—an undoubted advantage from the point of view of those who, while admitting the necessity of morphine, are disposed to associate it with the intestinal atony and consequent flatulent distension which lead to much discomfort, and with the post-operative circulatory depression which may be the initial factor in the causation of a subsequent pulmonary embolism. In respect of safety and certainty of action, paraldehyde premedication appears to compare favourably with that effected by such drugs as hyoscine, nembutal, luminal, and avertin. Comparison with avertin is particularly interesting. This would appear to favour paraldehyde by reason of its intrinsic safety as a drug, the absence of any blood pressure fall after its use, and the simplicity of the technique involved, while results are at least as certain and as consistent as those obtained with avertin.

Disadvantages are few. The unpleasant odour of paraldehyde appears in the breath shortly after the rectal administration; this, however, is a disadvantage of which the patient remains unaware, and of which only the nursing staff are conscious. The quiet respiration characteristic of the somnolent period following operation does not appear to increase the risk of respiratory complications. In some 500 cases no trouble of this kind has been experienced, nor has the carbon dioxide cylinder been more than ordinarily employed. Transient excitement occurs in a small number of cases, either immediately after the drug has been administered or on awakening. The occasional occurrence of this phenomenon, which is always of short duration and is of little significance, is characteristic of any drug given for purposes of premedication.

SUMMARY

Rectal paraldehyde provides a safe and certain method of eliminating for the patient the more unpleasant accompaniments of operation. He simply sleeps, and when he awakes finds that the ordeal is over—a state of affairs regarding the advantage of which the patient with previous experience of anaesthesia and operation is usually most emphatic. He remains relatively comfortable during the trying twenty-four hours following operation, and subsequent distressing recollections are absent. Preliminary rectal paraldehyde, while facilitating the anaesthetist's task, adds nothing to his anxieties concerning the patient either during or after the operation. His patient's gratitude provides a somewhat novel and not unpleasing experience.

TROPICAL TYPHUS*

BY

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The great epidemics of the war, the discovery of the Weil-Felix reaction, and the study of *Rickettsia* stimulated the investigation of typhus all over the world. The results have shown that it is but one of a group of *Rickettsial* diseases carried by arthropods, and that in this group rodents play an important part as reservoirs of infection. It is possible that *Rickettsiae* were originally parasites of the plants which form the food of adult mites, and that the earliest typhus-like diseases were those carried by mites or ticks. Typhus exanthematicus probably appeared when men took to wearing clothes, and the virus became adapted to the body-louse. There is no evidence that an infection with mite- or tick-borne virus can at any moment give rise to an epidemic of typhus in the presence of human lice, but Anigstein¹

states that he has succeeded in infecting the latter with the virus of the non-louse-borne tropical typhus, both by feeding and by injection.

FEATURES OF THE DISEASE

The symptoms of tropical typhus are those of typhus exanthematicus, but as a rule the fever is less severe and more remittent, the rash is often inconspicuous or absent, and the nervous symptoms are less prominent; occasionally, however, a severe case occurs, with petechial rash, coma, and other symptoms indistinguishable from those of typhus. The morbid anatomy and serology of the disease, together with the results of animal inoculations, show conclusively that it is a member of the typhus group. Lewthwaite² has found, both in the brains of fatal human cases and in those of guinea-pigs and rats inoculated with infective material, vascular lesions similar to those occurring in typhus fever, and he has also demonstrated *Rickettsiae* within the swollen endothelial cells of the affected vessels. Guinea-pigs react less readily than is the case in typhus exanthematicus. Only 5 to 10 per cent. give a febrile reaction after inoculation with human blood, but, according to Lewthwaite,² there is a pronounced loss of weight in about 25 per cent. Rats are more susceptible, and a febrile reaction occurs in 27 per cent. Anigstein¹ has reported the occurrence of the Pinkerton-Mooser reaction in about 6 per cent. of inoculated guinea-pigs. This reaction, which occurs regularly in Mexican typhus, consists of swelling of the scrotum and injection of the tunica vaginalis, in the exudate of which *Rickettsiae* are found in great numbers. A positive Weil-Felix reaction is obtained in many of the rabbits and rats inoculated with patients' blood (Anigstein¹). Lewthwaite is now employing with success the intraocular method of inoculating rabbits, which Nagayo has used both in the tsutsugamushi disease and in typhus.

In spite of these numerous points of close resemblance, tropical typhus differs utterly from typhus exanthematicus in its epidemiology; it neither spreads from man to man nor occurs in epidemics. We⁴ had not been working at it for long before we found that it was not a single disease, but two, there being an urban and a rural (or scrub) form. The two are clinically indistinguishable, but in their aetiology and epidemiology they are as different from each other as Rocky Mountain fever is from typhus exanthematicus.

Urban Form

The urban form attacks more especially those who work in stores—particularly food stores—and in Kuala Lumpur many of the cases come from streets where sporadic plague sometimes occurs. As in Brill's disease, the reservoir of infection is probably the rat, and the vector *Xenopsylla cheopis*. The disease is never epidemic because it does not kill the rats, and therefore the rat-fleas are not constrained to seek strange and unpalatable hosts. The Weil-Felix reaction is positive with X 19, and this urban form is evidently very closely related to Brill's disease, in which the virus is almost identical with that of typhus exanthematicus. The mortality is negligible. The rural form is also very mild as a rule, but occasionally it is severe, and in 1929 there were eleven deaths among 154 cases.

Scrub Typhus

The rural form, or scrub typhus, occurs in all parts of the Malay States and in the Dutch Indies, but though its distribution is wide it is patchy, and the infected places are circumscribed areas of untilled open country, especially land which, after being cleared of jungle, has been allowed to grow up in weeds and scrub. The lack

* Read in the Section of Tropical Medicine at the Centenary Meeting of the British Medical Association, London, 1932.

of contagion from person to person made it probable that there was some reservoir of the virus other than man, and rats had long been under suspicion, when, among 200 caught in an endemic area, Anigstein¹ found several whose blood agglutinated either X 19 or XK (the Kingsbury strain), and in nine a typical scrotal swelling, with abundant Rickettsiae in the exudate.

Scrub typhus is essentially a place disease; the infection does not lie in man or his belongings, but lurks in the rank weeds and vegetation of certain limited foci. A striking example of this is afforded by a plantation of some 3,000 acres where African oil palms are cultivated, and where several cases have occurred almost every month for the last six years. The infection is not distributed generally throughout the plantation, but is concentrated in those parts of it where young trees are being pruned of their dead flowers. Lewthwaite² has found that the disease is almost completely limited to the coolies whose work brings them into close contact with the trees, and that those who are employed in making roads and ditches are rarely infected; the watchmen and others employed about the lines escape entirely, and so do the children until they are old enough to go to work. It seems probable that the palm trees harbour the vector, and Gater³ has found that the dead flowers are infested by enormous numbers of mites. Numbers of mites, notably *Trombicula deliensis* and *T. akamushi*, are also present in the ears of the rats which live in the infected areas, and they are sometimes found on the coolies when they return from work. The disease is by no means limited to oil-palm estates, but is often associated in a curious way with the coarse grass which is used as fodder for cattle, and sixteen of the first thirty cases recognized in the Malay States occurred either in cowherds or bullock-cart drivers. The rural form of tropical typhus is not so nearly related to typhus exanthematicus or to the urban form of tropical typhus as it is to the mite-borne tsutsugamushi disease, which it resembles closely both in its clinical features and in the kinds of places where it is found. The two diseases have, in fact, occurred side by side within the same endemic area. Further, the "K" strain of *B. proteus* is agglutinated in both diseases (though not to the same extent in the tsutsugamushi disease), but in neither of them is the Weil-Felix reaction positive with the X 19 strains, which are agglutinated in typhus exanthematicus and in the urban form of tropical typhus.

WEIL-FELIX REACTION

It was generally accepted a few years ago that the Weil-Felix reaction was a heterologous agglutination due to the power acquired by the serum in typhus of agglutinating various organisms, such as Plotz's diphtheroid and Wilson's "U 3," which clearly have no causal connexion with the disease; but evidence is accumulating which shows that the relation of *B. proteus* X to the virus of typhus is something closer than this. In the flea-borne endemic typhus (Brill's disease) of the United States, which is so closely related to typhus exanthematicus that cross-immunity between them is complete, the Weil-Felix reaction with X 19 is positive. In the tick-borne fever of the Rocky Mountains—less closely related to typhus exanthematicus, and with no cross-immunity—the reaction is irregular, suggesting a group agglutination. Lastly, in the third section of the typhus group, which comprises the mite-borne tsutsugamushi disease and the closely related rural form of tropical typhus, *B. proteus* X 19 is not agglutinated, but the "K" strain, which is probably a modification of X 19, is agglutinated in high dilution; and it is interesting to note that Anigstein¹ has recently stated that he has recovered a strain of XK from the urine in a case of tropical typhus.

These facts are evidence against the view that the Weil-Felix reaction is a non-specific para-agglutination, and, as Felix⁶ has pointed out, they suggest that the several diseases of the typhus group are due to modifications of the same virus associated with special modifications of the "X" type of *proteus*. Infection with typhus virus produces finely granular-agglutinating O-type agglutinins, but infection with *B. proteus* produces coarsely granular-agglutinating H-type agglutinins. Felix⁶ has described the examination of a serum from the Malay States which contained only H-type agglutinins, thus indicating an infection with *B. proteus*; but Dr. R. Lewthwaite, who sent this serum to the Lister Institute, has since told me that the course of the patient's illness, the symptoms, and the rash were indistinguishable from those of typhus. Such cases as this appear to afford another connecting link between *proteus* and typhus. Weil and Felix⁷ advanced the hypothesis some years ago that *B. proteus* X was a saprophytic stage of *R. prowazeki*, and in support of this Anigstein¹ states that the XK strain which he isolated from the urine of a tropical typhus patient became transformed into Rickettsia when he injected it into lice.

RICKETTSIA

The plentiful supply of organisms found both in the tunica vaginalis of guinea-pigs infected with Brill's disease or with Rocky Mountain fever, and in the eyes of rabbits and guinea-pigs after the inoculation of tsutsugamushi or typhus virus into the anterior chamber, has greatly facilitated the study of mammalian Rickettsia. Several workers have cultivated Rickettsia in the presence of living tissue. Nigg and Landsteiner⁸ succeeded in doing this, without loss of virulence, from the tunica of guinea-pigs infected with Brill's disease, in a medium consisting of salt solution with serum, with the addition of minced normal tunica or peritoneum; but they were unable to grow the organisms apart from the living tissue. A few investigators, on the other hand, claim success in this respect with the Rickettsia of both arthropods and mammals, but their results have not, so far, been generally accepted. In tropical typhus Anigstein¹ reports that he succeeded in cultivating seventy-six strains in a digested meat broth containing glucose and ascitic fluid, with subsequent growth on chocolate agar. These strains comprised thirty from the blood and organs of human cases, twenty-four from guinea-pigs and rabbits, twenty from rats, and two from lice fed on patients. The inoculation of some of these cultures into guinea-pigs caused a typhus reaction with a typical scrotal swelling and associated Rickettsia, and some of the rats and rabbits which were inoculated gave a subsequent Weil-Felix reaction. The cultures all resembled Rickettsia when first isolated, but on subculture, or passage through animals, fifteen of them grew as spreading films consisting of long threads, and twelve of the fifteen were agglutinated with serums prepared with X 19 or XK, and by the serums of patients. Anigstein's work needs confirmation, but apart from it there seems to be sufficient evidence that Rickettsia constitutes the virus of tropical typhus.

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