostal neuralgia, or sciatica may be set up. In rare cases the acute stage is accompanied by general cerebro-spinal irritation, characterised by mental irritability, delusions, sleeplessness, cutaneous hyperæsthesia of variable extent, girdle pains, &c. Severe pain and hyperæsthesia of the soles of the feet is a not uncommon condition. Paralysis, partial or complete, of certain muscles is a late symptom. The extensors of the foot and the deltoid are most commonly affected. The muscle slowly atrophies, and as slowly regains, first its function and then its proportions,

recovery being complete. The special senses of hearing and touch become temporarily diminished in a number of cases without the administration of quinine. Taste is usually impaired, vision to a small extent occasionally. The decubitus is lateral until the patient becomes dangerously ill. Delirium is not common except in very severe cases, when it may pass into coma before a fatal issue. The writer has not met with mania or imbecility following attacks of this fever. The mind is clearer at the beginning than in enteric fever, but during convalescence the power of concentration of thought and of remembering names or figures is often temporarily impaired. Wakefulness and sleeplessness are common at first, and the nervous prostration following an attack is most marked. Retention of urine may occur during the acute stages. The effect on the mechanisms of heat regulation have been mentioned.

Effusion into one or more joints is a very common and characteristic symptom, which may occur during the acute stage, but is more common during the third week or later. In some cases this condition, combined with very slight pyrexia, may be the only symptom complained of on admission, leading to a first diagnosis of rheumatism or even synovitis. The joints are attacked in something like the following frequency:—Hip, knee, shoulder, ankle, wrist, fingers, toes, elbows, sacro-iliac synchondroses, intervertebral joints and lower jaw, &c. This may come on suddenly in the course of an hour or two, and may disappear in a few hours or days, only to be replaced by a similar affection in some other joint, and this may be repeated over and over again, usually finishing up with the fingers or toes, having no regard to symmetry. The joint rapidly fills up, with great pain and occasionally some redness. Neither suppuration nor ankylosis occurs, but if the condition persists for long some œdema may be present in the surrounding tissues, causing it to resemble a severe gonorrhœal joint. Pain and stiffness in the aponeuroses or muscle sheaths may occur.

These symptoms appear to have a special predilection for those who have previously suffered from rheumatism or rheumatic fever elsewhere.

The rheumatic and neuralgic symptoms have often a relation to chills received during an attack of the fever.

Epididymitis and orchitis (usually single) occur at a late stage in a few cases, mastitis very rarely. The testicle swells in from twenty-four to forty-eight hours to the size of an orange, is extremely painful, while there may be some redness of the skin and effusion into the tunica vaginalis. It is often long in disappearing.

Abscesses occasionally occur, but are probably unconnected with the disease in question.

Ætiology.

(a) *Bacteriology.*—Although the disease has existed in the Mediterranean for so many years, it was not until 1886 that a micro-organism was discovered in Malta by Surgeon-Major Bruce (recently Assistant Professor of Pathology in the Army Medical School, Netley), to the effects of which the phenomena of this fever could be attributed. Bruce's first case died on the fifteenth day of the disease, when he found nine hours after death, in splenic sections, "enormous numbers of micrococci" scattered through the tissues. In May, 1887, with Dr. Caruana Secluna, he made between thirty and forty inoculations into sterilised agar-agar with blood aseptically taken from the fingers of ten cases of this fever without result. One of these cases, however, proving fatal, eight tubes of agar-agar were inoculated with the usual precautions at 6.30 p.m., less than one hour after death. These were kept at the temperature of the air (25° C.) until 11 a.m. the following morning, when six were placed in an incubator at 37° C., while two remained at the temperature of the air. Colonies of a micro-organism, which the writer has named the *Micrococcus milletensis*, appeared in all these tubes. In the

next case Bruce was unable to make an autopsy, but seven hours after death, by means of a sterilised trocar and cannula, he obtained some splenic pulp, with which he inoculated six tubes; these being placed under similar circumstances produced similar growths. These, with six other cases in which he obtained the micro-organism from the spleen after death, and one case in which he obtained it from the spleen during life, making ten cases in all, have all been published in the 'Annales de l'Institut Pasteur' and elsewhere with full details.

Surgeon Gipps, R.N., describes two cases in the 'Transactions of the Epidemiological Society,' vol. ix, in which he isolated a micrococcus, of which he gives drawings. Though his work was done in Bruce's laboratory he does not appear to place much confidence in its causal connection with the disease.

I worked for a short time with Bruce, and have isolated from the following thirteen cases a similar micro-organism, the fullest precautions being taken to eliminate error.

CASE 1.—Admitted July 27th, 1891, æt. 22. Service two years, previous health good. Admitted with the usual febrile symptoms, onset being sudden. On the tenth day the symptoms partook of a typhoid character, the tongue became dry and brown, the pulse quick and feeble, the abdomen tympanitic; there was also subsultus tendinum, and abundant crops of sudamina. This continued until the twenty-fourth day, when he began to improve, the disease being characterised by constipation and rheumatic symptoms to the end, whereas from the thirteenth to the twenty-sixth day there had been a tendency to diarrhœa. From the fortieth to the forty-fifth day there was an apyrexial period, after which there was a severe relapse. The condition gradually became worse, tympanites set in, and was a prominent symptom. There were signs of hypostatic congestion at the bases of the lungs at the back. He died much exhausted at 6.30 a.m. on the

seventy-third day of the disease. The pyrexial curve was similar to that of Case 2, except that the first or primary wave lasted thirty-nine, and the second (fatal) wave twenty-seven days.

Treatment.—No solid food, stimulants, antipyrin, salicylate of soda, diaphoretics, sponging, &c. Quinine in various doses from two to fifteen grains three times a day.

Though not in clinical charge of the case, I had constant opportunities of visiting the patient during life, and there was no doubt as to the diagnosis of Mediterranean fever. At the post-mortem examination four hours after death, six army and three civilian medical officers were present, who all confirmed the diagnosis. The body was fairly well nourished, and the heart normal. The lungs showed some hypostatic congestion of both bases, with sero-purulent exudation in the bronchioles. Liver weighed 74 ounces, was slightly fatty. Kidneys normal. Spleen 12 ounces, enlarged and dark, but firm in texture. Stomach and duodenum normal; the jejunum had a patch of congestion, four and a half inches long, a foot below the duodenum. The ileum, Peyer's patches, and the solitary glands were all normal. In the large intestine the cæcum was normal, but just below this for one foot in extent, and again for six inches at the upper part of the sigmoid flexure, were patches of congestion and exudation. There was no sign of ulceration along the whole extent of the alimentary tract.

Experiment.—The spleen was removed as aseptically as possible, and without tearing its capsule; at once wrapt in a towel soaked in a solution of perchloride of mercury, and removed to the laboratory. There three cuts were made in the spleen with three sterilised knives, each cut being through, and at right angles to the plane of the preceding one, the innermost cut being used for inoculation purposes, the cuts being allowed to fall together between each operation. Three tubes of agar-agar were inoculated by a small drop of blood removed on a sterilised platinum ooze, two tubes were at once placed in the incubator at

99° F., and one left at the temperature of the air (about 75° F.). Characteristic colonies of the *Micrococcus mile-tensis* appeared in both the tubes placed in the incubator after 124 hours, but the tube left at the temperature of the air remained sterile. These growths were passed through six generations of pure cultures on agar-agar, and were used for inoculation of monkeys. One primary and two secondary cultures forwarded to Bruce at Netley were identified by him as the same micro-organism that he had previously found in such cases.

CASE 2.—Similar to the last in character. Admitted July 10th, 1892. Age 20; service six years, two of which had been in Malta. This man slept in a bed from which his comrades in his room said that other cases had been admitted to hospital. The bed in question was under a roof ventilator, placed next a main drain ventilator, the smell from which was complained of in the room.

Previous history.—Had suffered from slight attacks of febricula and bronchial catarrh in Cairo in 1887; from gonorrhœa four times in Malta between October, 1891, and June, 1892. Habits latterly intemperate, physique on admittance fairly good.

Clinical history.—Onset somewhat sudden, admitted on the third day of the attack with pains in the back and limbs, epigastric tenderness, and some vomiting, the last relieved by bismuth. Primary attack lasted twenty-four days, during which time there was a tendency to diarrhœa, but no other symptom of an enteric nature. After an apyrexial period of about five days the second wave began on the twenty-fifth day of the disease, the temperature remaining high, and the patient becoming daily worse. On the forty-ninth day he suffered from subcutaneous hæmorrhages over the sacrum and buttocks, but no bedsores appeared. There was tenderness on pressure in the epigastric, splenic, and left iliac regions, a tendency to diarrhœa with loose yellow stools throughout the relapse; while during the

last four days the stools were passed involuntarily. Death occurred on the fifty-fourth day at 7.15 p.m. from heart failure and exhaustion.

Treatment.—Careful dietary, and free use of stimulants. Gastric sedatives, antipyrin, cold sponging. Lead and opium internally, and opium and starch enemata for diarrhœa.

Examination one hour after death.—Body emaciated. Heart normal. Lungs showed hypostatic congestion of both bases. Spleen weighed 14 ounces, was very dark in colour, and soft in consistency. Liver weighed 59 ounces, was slightly congested. Stomach distended with gas and fluid food, but was otherwise normal. Duodenum normal. Small intestine contracted and shrunken, and about two and a half feet from the cæcum it was hyperæmic, with arborescent congestion in the course of the vessels. Peyer's patches and the mesenteric glands were all normal. The large intestine for two feet from the ileo-cæcal valve was intensely congested and offensive, which explained the presence of diarrhœa during life.

Experiment.—Cover-glass preparations of fresh splenic substance showed micrococci here and there. Three tubes of agar-agar were inoculated in the same manner as in the last case, and placed in the incubator at 99° F. Characteristic growths appeared in every tube within 120 hours of inoculation.

CASE 3, a malignant one, proved fatal on the twenty-third day from hyperpyrexia. He was the only fatal case that occurred in the epidemic mentioned on page 239 (2). For temperature see Chart IX. At the post-mortem examination the lungs were found to be much congested at the bases; the spleen congested, friable, and weighing 15 ounces; the liver congested, but Peyer's patches and the mesenteric glands normal. Inoculations were made in broth and on agar-agar, characteristic colonies appearing on the seventh and sixth days respectively at 99° F.

CASE 4, also a malignant case in a delicate subject, proved fatal from cardiac failure on the twelfth day. At the post-mortem there were mitral vegetations, with fatty degeneration and infiltration of the heart. The spleen weighed 13 ounces, and was extremely congested; liver enormously enlarged (88 ounces), but Peyer's patches and the mesenteric glands normal. The spleen was removed one hour after death, and three tubes of agar-agar inoculated, characteristic growths appearing on the fifth day at 99° F.

CASE 5 died on the eighteenth day of continuously high pyrexia, in a comatose condition. At the post-mortem examination, seven hours after death, the lungs showed basal congestion; the liver (73 ounces) was congested and friable; the spleen (21 ounces) was almost in a state of liquefaction, its substance breaking up on the slightest pressure. The mesenteric glands were slightly enlarged, but Peyer's patches were normal. The great gut for eighteen inches, including the cæcum, was deeply congested, somewhat swollen and thickened, and the solitary glands were prominent. Characteristic growths were obtained from the spleen on agar-agar in five days.

CASE 6 died of collapse, vomiting, and exhaustion on the thirty-fifth day of the disease, the temperature having fallen the day before death only to rise again. After death the bases of the lungs and the spleen (18 ounces) were found to be congested, the mesenteric glands slightly enlarged, but Peyer's patches and the intestines normal. Characteristic growths on agar-agar were obtained from the spleen in 130 hours at 99° F.

CASE 7 died of heart failure and pericardial effusion on the nineteenth day of a very remittent case. After death the autopsy showed lobular consolidation of the lungs, the spleen (12 ounces) congested, the liver nutmeg, and the heart with mitral vegetations. Peyer's patches and the

mesenteric glands normal. The micro-organism was visible in cover-glass specimens of splenic substance, and was obtained from the spleen on agar-agar in pure growths on the sixth day.

The last two cases slept near a broken drain in a previously healthy barrack.

CASE 8 died of hyperpyrexia on the twenty-fourth day of continuously high pyrexia, after admission to hospital. After death there was basal congestion of both lungs, the spleen (12 ounces) was congested, the large gut much congested, the mesenteric glands slightly enlarged, but Peyer's patches normal. One hour after death the micro-organism was visible in cover-glass preparations of fresh splenic substance, and characteristic growths were obtained on agar-agar on the fifth day.

CASE 9, a long case of short undulations (see Chart IV), died of sudden hyperpyrexia on the fifty-seventh day of the disease. After death the lungs were œdematous and congested at the bases, the liver (80 ounces) intensely congested, spleen (11 ounces) congested but firm, mesenteric glands and Peyer's patches normal. Micrococci visible, and growths obtained as in the last case.

CASE 10, a somewhat unique one, was admitted to hospital for three weeks' fever and then discharged, apparently cured. Four months afterwards he was again admitted with fever of a typically intermittent character, which proved fatal from cardiac failure on the 154th day of the attack. After death the heart was flabby, there was a small aneurismal dilatation above the posterior left semilunar valve, and all three of these valves had vegetations on them. There was much serous fluid in the pleural cavities, the bases of the lungs being congested and œdematous. The liver (76 ounces) was nutmegged, the spleen (14 ounces) congested; but Peyer's patches, the

mesenteric glands and intestines were normal. Six tubes inoculated from the spleen all showed characteristic growths on the sixth day.

CASE 11 died of hyperpyrexia on the twenty-fourth day of acute fever. After death there was considerable congestion of the bases of both lungs; the liver was nutmeg; the spleen (14 ounces) engorged with venous blood. There were patches of congestion here and there in the intestines, most marked in the colon. Peyer's patches and the mesenteric glands were normal. Characteristic colonies were obtained from the spleen as in the other cases.

CASE 12 had served for three years in Gibraltar, and for five months in Malta. He died suddenly of cardiac failure, after a slight excitement on the 111th day of the disease. At the post-mortem examination warty vegetations were found on the mitral valve, there were recent pleuritic adhesions at the base and posterior parts of the right lung, the lower lobe of which was consolidated. The spleen (15.5 ounces) was congested, soft, and friable, the liver congested. The kidneys showed the characteristic appearances of "large white kidney." The intestinal walls were attenuated, but were otherwise healthy. The spleen was removed three hours after death, and from it characteristic growths were obtained, while sections were made of portions of the different organs.

CASE 13 died somewhat suddenly on the sixty-second day of the disease, of effusion into the pericardium, during a relapse after his temperature had been normal for seventeen days. At the post-mortem examination 17 ounces of fluid were found in the pericardium, the right pleura was obliterated by organised lymph; the right lung œdematous and congested; the liver nutmeg; the spleen (15 ounces) congested, but the intestines, Peyer's patches, and the mesenteric glands normal.

Characteristic growths were obtained from the spleen on the fifth day after inoculation.

These altogether make thirteen cases in which I have successfully isolated the micrococcus from the spleen after death. If Bruce's ten cases and Gipps's two cases be added, we have twenty-five cases,¹ which make more than a coincidence.

The only case in which the growth was not found was in one published by Bruce. The failure was due to the use of too alkaline agar, a fact proved later by control experiments with growths from my cases on the same agar.

No other micro-organism has been found present under similar circumstances, nor has the writer met with a similar organism present in many other cases in Malta which he has tested, and which died from other causes.

Description of the Micro-organism.

The *Micrococcus miletensis* grows best on nutrient material, the alkalinity of which is slightly less than that of human blood, and at a temperature of from 37° to 38° C. At temperatures between 40° and 42° C. growth is suspended; above 42° C. artificial growths die. Below 18.5° C. growth is also suspended, while if they are kept at a moist temperature of 15.5° C. for long they die. Colonies that were allowed to dry completely were found to be dead when tested three years after. On the sloping surface of 1.5 per cent. peptone agar, at a temperature of 37° C., its colonies become visible to the naked eye in from 90 to 125 hours after primary inoculation from the human spleen. They first appear as minute transparent colourless drops on the surface of the agar, appearing somewhat like the agar itself. In about thirty-six hours more they become a transparent amber colour, and increasing very slowly in size, on the fourth or fifth day of their appearance become opaque. At this stage they

¹ I have since isolated this micro-organism from a further case, fatal on the 117th day of the disease.

resemble split pearls on the agar surface. Under a low power and with transmitted light such colonies appear to be orange in colour, quite round, with a definite but granular margin. If kept on moist agar they increase slowly in size, and while retaining their circular shape individually, may gradually coalesce. In the course of three months these colonies turn to a buff or even orange colour to the naked eye, and increase in thickness by heaping up material in the centre of the colony. The individual colonies never grow to any great size when compared with other growths, ceasing to grow when a little larger than a split pea. No liquefaction takes place. Though they do not increase in size after two months' growth, the colonies retain their vitality, at a suitable temperature, for over three months. The micrococcus will not grow on agar, the alkalinity of which is in excess of that of the human blood; but if cultivated on successive media of increasing alkalinity they can be educated to grow on very alkaline media. In this case, however, they are longer in appearing and grow more slowly in a very diffuse manner on the agar surface, with only abortive attempts at the formation of definite colonies. These diffuse growths, however, when transferred to agar having a suitable alkalinity, again revert to their original characteristic mode of growth. In making primary inoculations on old agar, the blood transferred from the spleen by drying, occasionally interferes with the growth of the colonies. This never occurs when the primary inoculation is made in broth, and secondary inoculations from this to agar made a few days later.

The micrococcus grows also in bouillon and gelatine. On the latter it grows very slowly at 22° C. without liquefaction. In the latter it gives rise to a general and increasing opaqueness, commencing on the fifth or sixth day, and afterwards forms a white precipitate consisting of these cocci, but without forming a surface pellicle.

Microscopically in the hanging drop they appear as very minute cocci, ovoid in shape, and in rapid molecular

motion. Many are seen in pairs, and a few in temporary short chains of four, the latter more especially if they have been growing on alkaline agar. The chains are never seen in dried cover-glass preparations. They stain very readily with all the aniline dyes, but lose their colour very rapidly if treated with alcohol or any of the usual decolourising agents.

The slow growth, peculiar appearance on agar, the small size that the individual colonies attain, the minute coccus, and the readiness with which the micro-organism decolourises, serve to differentiate it from others.

Inoculation Experiments.

(a) *By Bruce.*—(1) A male Bonnet monkey was inoculated in the left forearm with growth obtained from the human spleen, by means of a perfectly clean Pravaz syringe, the growth having been growing on artificial media in a pure state for a month previously. No changes appeared at the seat of inoculation, but on the day after his temperature began to rise,¹ and reaching 106° to 107° F., he died on the twenty-second day from inoculation. On post-mortem examination the lungs showed no signs of tuberculosis; the liver and spleen were enormously enlarged, and the intestines were free from ulceration.

Six tubes of agar were inoculated from the spleen, and two from the liver with full precautions. In all those from the spleen, and in one of those from the liver, the *Micrococcus miletensis* appeared after 168 hours. In the remaining tube no growth appeared.

(2) Another male monkey (Bonnet species) was similarly inoculated. The temperature rose rapidly, and he died on the thirteenth day. Growths were obtained from the internal organs, making their appearance after four days.

Bruce further found that rabbits, guinea-pigs, and mice, gave negative results.

¹ See 'Practitioner,' xl, 1888, p. 241.

(b) *By me.*—(3) A small male monkey (Bonnet species) was kept under observation for two months, during which time his appetite was good and his temperature stationary (about 99° F.). He was inoculated in November, 1891, by the injection of a colony of *Micrococcus miletensis* obtained from the spleen of the first of the writer's cases, which had been growing in a pure state in the incubator for three weeks. The site of inoculation (the muscles of the forearm) had been previously shaved, cleaned with soap and water, and washed with a solution of perchloride of mercury. The syringe and all other apparatus had been carefully sterilised; the growth being mixed with 1 c.c. of sterilised bouillon, which had been under observation for one month previously.

Forty-eight hours afterwards the temperature began to rise, and daily increasing with a remittent curve, reached 106° F. on the fifteenth day, when he was killed, 362 hours after inoculation. For the first ten days the monkey was lively and continued to eat his food, but after that he lay about and refused it. See further, Chart XIII.

Five minutes after death the lungs were found to contain sero-purulent exudation in the bronchial tubes; the liver was congested; the spleen congested and very large in proportion to its body weight; there was slight congestion near the ileo-cæcal valve, but Peyer's patches were quite normal, and no other pathological condition was present. Seven tubes of agar were inoculated from the spleen in the usual manner; two tubes were inoculated from blood collected with an aseptic syringe from the centre of the unopened heart. These were placed in the incubator at 37° C., and of the seven splenic cultures five showed colonies of the *Micrococcus miletensis* in 168 hours, two showed contamination with *Micrococcus albicans* the next day; while of the blood-cultures, one showed the typical growth after 168 hours, the other proved sterile. These growths were identical with those obtained from human spleens, macroscopically and microscopically, were

cultivated in bouillon, were carried through six generations of pure cultures on agar without change, and were identified by Bruce at Netley.

(4) A small African monkey was inoculated in the muscles of the forearm with growth from the cardiac blood of the last monkey, the same precautions being taken. The temperature began to rise the following day, though it had remained steady for a month previous to inoculation, and for eleven weeks he suffered from remittent pyrexia (see Chart XIV). He finally made a complete recovery.

(5) A female monkey (Bonnet species), under observation and in good health for three months previously, was similarly inoculated in the muscles of the right thigh with virus obtained from the spleen of the writer's first monkey, which had also been for some time under observation in the incubator to insure its purity. This monkey developed pyrexia consisting of intermittent waves of a remittent type, lasting over ninety-four days. She ultimately made a good recovery, and lived in good health for three years until killed by a dog. During the attack she lost weight, and like the last case seemed to suffer from pain or rheumatism of the extremities at irregular intervals, with irregularity of the bowels (see Chart XV). These monkeys' temperatures were taken three times a day by the same two persons throughout, a large amount of petting, time, and thermometers being expended. In no case did any changes occur at the seat of inoculation.

(6) A very savage and impatient monkey was also inoculated with human virus, and his temperature was taken at various intervals. No changes occurred at the seat of inoculation; he suffered severely from pyrexia, and ultimately recovered, but little more can be said.

Thus it may be said that when pure growths of this micro-organism are introduced into the tissues of healthy monkeys a pyrexial condition closely analogous to the Mediterranean fever of man is set up, and that after

death a similar micro-organism can be isolated from their tissues in a pure state which is capable of producing a similar disease in other healthy monkeys.

More experiments are needed, but unfortunately neither the time nor the money necessary are available. The above experiments, however, fulfil the requirements of Koch's postulates entirely.

(b) *Age and sex*.—All ages are liable to this fever. Among soldiers and their families the ages have usually varied between five and thirty years. Infants under two have not often suffered. In the old long-service days at least half the cases were over thirty. Among the inhabitants of Italy and Sicily Guiffré gives between fifteen and forty years as the most susceptible ages, and states that children under six and adults over fifty are relatively exempt. This would appear to agree with the cases among the native population of Malta. Though no rule is absolute the average age of enteric cases in Malta among soldiers is lower than that of Mediterranean fever.

In a given number of families the women are attacked oftener than the men, the reason appearing to depend rather on age and occupation than on sex.

(c) *Season and climatology*.—In Malta the admission rate is lowest during the first quarter of the year, rises rapidly in May to a maximum in July, August, and September, after which it gradually falls until November and December, which two months are somewhat higher than those of the first quarter (abstract of 1339 cases). The same is the case in Gibraltar, Rome, Palermo, and Cyprus.

In Malta and Gibraltar its prevalence has been found to be in an exact inverse ratio to the amount and continuance of the rainfall from month to month. While the surface of the ground is kept constantly wet by rainfall the admission rate keeps down, but the cessation of rain in warm weather is at once followed by an increased activity of the poison, and a sudden excess in the attack

rate. Since 1859 the greatest prevalence has been during the driest summers, while the attack rate has become of increasing importance when the average monthly temperature has exceeded 60° F., and the rainfall descended below two inches a month (see Chart XI). The attack and mortality rates have shown a tendency to form quantitative waves of about seven years' duration.

(d) *Length of residence.*—This does not appear to confer immunity, for while in Malta, Gibraltar, and elsewhere enteric fever specially favours new-comers, Mediterranean fever attacks those who have been in residence for even six or more years. When a regiment is placed in an unhealthy barrack, if the susceptible element is very great, it suffers accordingly, nor does previous Mediterranean service confer an immunity.

(e) *Mode of prevalence.*—The disease is not propagated by contagion from man to man, nor does it appear to have any causal connection with milk or food supply. The distribution of the main water supplies does not in any way account for its localised distribution, and whatever effect polluted tank water may have on the native population, many hundreds of soldiers and Maltese are attacked, who have no access to such water. The season of prevalence and the distribution of cases of water-borne enteric fever in Malta are quite different from those of Mediterranean fever, and when both fevers occur together a dual cause is found to be at work.

In the past, Marston, Boileau, Chartres, Donaldson, Oswald Wood, Notter, De Chaumont, Duncan and Moffet, have ascribed this fever to insanitation, and more particularly to defective house drainage and fæcal pollution of the soil, the latter giving an accurate illustration of an outbreak at Gibraltar from such causes. In Italy opinions are divided, but those who disbelieve in a fæcal origin give no other explanation.

In my experience nearly all cases are localised, even when in epidemic form, to certain rooms in certain buildings, which rooms yearly produce their fever cases

until some insanitation is rectified ; the most constant factors present being fæcal contamination of soil (and air) by persons suffering from the fever, together with warmth and moisture ; the factors necessary for its diffusion being the subsequent drying of the soil, the presence of air currents, and the close proximity of the human subject (a question of from two to twenty feet perhaps). Numerous outbreaks, confined to one household, have occurred simultaneously with the flooding of the floors with sewage from a choked and burst house drain, or overflowing cesspit. Many sporadic cases can be traced to escape of sewer gas from neighbouring drain ventilators, which, though above one roof, may be on a level with, and only a few feet off the windows of neighbouring houses, or to direct communication between rooms and the main drains by means of untrapped sinks or cupboard latrines ; the virus being often concentrated in such cases by insufficient room ventilation. Occupants of healthy houses are exempt, but come under its influence on moving into infective areas. It is most difficult in so short a space to deal with this important and necessarily much-debated subject ; especially as the evidence is, like that of all early epidemiological investigations, of a somewhat circumstantial nature ; but, as Bishop Butler has said, " probability is the very guide of life." Out of a number of instances, the following will serve to illustrate the above points.

(1) In a new and well-constructed flat in Valetta the first occupant was invalided home with this fever. The next also suffered from the same fever, together with his wife and child ; the child died, and the man and woman were invalided home. The next occupant was a man with a wife and sister. The sister suffered severely and the wife slightly from this fever. An inspection of the quarter disclosed a leaking pan-latrine on the verandah off the bedroom, and a leaking drain ventilator running in a circular turret staircase communicating with the same room. The smell from both, neither of which

was ten feet distant from the bed, entered the room, and was most offensive. People of the same rank in life occupying other portions of the block were unaffected. The water-supply was excellent and common to the whole of Valetta; the milk was obtained from goats milked at the door. The latrine was rectified and the ventilator placed outside the building, with excellent results.

(2) A regiment was quartered on a small island in one of the harbours of Valetta from January 2nd, 1892, until October 10th of the same year. During this period it suffered severely from "simple continued fever," 197 cases being admitted from a total strength of 760 men. The regiment had suffered severely from this fever elsewhere during its first year of service in Malta, had been seasoned by three years' residence, and was composed of men whose ages were not below the average of the station, yet their fever rate for 1892 far exceeded that of any other regiment. Of these men 480 were quartered in wooden huts, and the remaining 280 in an old fort close by, which had been built by the Knights in 1775. A careful analysis of the fever admissions divides them into two classes :

(a) Cases of true Mediterranean fever.

(b) Relapses or slight cases of the same fever (?), cases of simple ardent fever (febricula), and other obscure but slight febrile ailments without localised symptoms. The latter class were in hospital but a short time, and there is little to note except that the numbers were greater than from any other barracks in the island, and that in proportion to strength the admissions from the fort were double those from the huts.

The admission rate per mille for true Mediterranean fever in Valetta district (strength 3511, including the island in question) in 1892 was 52·2, while those of the huts and fort in question were 46·3 and 178·6 respectively, showing that some local cause of fever must exist within the fort. The men in the fort and huts belonging to the

same regiment were of the same age and class, and under identical conditions as regards food and water supplies, the latter being common to a very large area of unaffected population, civil and military. In the fort thirty-eight men, two women, and five children were affected; and of the men one died (see Chart IX, Case 3), six were invalided, of whom one was finally discharged from the service, fourteen were sent to the sanitarium, and seventeen returned to duty straight from hospital, but were in many cases readmitted with relapses after leaving Valetta in October. The average stay in hospital was 109 days each for the men. The majority of the rooms in question were dark, close, and damp, and were never intended for barrack rooms. Round the back of the rooms ran large channels cut in the extremely porous rock, and passing on each side of the fort down to the sea. From 1870 these channels were used as sewers until the substitution in 1885 of the present dry-earth system. Mediterranean fever occurred in the fort as an epidemic in 1870 and 1872, but was not excessive from 1885 to 1891. During the latter period a quantity of sewage remained boxed up, with the result that the stone became soaked with sewage, even through the walls and flooring to the adjacent rooms. Analysis of portions of the walls of the channels and rooms showed a larger percentage of chemical constituents of sewage, much organic matter, and a very large number of putrid and non-pathogenic organisms, when compared with similar but unpolluted stone. Again, though unpolluted stone was highly alkaline, the stone of these walls was neutral or faintly alkaline, forming therefore a suitable nidus theoretically for the micrococcus of this fever. Between September and December, 1891, a thorough overhauling of the drains took place, these channels being cleaned and converted into surface-water drains, gratings being placed at intervals almost on a level with, adjacent, or even opposite the windows of the barrack rooms. Owing to their situation and construc-

tion there was a varying yet constant current of air from the sea travelling up these channels, and passing out of the gratings into the fort, the porous walls at the same time being wet or dry according to the state of the atmosphere and the amount of rain. There was ample opportunity for miasmata to pass from the rock channels into the barrack rooms, and it is a significant fact that these forty-five cases slept in beds grouped in close and definite relation to the rock channels and sewage-soaked walls, and in direct proportion to the amount of varying dampness present. The first case was admitted four days after the cessation of the heavy rain. There was no other apparent cause for the outbreak, and obvious sanitary measures have resulted in a cessation of this fever prevalence.

(3) In a large modern and well-built hospital, standing on one of the best sites in Malta, a number of cases of this fever (20—40) have for many years past been treated in wards on the top floor, without the disease spreading to others in the same wards. The hospital had always been considered a very healthy one until recently, when a few cases of this fever began to occur among venereal patients on the middle floor, and the patients and sick attendants occupying the ground-floor suffered severely from this fever. In the kitchen behind the hospital two cooks died of its effects, and patients suffering from slight ailments, such as sprains, &c., and who occupied tents immediately behind the building, also developed the fever. Many of the sufferers had been in hospital over a month, while others had resided in the building for many months previously. The water-supply was good and common to a large district, the milk-supply was above suspicion. On investigation it was found that the hospital drain-pipe, which ran along the back of the hospital between the main building and the ground-floor occupied by the kitchen and tents, had been blocked for some time beyond the main building, and that the fæcal

sewage from the fever and other wards had forced the joints of the pipe and leaked in all directions under the hospital foundations, and through the ground on which the kitchen and tents were situated.

At the same time in three officers' quarters in the same grounds, but well detached and for many years considered to be among the healthiest in Malta, six cases of this fever occurred in one summer. In this case the main and house drains were found blocked, and the backflow of sewage caused offensive odours of sewer gas to enter the back rooms from adjacent drain ventilators.

Though the details are not exactly laid down in this last instance, I have preferred it to other smaller instances with exact details on account of the large number of cases occurring in an English-built hospital, which had for a number of years been healthy.

Numerous sporadic cases occur in the old barracks built by the Knights during the last century, the causes of which are not always apparent. When we remember the state of filth in which these buildings must have been in those days, the soft porous stone with which they are paved, and of which their foundations are made, and, moreover, the way in which the whole foundations of the towns have during the past been riddled with leaking sewer conduits and cesspits, with the denseness of the population in Maltese and other towns, we can only wonder that the disease is not more prevalent. As these sporadic cases occur over and over again in the same rooms, doubtless further research will extend our knowledge.

Lastly, I wish to draw attention to a theory that the soldiers and sailors catch this fever while bathing in faecally polluted harbour water. This could only account for a portion of the cases, and is at present but a matter of opinion, unsupported by accurate data, and needing further investigation.

(f) *Immunity from second attack.*—Though the medical

histories of many thousands of soldiers have been examined—these histories being accurately kept official documents in the case of every enlisted soldier—no record but one has been found indicating two attacks of this fever in the same individual. Though this may be owing to the short period that men are now stationed within the infective area, yet it has not prevented men from suffering from both enteric and Mediterranean fever on separate occasions. Guiffré does not believe that it confers immunity. From its behaviour to native Maltese it is probable that a temporary but not an absolute immunity is conferred, comparable to that met with in attacks of enteric fever.

Diagnosis.

Enteric fever is the most important disease, from a diagnostic point of view, that this fever can be mistaken for. The mistake is most likely to be made in severe cases with a tendency to pass into the so-called "typhoid state." Mediterranean fever is specially marked by its uncertain duration, irregular course, and the tendency in many cases to approach or reach normal during the first week, without apparent reason such as hæmorrhage, &c. (see Chart X); by the absence of hæmorrhages, rash, and iliac tenderness; by the rarity of diarrhœa and meteorism, by the physiognomy, moist tongue, smell, and an indescribable something about the fevers felt by the experienced; and lastly by the peculiar diaphoresis, neuralgic and rheumatic symptoms, and an absence of a rose-red reaction with Ehrlich's urine test.

From *paludism* it is distinguished by its non-paroxysmal nature, its resistance to quinine, and by the entire absence of the hæmatophyllum of Laveran.

From *phthisis*, *liver abscess*, and other suppurating diseases it is distinguished by the want of any local lesion to account for an apparently hectic temperature.

Prognosis.

This is good as regards danger to life and ultimate recovery, the case mortality being under 2 per cent. ; as regards the length of time on the sick list, however, it is very unsatisfactory, the average time spent on the sick list being about ninety days. A previous history of cardiac or pulmonary disease, the presence of organic cardiac or renal disease, of excessive pyrexia, intermittent heart's action, pericardial effusion, diarrhoea from involvement of the large gut, broncho-pneumonia, tendency to dry brown tongue, and bedsores are all grave symptoms calling for constant attention and a guarded prognosis.

Pathological anatomy.

Based on reports of sixty post-mortem examinations on soldiers (duration of disease 4 to 156 days), at thirteen of which I was present. The general congestive appearances in cases which proved fatal during the first thirty days will, when necessary, be kept distinct from the generally more localised lesions in later cases.

Brain.—In thirteen cases in which the cranium was examined, the meninges and choroid plexus were congested (most marked in early cases), and in some there was effusion into the ventricles.

Heart.—The muscular walls are described as pale and flabby. In two cases (duration seventeen and sixty-two days) there was thickening of the mitral valves with pericardial effusion, the latter being the actual cause of death. In three short and three long cases mitral vegetations were present, and in one of the latter (duration 156 days) there were also aortic vegetations, a small aneurismal dilatation at the root of the aorta, and old pericardial adhesions.

Lungs.—In 87 per cent. of all cases, basal pneumonic congestion, injection of the bronchial tubes, with serous

or sero-purulent exudation, were present. In 80 per cent. of early cases this had gone on to lobular consolidation, generally more marked on the right side. In 25 per cent. of cases there were pleuritic adhesions on one or both sides, in early cases apparently of former origin, but in later cases often undergoing vascular organisation. The bronchial glands were enlarged in proportion to the lung mischief present.

The *alimentary canal* is subject to patches of congestion, which, however, are not specially characteristic of this fever. These occurred in the stomach in 18 per cent., in the duodenum in 17 per cent. of short cases; and in the small intestines in 68 per cent. of all cases; while in the colon the condition occurred in 27 per cent. of all cases, of which thirteen had that peculiar swollen, inflamed, and œdematous condition of the mucous membrane which characterises certain severe cases of this fever. The congestion occurs in patches, following the arborescent course of the vessels, is not confined to nor constant in any one situation, and has no relation to Peyer's patches, which latter are unaffected. In early cases the mucous membrane is swollen and softened, but in late cases the intestines become extremely attenuated, the muscular and mucous coats having shrunk.

The *mesenteric glands* are enlarged in proportion to the intestinal congestion, being of normal size in most of the late cases.

Liver.—In half the cases this is congested and slightly enlarged, while in very late cases it is often nutmeg.

Spleen.—The spleen is always enlarged and congested. In early cases its weight averages 18 to 19 ounces, of a dark reddish-black colour, and in some 70 per cent. of such cases it is soft and friable like blood-clot, and in about 18 per cent. it is absolutely diffuent. In late cases the average weight is about 15 ounces, and it is of firmer texture.

Kidneys.—These are congested in early cases and often slightly enlarged; while in two long cases a condition of

large white kidney was present. The capsules are usually somewhat more adherent in long cases.

Microscopical appearances.—The microscopical appearances are scarcely characteristic, but are more or less common to other acute fevers. In acute cases, according to Bruce, “the Malpighian bodies of the spleen are enlarged from an apparent increase in the number of the round lymphoid cells; the endothelial cells of the marginal sinuses are proliferating and swollen; a condition of intense congestion is seen in the section, the sinuses being enormously distended with blood; there is a marked exudation of small round cells along the lines of most of the venules. The liver is congested, the cells in a condition of cloudy swelling, and there is an infiltration of small round cells in the interlobular fissures. The kidney is congested and in a state of glomerular nephritis. The mesenteric glands when enlarged show proliferation of the cellular elements of the lymphoid tissue. The only change in the Peyer’s patches is a slight proliferation of the cellular elements of the mucous and submucous layers.”

Dr. R. T. Hewlett, of the British Institute of Preventive Medicine, has kindly examined the tissues of Case 12, in which death occurred on the 111th day of the pyrexia. He reports as follows :

“*Heart* (mitral valve), a small vegetation is present, which has become nearly fully organised into fibrous tissue.

“*Lung*, many of the air-vesicles contain large catarrhal cells and shreds of fibrin.

“*Liver*, neither fatty nor fibroid change; some slight amount of cloudy or granular degeneration of the liver cells.

“*Spleen*, nothing abnormal detected. *Mesenteric glands*, ditto.

“*Peyer’s patch*, a slight increase in the lymphoid cells, no ulceration.

“*Kidney*, some tubular nephritis, evinced by cloudy swelling of the protoplasm and loss of nuclei of the epithelial cells of the tubules. In some places there is

some infiltration of round cells into the intertubular tissue. The glomeruli are normal.

“These changes are such as would be met with in the lungs, liver, and kidneys of any case of severe and prolonged fever.”

Prophylaxis.

The institution of sound water drainage for all new houses when first built, constant and efficient flushing of both main and house drains, the raising of all drain ventilators well above and away from all windows, the abolition of all leaking cesspits in porous soils in thickly populated districts, the paving of cellars, yards, and in some cases of the streets, and the proper trapping and disconnection of all sinks, &c., the avoidance of polluted ground for camping purposes, and the prevention of pollution to the ground round camps and buildings, and due attention to all latrines and urinals, proper ventilation, and avoidance of damp and overcrowding. I here assume that the virus is of an aërial and fæcal nature—a conclusion I adopt from the nature of the virus, the season of its prevalence, and the distribution of cases. Finally, avoid Mediterranean towns between the months of June and October, and send all women and children away when possible during those months, and always remember that the Mediterranean, except in the hot summer months, is subject to sudden changes of temperature and that the air is very moist, necessitating the possession of the warmest of clothes, an extra cloak at sundown, and teaching the desirability of always sleeping in flannel, and wearing it next the skin.

. *Treatment.*—There is no specific drug at present known which will cut short an attack of this fever. The treatment consists of placing the patient under the best circumstances for Nature to effect her own cure. Although many cases do well with careful nursing and dietary alone, it is a great mistake to think that that is all that

is necessary, for we each find that as our experience increases our deaths decrease, our cases become milder and shorter, and complications are less frequent.

The patient should first be removed from any insanitary surroundings; he should be confined to bed entirely, and placed on fluid diet, as would be done in the case of enteric fever, bearing in mind that beef tea is incompatible with the presence of diarrhœa. Lemonade made from fresh lemons, grapes, or lime juice should be given to prevent any tendency to scorbutic symptoms, while soda water and fluids should not be restricted. If dyspeptic symptoms, nausea, or vomiting be present lime water should be added to the milk, and bismuth given internally; while if this condition becomes serious beef-juice, peptonised food, and champagne are very useful. There is a great tendency to overfeed patients with high temperatures. Patients should have abundance of fresh air, but be screened from direct draughts, and on account of the tendency to lung symptoms care should be taken to lay the dust with tea leaves before sweeping, especially in the case of the soft stone floors of Malta. All patients should wear flannel or flannelette sleeping suits, which in the case of children should be in the form of "combinations." As these will need frequent changing during the night a good supply should be available. Sheets should be of cotton.

Should the diagnosis be sure, the bowels should at once be opened. For this nothing works better than a good dose of calomel, combined with Pulvis Jalapæ, which frequently alone is sufficient to reduce the temperature in a constipated case. The bowels must further be kept open every other day at least, with occasional doses of calomel, cascara, or Pulvis Glycerrhizæ Co., or by enemata where any doubt as to the diagnosis exists. As diarrhœa is usually due to congestion of the large (or less often of the small) bowel, such treatment tends rather to prevent than to produce diarrhœa, and further appears to prevent the necessity for their constant use at later

stages when persevered with at first. If diarrhœa be present, the greatest care must be taken to prevent it becoming serious. The diet must be attended to, and in the case of the large bowel, enemata of starch and opium must be given frequently. These enemata should be made with sufficient boiled starch to produce a consistency like cream, be given warm, and retained as long as possible. Rectal irrigation with a solution of boracic acid has been advocated. Diarrhœa of the small bowel is often due to unsuitable food or medicine, when otherwise it may generally be checked by a lead and opium pill, or by a mixture of opium, aromatic chalk powder, and astringents. The teeth, gums, and tongue must be attended to, and in summer a net is useful to keep off the flies which swarm round severe cases.

The skin should be sponged daily with tepid water and acetic acid, while a warm dose of diaphoretic mixture and brandy at night is often beneficial when the skin in severe cases remains dry. Sudamina and prickly heat should be bathed (but not rubbed) three times a day with a solution of boracic acid, while the extreme irritation of the latter may often be allayed by a coating of mild soap, left to dry on the surface until the next application of the boracic solution. Precautions should be taken against bedsores, especially towards the end of an attack, and when boils are present. The pulse must be carefully watched, its condition being taken as an index of the amount of stimulants necessary. When intermittent or weak in action, small doses of strychnia and digitalis with the exhibition of good champagne have worked well. In two cases of effusion into the pericardium without other complication, aspiration was not tried, and both proved fatal. Sleeplessness and nervous irritability are best treated by a full dose of morphia with bromide of potassium at night, or by Dover's powder when diaphoresis is desired; acute affection of individual nerves by the application of heat, flannel, and cotton wool, with perhaps opium or belladonna locally. Chronic sciatica during

convalescence by constant flannel next the skin, warm ironing, gentle massage and rubbing with counter-irritant liniments. Painful and acutely swollen joints are soon relieved by continuous hot fomentation, followed by wrapping in cotton wool and flannel; acute orchitis by warm hip-baths, followed by support and belladonna. The painful hyperæsthetic condition of the feet yields best when soaked in cold water or wrapped in cold water bandages, any application of heat or warmth being intolerable. Lung complications should be at once treated with sal volatile, alcohol, and other stimulating expectorants, and when severe by jacket poultices, which followed by a cotton-wool jacket are most efficacious.

The bladder must be watched in severe cases lest retention be missed, while any irritability is generally removed by the administration of acetate of potash, soda water, and saline diuretics.

One of the greatest advances, however, in the treatment of this fever consists in the moderate regulation of the pyrexia by the application of tepid, cold, or iced water externally. By this means the commonest cause of death (hyperpyrexia) is avoided; the exhausting effect of high temperature on the heart, respiration, and higher nerve-centres abated, and death from these causes postponed or averted; chest and other complications become less common, while severe cases are converted into mild ones. We find that this form of treatment, while acting strongly on a special symptom, at the same time by stimulating the circulation and respiration, the metabolic and eliminatory processes, improves oxygenation, and aids in the elimination of toxic substances from the blood. At the same time, by giving rest to the heart, it restores equilibrium to the internal organs, increases the resistance and fighting power of the body, and so without injuring the patient has an almost specific action in this fever, beyond that met with in any other form of pyrexia.

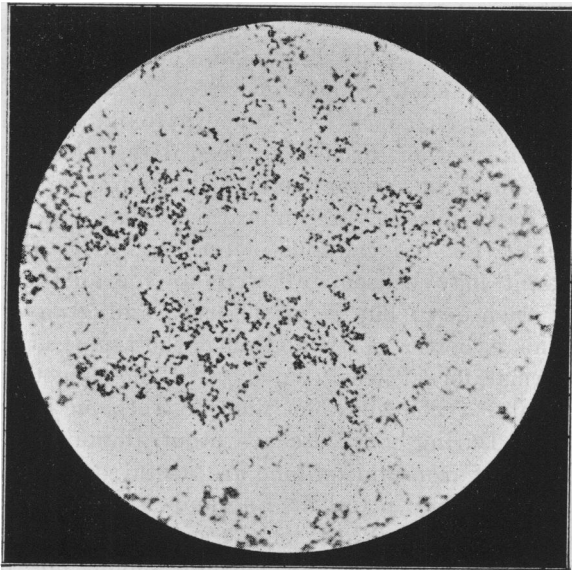
To produce a satisfactory result, this treatment must be begun early, and before a fatal result is anticipated, or

the patient may be found to have already lost the strength necessary for successfully combating with the disease. The form of application which I have found most satisfactory has consisted of keeping the temperature systematically below 103° F. by means of cold water sponging, the application of iced water or ice packing according to circumstances. A great deal may be done in all cases by tap-water sponging, but ice packing should always be supervised by an experienced individual, the temperature being taken frequently and the pulse watched. Bad results have not followed this treatment when reasonably applied. The great secret of success lies in the avoidance of too great reductions, the temperature being reduced 2°—3° F. to a safe range, and no further. The administration of stimulants before and the avoidance of chills after treatment should be borne in mind, and also that no two patients respond with the same rapidity to this treatment. The immediate relief of headache, the refreshing sleep which follows such reduction, are marked; while the return to consciousness from hyperpyrexial coma is too well known in other diseases to need description.

The cleaning of the tongue and shortening in duration of the daily pyrexia are indications that the time is approaching for the cautious increase of diet, and that the patient may be soon allowed up for an increasing amount each day; but in most cases, and always when acute, this is better postponed until the temperature has been normal for at least ten days. The mucous membranes take a considerable time to recover their full function. During convalescence Stout, Bland's pills, and the Citrate of iron and quinine are useful. Change to a warm, dry inland place in England is very beneficial during the enervating heat of the summer, but the trials of a sea voyage or overland journey should not be encountered until the acute stages are over, nor until an enteric diagnosis has been excluded. During the autumn and winter months patients are best away from the rigor of the English climate, and most cases recover well if

kept in Malta or sent to the dry atmosphere of Cairo or to the hill towns of Italy or Sicily at that time of year. It is not justifiable to send acute cases away from the attentions and comforts of home or hospital, to the fatigues of travelling, the doubtful comforts of foreign hotels, and away from skilled and friendly advice, for the sake of an over-estimated treatment by change of air, and often to places where the same fever is known to exist. The beneficial effect of fresh air and change of environment during convalescence is, however, not to be denied.

Quinine in acute stages acts as an acute stomachic irritant and depressant, and does more harm than good. In very late stages when the appetite has returned, and the patient, though up and about, is still subject to



Photograph (1000 diam.) by Mr. Pringle.

slight nocturnal rises of temperature, small doses given three times a day often act as a tonic and assist in

steadying the temperature. Arsenic is injurious in acute stages, aconite dangerous from its effect upon the heart. Antipyrin at the beginning of an attack reduces temperature, relieves headache, and promotes perspiration, but is inferior in action to sponging, and in severe cases has a most dangerous effect upon the heart. Germicides, such as carbolic acid, boracic acid, and mercury, have been tried without proving of specific value.

In conclusion I may point out the importance to the State of the study of this fever. Its prolonged duration and high invaliding rate cause a very large amount of non-effectiveness among the 25,000 soldiers and sailors composing the Mediterranean garrison. In the Malta garrison in 1891, the loss to the State on account of this fever alone was equal to the loss of the services and cost of a whole regiment 1000 strong in hospital for twenty-five days. The first step needed is to give this fever a place in the Official Nomenclature of Diseases.

(For report of the discussion on this paper, see 'Proceedings of the Royal Medical and Chirurgical Society,' Third Series, vol. viii, p. 176.)

EXPLANATION OF CHARTS.

CHART I.—Case of undulatory Mediterranean fever, admitted during the primary wave, with constipation (P. = aperient) and well-marked waves. Pyrexial duration, eighty-six days.

CHART II.—Similar case, with more regular waves, admitted to hospital in December, 1891, after nineteen days' treatment in quarters. Suffered from obstinate constipation (E. = enema), anorexia, anæmia, and extreme debility, but was never dangerously ill. Invalided to England on the 114th day of the pyrexia, where he suffered from occasional rises of temperature and severe rheumatic symptoms. Returned to duty in Malta in January, 1892, and has remained perfectly well since but for a slight attack of febricula in the summer of 1892, lasting three days.

CHART III.—Mediterranean fever with prolonged wave, associated with symptoms of cerebro-spinal irritation (P. = aperient).

CHART IV.—Chart of Case No. 9, "Bacteriology."

CHART V.—Illustrates a final wave of excessive symptoms at the end of a long case.

CHART VI.—Case of intermittent Mediterranean fever with constipation (P. = aperient), night sweats, malaise in the afternoon and evening, but no other complicating symptoms, ending in complete recovery. Treated on separate occasions with quinine (large doses once a day and also with small doses three times a day), arsenic, salicylates of quinine and soda, and anti-pyrim, without apparent effect.

CHART VI (a).—Complete diurnal curve, same case, days 43—51, with usually taken morning and evening curve in dotted lines.

CHART VII.—Mixed case commencing with the undulatory and ending with the intermittent type.

CHART VIII.—Case 2 in "Bacteriology."

CHART IX.—Case 3 in "Bacteriology."

CHART X.—Early sudden pyrexial drops in cases of Mediterranean and enteric fevers contrasted.

CHART XI.—Admission rate and rainfall contrasted.

CHART XII.—A common type of case with the waves less clearly marked.

CHART XIII.—Monkey experiment No. 3 (Hughes).

CHARTS XIV AND XV.—Pyrexial charts, monkey experiments 4 and 5 (Hughes), inoculated from last.