NOTES ON MEDITERRANEAN OR MALTA FEVER

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MDCCCXIII.
The chief interest in the action of the nitrates centres on the powerful and long-lasting influence they exert on the circulation in man. If 5m. of ethyl nitrate be taken internally the pulse tension falls in three or four minutes, but usually not after a dose has been taken. (See Fig. 20A.)

As after nitrates, the pulse is somewhat quickened, but this effect is by no means marked. One minim has a distinct effect on the pulse. Propyl, isobutyl, and amyl nitrates all act in a similar manner, and as far as I have examined their effect is by no means marked. One minim has a distinct effect on the pulse, and the corresponding nitrates. Fig. 20b shows the effects of isobutyl nitrate on the man from whom the tracings after amyl nitrite were used.

The test tubes containing the inoculated medium should be placed in an incubator at the temperature of the blood. This necessitates the use of a nutrient medium such as agar-agar, which remains solid at this temperature; and it is most essential that the medium should be as nearly neutral as possible, since any excess of alkalinity completely inhibits growth. The following is a list of the cases in which the presence of a definite micro-organism has been established by means of such cultivation experiments.

**CASE I.**—H. D., aged 24; duration of illness twelve days. Eight tubes of agar-agar nutrient jelly were inoculated from the spleen shortly after death, and remitted at the ordinary temperature of the air (about 20° C.) until the following day at 11 a.m. Six of these tubes were then placed in an incubator kept at 37° C., while two were left at the ordinary temperature of the air. No growth appeared in the tubes in the incubator until the end of 84 hours, when the same growth was observed. In the sixth tube, which had been left at the ordinary temperature of the air, no growth appeared after a period of 51 hours, and in the two others at the end of 108 hours. (See chart)

**CASE II.**—A. B., aged 24; duration of illness 15 days. As this case happened out of hospital I had no opportunity of making a post-mortem examination. I succeeded, however, in making inoculations into six tubes containing agar-agar in the following manner. Seven hours after death, having previously cleansed the skin over the region of the spleen by means of a strong solution of corrosive sublimate and alcohol, I drew off a small portion of the splenic pulp by means of a sterilised trochar and cannula. Next morning five of these test tubes were placed in the incubator, and one left at the ordinary temperature of the air. No growth appeared in the tubes in the incubator until the end of 84 hours, when the same growth was observed. In the sixth tube, which had been left at the ordinary temperature of the air, the colonies appeared at the end of 110 hours.

**CASE III.**—B. E., aged 23; duration of illness eight days. Six tubes of agar-agar were inoculated from the spleen and placed in the

1 Surgeon-Captain Hughes informs me he has succeeded in one instance in cultivating the micro-organism from blood taken from the heart of a monkey dead of the disease.

2 This organ ought to be removed from the body as soon as possible after death, protected from contamination by being wrapped in a cloth saturated with a solution of corrosive sublimate (1 in 1,000), and taken to the room set apart as a laboratory. In transferring traces of the splenic pulp to tubes containing the nutrient material, certain precautions should be taken not to cut the spleen in the plane at right angles to the first, and the third at right angles to the second and parallel to the first, are made with three knives previously thoroughly sterilised by heat. A platinum needle held to redness before each inoculation is then used to convey a small portion of the pulp from the depth of the third cut to the solid nutrient jelly.
incubator. In these the characteristic growth appeared after 67 hours. The following chart illustrates the course of the disease.

CASE IV.—J. V., aged 22 years: duration of illness twenty-four days. The six tubes inoculated from the spleen showed the usual growth after the usual time. (See chart.)

CASE V.—J. V., aged 23; duration of illness fifty-three days. Inoculations were made from the liver, kidney, and spleen, but all remained perfectly sterile except one, in which the usual growth appeared after several days. I can only account for this scarcity of the microorganisms by supposing that most of them had died out owing to the long duration of the case. The following chart illustrates the course of the disease.

CASE VI.—T. G., aged 23; duration of illness eight days. This case resembled one of typhoid very closely. The stools throughout were fluid, 19 ounces in weight; no enlargement or ulceration of Peyer’s glands or other glands of the small intestine; large intestine normal. Six agar-agar tubes were inoculated from this organ and placed in the incubator. The characteristic growth appeared in all the tubes on the morning of the fourth day.

CASE VII.—C. D., aged 28; died on the eighth day of illness. Body of a strong muscular man; mesenteric glands not enlarged; large and small intestines showed no appearance of glandular enlargement or ulceration. The spleen weighed 19 ounces, and was soft and pulpy. Six agar-agar tubes were inoculated from this organ and placed in the incubator. After four days the characteristic growth appeared in all. (See chart.)
transmitted light, the centre of each is seen to be yellowish in colour, while the periphery appears bluish-white. On looking at the same colonies by reflected light no appearance of yellow can be seen; they then simply appear to be milky white in colour. The separate colonies on the surface of the coccus can be seen by the naked eye on the surface of the about half that time. When stab cultivations are made into nutrient medium is fairly constant, and is a valuable character for the identification of the species. Kept at a temperature of 10 per cent, nutrient gelatine, and kept at 22° C., little or no growth takes place. The material used for inoculation was a portion of a colony removed from the surface of an agar-agar tube of the coccus of Malta fever appeared after the usual time. In the second liver tube the material was taken was a cultivation from Case i, and had been growing outside the body for nearly a month. The monkey's temperature went rapidly up, reaching 107° F., and after a month the needle track has been seen a minute smooth white growth not larger than a pin's head. No liquefaction of the gelatine takes place.

Plate cultiavations in gelatine of this species have not been satisfactory, on account of the extreme slowness of its growth. For the first ten days the monkey was lively, and continued to eat and appear healthy; liver, enlarged and congested; intestines, some congestion at ileo-colic valve, otherwise normal; spleen, much enlarged and congested. Immediately after death the viscera were examined, and injections made into agar-agar from the spleen and other organs. The characteristic growth took place in the tubes inoculated after the usual time. Experiments v and vi are interesting as exemplifying the chronic course of the fever as usually seen in man. They are also of interest from the fact that these monkeys were inoculated from pure cultures obtained from the blood and spleen of monkey, Experiment vi, and not as in the other experiments, from the organs of man.

**ON THE TRANSMISSION OF MALTA FEVER TO ANIMALS.**

The effect of the subcutaneous injection of small quantities of pure cultures of the micrococcus of Malta fever were first tried on mice, guinea-pigs, and rabbits, but with altogether negative results. With monkeys, however, the results were more successful, as the following experiments will show:

**EXPERIMENT I.**—Monkey No. 1, male, species bonnet. The temperature of this monkey for a fortnight before inoculation ranged between 99° F. and 100° F. He ate well, was very active, and to all appearance healthy. For the first ten days the monkey was lively, and continued to eat and appeared healthy; liver, enlarged and congested; intestines, some congestion at ileo-colic valve, otherwise normal; spleen, much enlarged and congested. Immediately after death the viscera were examined, and injections made into agar-agar from the spleen and other organs. The characteristic growth took place in the tubes inoculated after the usual time.

**EXPERIMENT II.**—Monkey No. 2, male, species unknown; inoculated in the same manner as in the last experiment. This monkey remained to all appearances in good health; his temperature, however, ran up to 104° F., at which it remained, with slight variations, for sixteen days. Some slight inflammation and pus formation occurred at the point of injection, but this passed off and the monkey recovered his usual health.

**EXPERIMENT III.**—Monkey No. 3, male, species bonnet. In this case the same material was used for inoculation as in the last experiment. The growth used was one from the surface of an agar-agar tube of the second generation, which had been growing for one month. This was mixed in the usual way in sterilised broth, and injected into the left arm. This monkey's temperature also ran high, and he died after thirteen days' illness. Inoculations made from the spleen into agar-agar tubes showed the first appearance of the micrococcus of Malta fever appeared after the usual time. In the second liver tube no growth of any kind took place. The following chart shows the temperature curve.

**EXPERIMENT IV.**—I am indebted to Surgeon-Captain Hughes, A.M.S., for notes of the following three cases. Monkey No. 4, male, species bonnet. This monkey was under observation for two months, during which time his appetite was good and his temperature normal. He was inoculated by injecting 1 c.c.m. of sterilised broth, in which had been rubbed up a small quantity of growth from an agar tube. This culture was obtained from Case x.
fairly prevalent in April the attack-rate reaches a maximum in July, August, and September, the hottest and driest months, and then falls until, in the wet and cold months of November, December, and January, very few cases of fever occur. In February and March, however, numerous cases occasionally occur. Enteric fever, on the other hand, becomes most prevalent after the first heavy rains, continuing during the autumn and early winter months.

IV. Localisation.—It has always been distinctly endemic in (1) the barracks, houses and hovels built by the Knights between the beginning of the sixteenth and end of the eighteenth centuries, and since then; and (2) the ships of war anchored in the harbours of Malta.

The fever is certainly not contagious from man to man, and both in localisation and general clinical characters it bears no analogy to enteric fever. The only similarity is that all fatal cases of fever were admitted from a barrack containing eighty men, though no cases of fever had occurred there during the preceding twelve months. Clinically they were somewhat analogous, but the post-mortem appearances and bacteriological tests clearly indicated that one was enteric and the other two Mediterranean fever.

Bacteriological facts in no way negative the theory of fecal transmission of infection, and hygienic authorities and my own experiments point to a suitable reception of fecal excreta of some 5,000 to 8,000 sailors employed on ships of war and mercantile vessels, being annually poured into the enclosed and tideless harbours, converting their basins into one large cesspool, which is never cleaned out, and must hold the accumulations of ages. The offensive state of the water becomes apparent at the sewer-outlets at all times, and in the enclosed creeks and docks on rough days, yet in summer soldiers and sailors may be seen bathing daily all round these very places. Moreover, this same water is used for washing down decks, etc., so that when drying it has ample opportunity of giving off in an enclosed space such miasma as it may contain.

There is no evidence in favour of infected food or drinking water having any causal connection with this fever, and the introduction of a pure water supply under pressure has not lessened its prevalence in Valletta. The facts point distinctly to a probable air-borne virus on shore, as does the following account of a recent epidemic:

A regiment was quartered on a small island in the Quarantine Harbour, Valletta, from January 2nd, 1892, until October 10th of the same year, during which period it suffered severely from "simple continued fever," 197 cases being admitted from a strength of 709, of which severe attacks followed this fever elsewhere during its first year's service in Malta, had been sanctioned by a three years' residence, and was composed of men whose ages were not below the average of the station, yet their fever rate for 1890 far exceeded that of any other regiment. Of these men, 400 were quartered in wooden huts, and the remaining 299 in an old fort close by, which had been built by the Knights in 1725. A series of cases occurred in 1872, and a careful analysis of the fever admissions divided them into two classes:

1. Cases of true Mediterranean fever.
2. Cases of intermittent fever (the latter possibly due to special individual power of resistance), cases of simple ardent fever (febricula), and other obscure but slight febrile ailments. The last class was present widely, and was little to note of consequence except that the numbers were higher than those from other barracks, and that in proportion to strength the numbers of admissions were considerably higher than the lists. The admission rate per mile for true Mediterranean fever in Valletta district (strength 3,511, including the island in question) in 1888 was 52.2, while those of the station in 1892, including the island in question, was 86.5; the average for this period was 74.1, being 22.8 higher than the 1892 rate.

II. ITS BEHAVIOUR AT MALTA.¹

By Surgeon-Captain M. Louis Hughes, A.M.S., Malta.

Abstract of a paper read to the Malta Branch of the British Medical Association.
used as sewers, until the substitution in 1883 of the present dry-earth system. The drainage of Valletta around seems to have some relation to the reported increase of this fever among the civil population. The drains originally consisted of very large, deep channels, cut by the Knights in the porous rock, with faulty gradients and no flushing. In these the sewage was semistagnant, keeping a fairly average level during the time of heavy rain. Between 1879 and 1885 new sewer pipes of a suitable size and well ventilated, were accurately laid at the bottom of these channels, the upper part being used as a surface and storm water drain. This upper part is wet in the rainy season, but dry and suitable during the hot months for the escape of miasmata, which by the way of the ventilators and numerous traps (also at this time dry) must pass into the houses. At the same time, on account of the hilly nature of the ground on which Valletta is built, many even of the more modern ventilators, though carried high above the roof, are yet on a level with the windows of houses across the street. Whether from insufficient flushing or other causes, their smell is often offensively perceptible in summer, to those almost exclusively affected; the extensor proprius paralysis is more completely paralysed than the others, and the big toe drops in a most characteristic manner. I have seen two cases in which the muscles of the shoulder and arm were affected, but they were exceptional. This symptom is a late manifestation, seldom appearing in less than four months, and in one case it occurred as early as the end of the second week of the disease. The paralysed muscles atrophy slowly, and recover their proportions long after power has returned to them. The alterations in the electrical reactions are both quantitative and qualitative. Diminution of the musculature response is the only quantitative alteration I have noticed. The qualitative alterations are both modal and serial; the former consists in a sluggish contraction and a marked duration of tetanus; in some cases this is the only change, but in those of long duration there is an overtaking of the cathodal closing contraction by the anodal closing contraction. Recovery is generally complete, but it takes place slowly.

Rheumatoid Pains: Neuralgia.—Rheumatic pains, especially in the back and lower extremities, and neuralgia, particularly of the back and legs, are symptoms which persist during the long convalescence.

Anaemia.—Anaemia is always present, and it does not seem to be influenced by the administration of iron.

A CASE OF TYPHOID FEVER FOLLOWED BY PERFORATION AND RECOVERY.

By ANTHONY McCALL, M.B., C.M.,

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