PHLEBOTOMUS FEVER (SANDFLY FEVER).*

PHLEBOTOMUS OR SANDFLY FEVER.

BY

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SANDFLY FEVER is of scientific interest because its causation has been established by means of experiments on volunteers, experiments which were justified by the fact that the disease does not endanger life.

Newcomers to tropical or subtropical places where the phlebotomus abounds are attacked during their first summer of residence with a fever which incapacitates them completely for several days. After an incubation period of four to seven days the onset of sandfly fever is usually sudden, although sometimes the pyrexia may be preceded by lassitude for a few days. Chilliness may be complained of, but the severe rigor of the ague fit is never observed. The writer, who had suffered from both ailments, recognized at once that the shivering and chattering of his teeth, so violent that he was constrained to hold his jaw with his hands; which were the prelude of his first ague seizure, distinguished the attack from the sandfly infection which he had experienced previously. Giddiness, severe headache, most often limited to the forehead and the back of the eyes, which is aggravated by the least movement of the head, pains in the back and in the legs, and general stiffness of the muscles of the body, induce the patient to take to his bed. He is drowsy and resents being disturbed, but sleep is broken or absent. His face is deeply flushed, and his features are tumid. His eyelids are swollen and partially closed; the conjunctivae are injected, but there is no lacrymation; his eyeballs are sensitive to movement and gentle pressure. He has complete loss of appetite, with pain or discomfort in the epigastrium; vomiting and diarrhoea occur in about one-quarter of the cases, but constipation is the rule. The tongue is coated with a thin white fur, except at the tip and edges. There is often congestion of the fauces and palate on which vesicles may be seen. Epistaxis is observed in a fifth of the attacks, mostly towards the end of the illness. The skin is generally dry, but may be moist; beyond flushing of the face, neck, and upper part of the chest, no rashes are present except the effects of blood-sucking insects. The temperature rises rapidly until it attains 101° to 103° F. on the evening of the first day; it is not quite so high on the second evening, and falls gradually on the third or fourth day—hence the termination of the attack is very different from that of ague, in which the pyrexia abates suddenly amidst profuse sweating. The pulse does not rise in frequency with the fever and generally becomes slow. Leucopenia with relative decrease in the polynuclears is an almost constant sign which persists throughout the illness and the early days of convalescence. The eosinophiles are decreased during the fever, but are increased afterwards as in dengue.

Depression, lethargy, and dyspepsia often continue for a fortnight after an attack, but epidemics vary in this respect. Sometimes vigour is restored rapidly.

In Malta the duration of 20 per cent. of 243 cases of sandfly fever was two days or less, of 30 per cent. three days, of 23 per cent. four days, of 12 per cent. five days, of 9 per cent. six days, and of 5 per cent. seven or eight days. Wymerley's figures of his observations on 160 cases of sandfly fever at Nashera, India, are—three days' pyrexia in 22 per cent.; four days' in 27 per cent.; five days' in 24 per cent.; six days' in 20 per cent.; and seven or eight days in 6 per cent.

The susceptibility of British troops is very high. Sometimes more than half a regiment has been attacked during its first hot weather. Ninety-five per cent. of all the cases occur in people who have resided two years or less in the endemic area. A high degree of immunity is afforded by the fever. Second attacks occur in only 5 to 10 per cent. of the cases. Relapses are sometimes caused by excessive exercise during convalescence.

* Papers read in the Section of Tropical Medicine at the annual meeting of the British Medical Association, 1914. Publication of these papers has been delayed owing to exigencies of space due to the outbreak of war.

Inoculation of non-immune persons with $\frac{1}{2}$ to 3 c.cm. of the blood or serum withdrawn from sandfly fever patients during the first twenty-four hours of the illness excites the fever without fail (nineteen experiments). Blood taken after the first day is harmless (five experiments). On fourteen out of sixteen occasions inoculation with infective serum which had been passed through a bacteria-proof filter induced the malady. In twenty-one experiments the bites of sandflies which had been fed seven to twelve days previously on sandfly fever patients during the first day of their illness gave rise to the disease. A single phlebotomus is sufficient to infect.

The disease is often called "summer influenza," but bronchitic symptoms are uncommon, and the influenza bacillus is not present. Atypical cases of the mosquito-borne dengue closely resemble sandfly fever; a dengue outbreak, however, is usually more explosive in character than a phlebotomus fever epidemic; rashes also are present in 70 per cent. of dengue patients.

Abortive attacks of enteric, paratyphoid, and Malta fevers may be mistaken for the sandfly infection.

In malarious climates it was formerly confounded with ague, and at the present time this still occurs. Bellile, writing in 1913 of the outbreaks of sandfly fever in Crete, states that the Cretans name it ague. In Malta, where endemic ague may be neglected, sandfly fever, which has caused much sickness among our soldiers and sailors quartered there, has been recognized during the last hundred years as a malady distinct from malaria.

In India, until ten years ago, sandfly fever was for the most part diagnosed "ague." Without doubt many of the cures attributed to quinine have been in times past nothing but the natural terminations of cases of sandfly fever. Since five or six thousand attacks of sandfly fever occur annually among the European and Indian troops, the amount of quinine which has been uselessly expended has been enormous. Great progress has now been made in the identification and classification of fevers in India. In a memorandum issued in 1913 by the Director of Medical Services of India instructions are given that the blood of every case of pyrexia is to be examined before the administration of quinine, by the thick film method, by which parasites can be detected in 94 per cent. of malarial patients. Leucocyte counts are to be made, including differential estimations. Serum reactions are to be undertaken every two days in order to trace the agglutination curve of the serum with the suspected microbe. Cultures of 5 to 10 c.cm. of the patient's blood are to be made in bile or taurocholate media. The dejecta are to be investigated bacteriologically. Given a short fever in which the results of these examinations are negative, except the leucocyte estimation which shows leucopenia, in a locality where sandflies are numerous and culices and stegomyia are few, then the diagnosis of sandfly fever is correct. In another memorandum it is suggested that experiments on volunteers with the above-named mosquitos should be carried out if these insects are abundant, as they are the suspected carriers of dengue-like fevers which may be prevalent in the station.

The advance which has taken place in the recognition of sandfly fever in India appears in the following figures: In the year 1910 among the 71,000 European troops there were recorded 512 admissions for sandfly fever; in 1911, 1,393; and in 1912, 2,163. The laboratory facilities for diagnosis are not so great in hospitals for Indian troops as in those for British; 508, 114, 1,316, are the numbers of the admissions on account of sandfly fever among the 131,000 Indian troops for the above-named years. Many sandfly infections are recorded under the headings of "influenza" and "pyrexia of uncertain origin" tables of the seasonal prevalence of which are given, from which it is estimated that five or six thousand cases of sandfly fever occur annually in the European and Indian armies of India.

It is to be regretted that the heading "sandfly fever" does not appear in the annual statistical reports of the health of the navy. In the report for the year 1912 326 cases are registered "pyrexia"; it is stated that many of these were instances of the sandfly infection.

Quinine is without effect prophylactically or therapeutically in sandfly fever. Aspirin and pyramidon are of some use for the relief of pain. An antitoxin is present in the blood of persons immunized by an attack of this

fever, for Doerr found that 1 c.cm. of virulent blood mixed with 1 c.cm. of the serum of a man who had suffered from phlebotomus fever two years before, was innocuous when inoculated into a susceptible individual. McCarrison, moreover, injected four immune men with doses of 2 c.cm. of virulent blood without exciting the disease. It seems probable, therefore, that the infection might be aborted by injections of the serum of convalescents.

Sandflies are widely scattered throughout the tropical and subtropical world. There is a close correlation between the number of sandflies and the fever. In Poona they are scarce and the admissions for sandfly fever are few. In the north-west of India these flies are abundant and the fever is very prevalent. The phlebotomus is so small and elusive that it often escapes notice at night. During the day careful search may find it resting in dark corners, behind clothes, etc.

In the *Transactions of the Society of Tropical Medicine and Hygiene* (1913, vol. vi, No. 7) a survey of our knowledge of the distribution of the phlebotomus and of the fever was made. We learn from the Army Medical Report for 1912, which has appeared since the date of this paper, that there were 104 attacks of sandfly fever registered among the British troops at Malta, 144 in Egypt, and 108 in North China.

The bionomics of the sandfly are being investigated by Howlett, the Imperial Pathological Entomologist of India, and by Marett in Malta. It breeds in caves and in the interior of rubble walls, and in collections of damp material, such as fragments of bricks and stones. *Phlebotomus minutus* feeds on the blood of the common wall lizard. King discovered the larvae of phlebotomus in cracks of the alluvial soil near Trinkitat on the Red Sea. Wenyon succeeded in keeping a sandfly alive in captivity for forty-six days. Doerr's observations tend to show that the summer epidemics of sandfly fever are bridged over by the virus being carried in the larvae, which hibernate in the winter.

The knowledge which has been acquired has been instrumental in reducing the incidence of sandfly fever among the British troops stationed in Malta from more than 300 attacks in 1908 to 104 only in 1912.

SANDFLY FEVER IN CHITRAL (N. INDIA).

BY

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DURING the three years 1911-13 I have had the opportunity of studying between 700 and 800 cases of this fever in its epidemic form in Chitral—a British outpost beyond the north-western frontier of India. Attention was first drawn to this fever in these parts in 1906 by Captain McCarrison of the Indian Medical Service, who called it the "three days fever of Chitral." It is now fully recognized as identical with sandfly fever, which occurs in many parts of India, especially in the north of India, Punjab, and Himalayan stations, and also in many other parts of the tropics and subtropics. As far as India is concerned, I shall have occasion to point out that probably this fever is by no means of recent appearance, but has previously passed under various names, as Peshawar fever, or pyrexia of uncertain origin.

Distribution of the Fever.

Sandfly fever appears to be a rare disease actually in the tropical zone, being much more frequently found in subtropical regions, and especially in stations at the foot of the Western Himalayas. Chitral itself, where this fever would appear to be most constantly and persistently prevalent, is a narrow valley in the Hindu Kush range of mountains to the east of Afghanistan beyond the Himalayan range. I may mention in passing that Chitral is about the same degree of latitude as the south of Spain. The disease is present throughout the whole of the Peshawar-Chitral Valley at all levels below 7,000 ft. It would appear that the sandfly cannot live and breed at any level over 7,000 ft. The highest level at which I have found it was 6,500 ft.

Climatology.

The disease is strictly limited to the summer months between May and September, more especially June, July,

and August. During these months alone are the sandflies prevalent in their active winged stage of development. In my experience of three successive annual epidemics a very dry season was most favourable to the spread and severity of the epidemic. During the months of June-August there is practically no rainfall at all in Chitral, which becomes exceedingly dry in parts. I found it very difficult to reconcile the necessity for moisture being essential for the life-history of the sandfly in its early development. The only water flowing through the Chitral fort in which the garrison were all quartered was a tiny brick-lined drain about one foot wide, with a very rapid flow of only a small quantity of water down the steep incline on which the fort is built. This drain was repeatedly searched for larvae or pupae, but invariably with negative results. No other open drains or tanks exist in the fort, in which and in similar buildings alone these pests were found. Heavy rainfall—which did occur on one occasion—appeared even to reduce the fever incidence somewhat, possibly by killing off some of the infecting sandflies. High temperatures up to 110° to 115° F. of the Punjab hot weather are favourable, but the cold season of the Himalayas stops breeding and development entirely. Apparently the temperature which is necessary for the imago to hatch out from the pupa is between 70° to 80° F. This temperature is reached as a shade maximum in Chitral about the end of May. It is almost certainly in the egg stage that the sandfly tides over the cold winter months, when the temperature frequently drops to 10° to 15° below freezing point.

Etiology.

It is now, I think, established beyond all possible question or dispute that this fever is spread by the agency of the sandfly, though the nature of the infecting virus is not quite certain. The sandflies, or Phlebotominae, belong to the family Psychodidae. The two special species which are known to convey the virus are the *Phlebotomus papatasi* and *P. minutus*, both of which species I have been able to identify in Chitral. These sandflies are of a light straw colour, with wings carried divergent and pointing backwards and upwards. The sexes are easily distinguished by the large and complex claspings apparatus of the male genitalia on the hinder end of the abdomen. The whole process of life-history from egg to adult fly lasts about one month, this period, however, varying with the surrounding conditions. The methods I adopted in examining specimens were as follows:

The sandflies, young and adult, were caught alive in small glass-covered entomological boxes. In this small cell they could be easily examined with a hand lens and the general characters of the specimen made out. If necessary it was transferred to a small glass cell and examined on the stage of a microscope with a low-power lens. Mounted specimens were also made by the following process:

1. Kill by inverting the small glass bottle in which they were caught over some cotton-wool or blotting paper soaked in a little chloroform, or, better still, over a board with some chloroform soaked into it.
2. Transfer the killed specimen to 60 per cent. alcohol.
3. Clear in oil of cloves.
4. Mount in Canada balsam, arranging the legs and wings carefully with a fine needle and cover over with a coverslip.

Large numbers of sandflies could easily be caught daily in the barracks of the Chitral forts during the summer months. Owing to their small size, they can easily pass through the meshes of an ordinary mosquito curtain used everywhere in India. This necessitates the use of one of much finer mesh to ensure their being unable to bite the individual while asleep at night. This, I need hardly point out, adds very considerably to one's discomfort, as circulation of fresh air through the curtain is greatly impeded by the fineness of the mesh. The flies exist in large numbers in all buildings, especially on the walls and near the ceilings or the roof of the building during the day-time. Towards evening they commence their search for food. The females alone are blood-suckers; they frequently feed by day, and are capable of easily biting through thin socks or cotton summer clothing. The males probably live on vegetables, juices, and other similar materials. The virus which exists in the blood of patients is only infective during the early stages of the fever, and the blood of patients, after being passed through a Berkefeld-Reichel filter, is still infective if injected into