CHAPTER 9

TYPHUS FEVER

BEFORE the war considerable interest had been taken in rickettsial diseases. Murine typhus was occasionally seen, mite-borne typhus had been revealed as one of the important endemic diseases of Northern Queensland, and Q fever, a rickettsial infection, though not apparently closely related to the typhus family, had been discovered in Queensland. These diseases had stimulated interest in insect vectors, fleas, mites and ticks. Rather contrary to expectations Q fever, though a feature of the medical conditions in some of the Mediterranean battle areas, was not found among the Australian forces. It is possible that some of the pneumonic illnesses of undetermined type may have been of this variety, but no evidence exists.

MURINE TYPHUS

In 1920 Hone recognised the endemic form of typhus among wheat workers in South Australia. Since then sporadic cases of this type have been encountered, with a few local outbreaks, the largest of which occurred in Toowoomba in Queensland in 1925. This was associated with a plague of mice, but no causal relation was ever established. Immunologically this endemic form is of the murine variety, which is due, as Burnet has said, to "man's accidental intrusion into that almost equilibrated biological system, rickettsia, rat-flea and rat". There is some evidence that smouldering foci may exist in urban areas on or near the coast. The number of endemic cases occurring in Australia yearly fluctuates, but is not inconsiderable. In 1939 there were 210 cases, in 1942 the number fell to 63, but in 1944 rose to 238. During the war murine typhus was not of any special importance in Australia, though cases were recognised in widely different areas, such as the central western coastal areas in Western Australia, where its features have been not unfamiliar, on the Atherton Tableland in North Queensland and in Port Moresby in New Guinea. In a few instances infections seemed to be related to working in partly demolished buildings. No eschar was seen on the skin, and the serum contained agglutinins for the Proteus type *OX* 19. No epidemiological problem of military importance was involved in these sporadic infections, nor was there at any time on any Pacific front a risk of louse-transmitted typhus. The possibility of an outbreak was considered during the Western Desert campaign, owing to the aggregation of large numbers of Italian prisoners of war under conditions of defective hygiene, but fortunately nothing of the kind happened. While the 9th Australian Division was still in Palestine and Egypt at the close of 1942, the potential dangers of epidemic typhus fever were set forth in instructions promulgated by the British Headquarters in Middle East. In these the precautions to be taken in the handling of civilian labour were detailed.

MITE-BORNE TYPHUS

Mite-borne or scrub typhus was, however, a serious problem especially during the earlier phases of the Pacific Island campaigns. This problem did not so much concern the total depredations of the disease on the forces, which were never comparable with those of malaria or dysentery, but rather the severity of the disease itself. The mortality varied under different conditions; the overall death rate was 9 per cent in the Services. Not only did scrub typhus impose an increased burden on medical and nursing resources, but it also was feared by the soldiers themselves more than any other disease. The need for early evacuation to hospital and for long convalescence created further strain on medical arrangements.

Clinical observations during the war began during the first New Guinea campaign. The symptomatology was already familiar to Australian physicians, following the studies of Unwin, Mathew, Heaslip and others in North Queensland, and Gunther in New Guinea. Scrub typhus had been proved to be one entity in a loosely named group of fevers called "coastal fevers" in Queensland, and the disease seen there was believed to be identical with the form known in Malaya and the *tsutsugamushi* fever of Japan.

It was known that mite-borne typhus varied considerably in severity in different localities. This fact had made studies of epidemiology more difficult, though it was realised that the disease had a wider incidence than was apparent. When Australian troops attacked the Japanese advancing over the Owen Stanley Ranges towards Moresby typhus soon appeared among them, and one of the most obvious features of this outbreak was its severity. This was greater than was expected, though it was soon realised that the extraordinarily severe strains of fighting in this difficult country, without proper rest and with monotonous and often insufficient food, would decrease resistance. To this imponderable factor of personal resistance perhaps must be added other biological factors, such as the greater toxicity resulting from passage through human bodies. Age was also most important. In one series the mortality was doubled in men over thirty; certainly the prognosis was more serious in patients over thirty-five. Not only did hardship thin and weaken the men, but they suffered too from dysentery, and later from malaria. During one phase of the Gona-Sanananda action the mortality from typhus rose to 25 per cent in a series of 150 men. In the whole of this 1942-43 phase in New Guinea 9.7 per cent died of 626 men admitted to the 2/9th Australian General Hospital, whereas the overall mortality in New Guinea during this period was below 7 per cent. In Burma and Thailand the men of the 8th Division also were attacked by scrub typhus. Here conditions of malnutrition and intercurrent disease could hardly have been worse; but the severity of the disease does not seem to have been as great on the whole as might have been expected. The question of local factors in determining incidence and severity may be left for later discussion.

The mortality rates for the Pacific areas were as follows:

Year	Total Cases	Total Deaths	Percentage of Deaths to incidence
1942	186	40	21.50
1943	1,870	112	5.98
1944	602	78	12.95
1945	181	27	14.91
Total	2,839	257	9.05

The disparities in these death rates are hard to explain: the high rate in 1942 is probably due in part to the nature of the campaign and also may be a fallacy of a small series.

A statistical analysis was made by Captain H. V. Napier for the period 11.12.43 to 8.12.44 when troops were engaged in a number of areas. This showed the following figures:

	Moresby	Buna Dobadura Oro Bay	Lae Nadzab	Madang	Finsch-hafen	Ramu	Total
Mortality rate per cent	10	8.3	12.1	18.3	6.7	6.1	8.3
Standard deviation	5.5	2.7	4.0	5.0	1.8	1.5	1.0

The total number of cases was 715. The dissected death rates for the first and second halves of 1944 showed a curious disparity, the first being 6.8 per cent (S.D. 1.0 per cent) and the second 17.0 per cent (S.D. 3.8 per cent).

It will be seen that scrub typhus can produce a high mortality rate in restricted series, and in restricted areas, but the consolidated rate for the island campaigns did not exceed 9 per cent of the incidence.

THE CLINICAL PICTURE

The military problems set by the disease were the provision of hospital care for men likely to be seriously ill, and the investigation of the possibilities of its prevention. During the rapid expansion of the 2/9th Australian General Hospital in the upper Moresby area made necessary by the first New Guinea campaign, opportunities were taken to make careful clinical studies of the disease as seen in these areas, and further observations were made later in other combat areas in the South-West Pacific and the Netherlands East Indies, and in the training area in the Atherton Tableland in North Queensland. In February 1943 a medical technical instruction was issued describing the chief characters of the disease, its diagnosis and methods of handling. Though the purely clinical features of mite-borne typhus are discussed at this stage, it must be realised that studies on its epidemiological features were proceeding simultaneously, and that important work on its prevention also began early in 1943. Williams, Sinclair and Jackson in an account of 626 cases studied in the

2/9th Australian General Hospital in 1942-1943 recognised four grades of clinical severity, ambulatory, mild, moderate and fatal. Not many ambulatory infections were observed, though later immunological studies in Australia of groups of men exposed to infection indicated that these may occur rather more frequently than can easily be proved. Despite the severity of the disease in some areas, even here numbers of mild cases were seen in which the characteristic diagnostic features were present. Complications and involvement of special systems were absent, and the illness was over within a few weeks. At the other extreme were the rapidly fatal infections, in which at the end of the second week death appeared imminent, and after the onset of circulatory failure coma was the herald of the end. Among the moderately severe infections were classed those in which recovery was achieved in some six weeks, allowing return to ordinary full military work in three months from the time of onset. To these types must be added another variant which is not uncommon among all kinds of typhus fever, the type which affects the desperately ill patient who contrary to expectation recovers. In few diseases are there seen such striking examples of the return of dangerously ill people from the shadow of death. This phenomenon when it is seen is all the more striking because of the rapid lysis which often terminates the fever in this disease.

A moderately severe course usually opened with a fever of rapid onset with shivering, malaise, headache, a little dry cough and frequency of micturition. The headache was characteristically persistent and severe. Not infrequently the initial diagnosis was malaria or a short-term fever, and until the disease pattern was recognised, the correct diagnosis was often made by failure of the symptoms to respond to anti-malarial treatment. Signs of toxaemia increased, and cough became more severe in the next few days, with constant fever, the tongue was heavily coated and the eyes were suffused. A small "eschar" was found on search in about 60 per cent of cases. Some stiffness of the neck usually appeared, and the mental state showed some deterioration, owing to increasing apathy. A rash was common towards the end of the first week, and superficial adenitis was often apparent. The temperature was usually remittent, rising in peaks to 103° and over. The pulse rate was increased, but usually not in proportion to the temperature. The cerebro-spinal fluid pressure was raised. In the second week of this continued fever cough often produced frothy blood-stained sputum. The eschar showed definite ulceration and the rash faded, and in severe infections a degree of subcutaneous oedema appeared in dependent parts. Few if any signs were found in the chest, though the respiratory rate was increased. The blood pressure fell, the systolic pressure often being below 100 mm. Hg. Apathy increased, and was often associated with an unhappy querulousness, yielding often to delirium and disordered dreams. In most infections of any degree of severity some anxiety was felt at the end of the second week. Nursing was a constant and arduous task, especially if incontinence added to its difficulties. Signs of renal involvement were not unusual, with the appearance of protein and casts in the urine, and a moderate rise to 50 or 60 or more milligrammes of

urea in 100 c.cm. of blood. The diagnosis could now be confirmed by the finding of a raised and rising titre of agglutination for *Proteus OXK*. Signs of involvement of the nervous system often included nerve deafness, and loss of deep reflexes.

During the third week, when the illness was most intense, improvement began in favourable circumstances, sweating increased, and the temperature fell by a rather rapid lysis. Clinical improvement often anticipated the subsidence of fever by a brief period, 12 to 24 hours, and recovery was thereafter usually uninterrupted. Residual weakness was frequently extreme. After a severe attack the wasting and incapacity for exertion were considerable, and for two or three weeks the patient could do little. Glandular enlargement often persisted for some time. Convalescence occupied at least as much time as the total period of hospital illness, and sometimes longer. Comparison of the signs and symptoms of diagnostic importance showed that these varied in incidence and nature in different outbreaks, as might be expected. Thus Williams, Sinclair and Jackson found an eschar in almost 60 per cent of their patients, but Sangster and Kay only in 41 per cent, while in other small series in New Guinea and Australia coming from localised areas the percentage was only 33. Severe headaches were practically invariable. A rash was seen in about two-fifths of cases; in the 2/9th Hospital series the percentage was 65. Fever was constantly high in most instances, sometimes less high in fatal cases: remission was invariable and was sometimes extreme, swings of 7 degrees being sometimes seen. The duration of the fever was usually about three weeks, but sometimes as long as nearly six weeks.

The various anatomical systems showed important and often characteristic signs.

Skin. The eschar was often difficult to find, especially as the patient was unaware of its presence, since it was painless, though the drainage glands were usually tender. It was rounded or oval, some 2 to 3 millimetres across, with a red areola some 3 to 4 millimetres wide. In the centre was a black slough which separated during or after the second week, leaving an ulcer. The areola was highly characteristic as it was not found to persist in other small non-specific lesions. Healing of the eschar was slow and usually not completed for over three weeks, leaving a small, pitted scar. Occasionally multiple eschars were seen. The site was nearly always on the trunk or proximal parts of the limbs, an indication of the larval mite's preference for skin covered by clothing. It also preferred skin folds, though the eschar was sometimes on flat, open surfaces. The rash was maculo-papular in type, usually appearing on the fifth to the eighth day on the front and back of the chest and the front of the abdomen. It was not infrequently spread over face, limbs, palms and soles within two days of its appearance. Probably it was present in more patients than recorded, it sometimes faded quickly, and mildly ill patients might not have been admitted to hospital. Desquamation was not observed.

Lymph glands and Spleen. Enlargement of lymph glands was common, often in parts remote from the eschar: it tended to be persistent. Enlarge-

ment of the spleen was not regarded as a clinical feature of the disease: when present it was probably due to malaria, but as in typhoid fever, a large spleen may not always be felt during life owing to its soft consistency.

Circulatory system. Rapid pulse rate over 120 per minute was usually an ominous sign, especially if associated with falling blood pressure, and a dicrotic quality could often be detected. Alternating pulse was occasionally observed; extra-systoles were unusual except in severe cases. In view of the known occurrence of myocardial cellular infiltration in patients dying of typhus, special attention was directed to the cardiac condition. Soft tick-tack sounds were often noted, and triple rhythm was noted also but no more than in other severe acute fevers. Electro-cardiographic tracings showed no abnormal rhythms. Some delay in intra-cardiac conduction was sometimes observed. Sangster and Kay out of 235 cases noted increase of the *P-R* interval in 20 per cent, exceeding 0.2 second and even reaching 0.3 second. In severely toxic patients a low *T* wave was occasionally seen, and in one instance a low voltage *Q.R.S.* complex. These signs disappeared during convalescence in surviving patients. Tachycardia at rest was sometimes slow to subside, and continued well into convalescence in a few patients who had been severely ill. The systolic blood pressure fell to a variable extent on rare occasions as low as 80 millimetres of mercury. Signs of peripheral circulatory failure were concomitants of severe infections, as shown by cyanosis and patchy pallor, cold extremities, and oedema. No elevation of venous pressure was found in a series of fifteen patients. Peripheral oedema was not at all uncommon in the severely ill: it was usually limited to the ankles and sacrum, but was occasionally more extensive. Peripheral failure of the circulation, as in other severe fevers, was a common terminal event.

Venous thrombosis was an occasional event, affecting large veins like the femoral: in view of the selective action of *rickettsiae* on endothelium it might have been expected more often. Pulmonary infarction occurred clinically in a small number of patients, with the usual signs; it was not necessarily of very serious import, but was found *post mortem* not infrequently. It may be that some of the pulmonary signs were due to multiple small thrombotic lesions in the lungs. A few cerebral accidents, probably thrombotic, were also observed. The blood commonly showed a mild anaemia, but the haemoglobin content seldom fell below 10 grammes per 100 c.cm.: the anaemia was due mostly to malaria. Series of white cell counts revealed very little change in the total numbers. Individual changes were found, but not sufficient or consistent enough to be of diagnostic value. In the 2/9th Hospital series a rise in the lymphocyte count was found to have some significance. This rise occurred typically just before clinical improvement began. A lymphocyte count of say, 5,000 per cubic millimetre was usually a good prognostic sign. Williams, Sinclair and Jackson regarded it as part of the lymphocytic response of the disease, as seen in the adenitis and the round celled infiltration which is a feature of the pathological pattern. They contrasted with this the lack of neutro-

phile response except in the presence of some secondary bacterial invasion. Thus a pneumonic complication of bacterial origin would give rise to a neutrophile leucocytosis which was regarded as an indication for the use of sulphonamides. A low lymphocyte count in typhus appears to resemble a low neutrophile count in bacterial diseases; it is of evil omen. Studies of blood chemistry showed that the protein, calcium and sodium chloride values were usually lowered. The blood protein content was reduced in the more seriously ill patients and reached its lowest level about the end of the second week. McGovern found that the average in 100 cases at this time was 5.3 grammes per 100 millilitres, and the lowest figure recorded 4 grammes. A rise in blood protein content usually coincided with a rise in the blood agglutinin levels. In some severe and fatal infections the rise in protein content did not occur. A fall in serum calcium content took place, too, but did not parallel the protein content. The average of a series of 58 cases was 8.1 milligrammes per 100 millilitres, taking the figure at the time when the calcium was expected to be lowest. Investigation of other infections seemed to show in the small numbers that could be studied in the field that scrub typhus caused a greater reduction of the levels of protein and calcium than other fevers. The sodium chloride level was also found to be lowered about the end of the second week in severe attacks. Its level was little affected by extra salt given by mouth or intravenous injection.

The question of affection of heart and circulation is important owing to the wide interest it aroused: it will be discussed in connection with treatment.

Respiratory system. Respiratory symptoms were almost universal in scrub typhus. Cough occurred early, more frequently than in typhoid fever, and at this stage bronchitic signs were often discovered on examining the chest. By the end of the first week nearly all severely ill patients showed these signs. When serious illness persisted the signs in the chest also persisted, and loss of resonance, diminished breath sounds and crepitations were frequently noted. Small effusions of fluid were sometimes found, also evidence of consolidation. The development of these conditions increased circulatory embarrassment, and about this time increased respiratory rate and cyanosis were often found. Broncho-pneumonia was diagnosed in over 10 per cent with scattered consolidation, blowing breathing and moist accompaniments. Lobar pneumonia was unusual. A complicating pyogenic pneumonia was not common; 3 per cent of the 2/9th Hospital series were thought to be so affected.

Kidneys. No serious renal complications were observed. Albuminuria and cylinduria were seldom seen except in severe infections in which too the level of urea in the blood was sometimes raised. Urobilin was always present in the urine during the febrile period, but no other clinical signs associated with liver disturbance were seen, such as enlargement or jaundice.

An interesting feature pointed out in a series studied on the mainland was the occurrence of diuresis immediately before the lysis of the fever.

This took place coincidentally with the beginnings of clinical improvement, and was an accurate forerunner of the subsidence of the attack.

Gastro-intestinal tract. Appetite was naturally in abeyance, but vomiting was seldom troublesome. A curious symptom present in a few ill patients was dysphagia. Diarrhoea was frequent in the early stages. As dysentery was a common ailment of the troops in many areas, the cause of this was not always apparent, but investigation did not suggest that a true dysentery was present.

Nervous System. Symptoms referable to the nervous system were universally present in all but the mildest infections. It was thought that even in the first few days the mental state of some patients was not normal, being unduly euphoric. Towards the end of the first week the rather peevish apathy which characterised most patients at that stage gave way to depression or to a confusional state. Delusions and hallucinations were common. Seriously ill patients often were stuporose and inert, the chief problem of nursing being the administration of food, but others were constantly restless and trying to get out of bed. Coma was always an ominous sign. Recovery from these disorders was complete once convalescence was established. An increase of cerebro-spinal fluid pressure was commonly associated with headache and neck stiffness, which were relieved by lumbar puncture. The pressure was raised to over 150-160 millimetres in a small proportion, and in few instances cells and protein content were also moderately increased. The chloride content was decreased below 700 milligrammes in more than half a series examined, which included some of the more severe infections. These abnormalities were more commonly found in patients in whom other neurological changes were present.

Affection of the 8th cranial nerve was frequently seen, in about a sixth of the series. It usually took the form of nerve deafness, and rarely tinnitus; it was variable in degree and mostly bilateral. Recovery was practically always complete and rapid during convalescence, though in one instance the deafness was complete and permanent. Reflex changes were very common; both deep and superficial reflexes were temporarily in abeyance during florid illness. Peripheral loss of motor and of sensory function were both observed in a few patients. The latter appeared to be of the nature of a peripheral neuritis affecting cutaneous sensory nerves of the limbs such as the ulnar nerve. Pareses of muscles were more difficult to evaluate, since a number of localised peripheral palsies were seen in troops, especially at the time when the first large series was studied. Whether these were always due to typhus or were due to neuronitis possibly of virus cause is uncertain. Scapulo-humeral and *serratus magnus* paralyses were seen among others: instances of these and other types, such as peroneal were observed among men who had not had typhus. It seems likely that some peripheral palsies in stuporose patients with toneless muscles were due to pressure.

Muscular tremor, sometimes of the Parkinsonian type, was prominent during the illness in a few patients. The condition was apparently of central origin and did not persist. Muscular fibrillation and wasting over

a wide area of the body were observed in convalescence in a few patients. This state was slow in resolving. In several instances vascular accidents occurred in the cerebral and retinal vessels. The former caused hemiparetic signs with some disturbances of higher cerebral function. In one case it is possible that subtertian malaria played a part. Retinal changes following thrombosis were observed in several patients. In two these were bilateral: one patient died, the other recovered with serious loss of both sight and hearing.

PROGNOSIS

The prognosis has already been touched upon. Inanition, exhaustion, and intercurrent infections were undoubtedly potent adverse influences. The speed with which men came under skilled care was most important. It was soon realised that in choosing medical casualties for prompt evacuation men with scrub typhus had high priority. Air evacuation was much preferable to longer and more exhausting methods. Certain other pointers were noticed. Age has been mentioned: 14 per cent of 101 men over thirty died, but only 7 per cent of 323 men under thirty. The early onset of prostration, mental deterioration, or conspicuous symptoms and signs involving any of the important systems of the body were also bad prognostic signs. The incubation period also appeared to be a certain index of the probable severity of an attack if it was known. Usually it was not known. Andrew reported a study of 21 men who contracted scrub typhus in Queensland after bivouacking in a heavily infected area. In all the most severe cases a period of 12 days was found, whereas all those infections of 15 days incubation and over were mild or subclinical. The suggestion was made that the prognosis of typhus arising from certain areas was worse than from others, but this is difficult to substantiate owing to many other factors, such as conditions of combat, nutrition, intercurrent disease and facilities for early adequate treatment. The serological diagnosis of scrub typhus was helpful in a general way, but, as it was not possible earlier than the second week of the fever, reliance was placed rather on the clinical pattern than upon the result of this test.

DIAGNOSIS

It was known that mite-borne typhus was serologically distinct from the other endemic and epidemic forms and that agglutinins appeared in the blood for *B. Proteus OXK* (Kingsbury strain), but not for the other strains of Proteus. The titre of agglutination rose slowly, and seldom reached a level necessary for positive diagnosis before the tenth day. Therefore it was found convenient to carry out the test at the end of the first and second weeks. A further test in the third or fourth week showed the peak level of agglutinins, but if the previous tests had shown a rising tide of agglutination and if the level attained about the fourteenth day was 1 in 120 or higher, a positive result was recorded. The Technical Instruction No. 41 issued by the army medical services laid down a titre of 1 in 80 as supporting evidence, and a titre of 1 in 160 as diagnostic. The

method of using white mice for intraperitoneal incubation of the blood of a suspected subject was also described. This afforded opportunity for the demonstration of *rickettsiae* in these experimental animals, but in field work this was not practicable. The agglutination tests were carried out in a standard way, with the use of a dropping technique and serial dilutions of serum, which had been preheated to 56°C. "O" agglutinins only were assessed for the purposes of the test, the naked eye being used. Jackson found that in tests from 582 cases the maximum level of agglutination was reached about the 19th or 20th day, and a demonstrable rise did not occur till the 8th day. Therefore the 7th day test showed the pre-infection level, and by the 14th a reliable estimate of the post-infection level could be gained. Very high maximum levels were sometimes reached: in one instance a titre of 1 in 50,000 was recorded. Considerable variation in antibody production was observed, but only in a very small number of patients was no rise found. Within its limitations the test was found very reliable; false positives were practically unknown provided a safe upper limit of agglutination was adopted. Study of this test by a number of pathologists failed to reveal any evidence of multiple rickettsial strains as indicated by different types of response in the agglutinin content of the blood serum. Nor could any support be given to the opinions of those who thought that a low titre connoted low resistance and therefore presaged a bad prognosis. A bedside method was devised by Professor H. K. Ward, of the University of Sydney, in which diluted serum was added to concentrated proteus suspension on a clean slide and mixed by rocking. Agglutination was easy to observe with the unaided eye, but it was found that though the upper and lower limits of agglutination titres were simply recognised, the middle zone was difficult to interpret. As a quick method in the field it had some value, though a negative result was inconclusive. J. de Vidas, surveying experience in the R.A.A.F. in New Guinea, found that agglutinins usually disappeared from the blood within two months. He also found that a slide agglutination test in which dried whole blood and a suspension of proteus were used, gave reliable results for specimens with a significant titre. The laboratory method had the usual troubles incidental to agglutination tests, such as the difficulty of obtaining smooth non-motile strains of proteus. P. de Burgh reported observations on the use of a polysaccharide of *Proteus OXK* in diagnosis. This method is based on the presence of a minor antigen in both *Proteus* and the *Rickettsia orientalis* which can be extracted in polysaccharide-like substance. By precipitation and extraction this substance was prepared and added to a suspension of collodion particles; this antigen gave a ring precipitation in a test with the serum of patients suffering from scrub typhus. This method, though not suitable for field work, proved to be accurate and is of immunological interest.

PATHOLOGY

The pathological changes found *post mortem* were fairly constant. A slight to moderate amount of fluid was usually found in the serous sacs. The heart was usually pale and flabby; sub-pericardial or sub-endocardial

petechiae were sometimes found in the ventricular muscle. Microscopically the most striking changes was infiltration by plasma cells, lymphocytes and monocytes, chiefly in the sub-endocardial and peri-vascular tissues, but to some extent also between muscle fibres. This small cell infiltration was also sometimes seen in the intima of some of the larger blood vessels, and in their adventitia. Like changes were observed more or less in most of the organs. In the brain round-cell infiltration was prominent, but perivascular cuffing was unusual. Meningeal infiltration was seen in a few instances, and occasionally thrombosis of small cerebral vessels. Small haemorrhages were sometimes seen in the brain. In general the changes of a meningo-encephalitis could be produced by this disease. The alveoli of the lungs had thickened walls with dilated capillaries; and mononuclear cells were present in the alveolar walls and interstitial tissues and also the lumina. Varying degrees of consolidation were produced, affecting some or all of a lobe. Haemorrhagic infarcts were sometimes present. The spleen was always enlarged, although this might not have been detected during life. It was soft and friable, most of the normal structure being obscured and the usual lymphoid tissue practically absent. The most striking features of the tissue changes in scrub typhus were an intense infiltration of the organs with mononuclear cells of various types and a great proliferation of reticulo-endothelial tissues. Those features which had the greatest bearing on the attitude of the clinician to treatment were the involvement of the heart, the lungs and the nervous system. In the heart there were undoubtedly signs of myocarditis, but during life the changes found in the circulatory system were no different from those found during other severe continued fevers. There was no warrant for supposing, on the strength of the histological picture seen in fatal cases, that typhus was selectively a cause of permanent organic damage of the heart. The changes in the lungs showed that while broncho-pneumonic complications occurred these were seldom of the usual bacterial kind; specific treatment could be expected to be of value only if specific bacterial invasion had occurred. The nervous phenomena indicated the widespread nature of the disease, and supported the belief that extensive involvement of the nervous system usually occurred in the more severe attacks.

These clinical and pathological studies expanded and diffused the knowledge of scrub typhus already existing in Australia.

EPIDEMIOLOGY

Epidemiological knowledge of scrub typhus was built up from observations on outbreaks of the disease, particularly with reference to locality, environmental conditions and distribution of vectors. The use of substances repellent or toxic to mites added an important weapon to research, as well as providing a means of prophylaxis. Transmission of the disease by larval mites was understood, and the identity of the mites was reasonably sure, but exact information was needed of the distribution of infected mites in the country where difficult campaigns were being fought. Heaslip's work had given strong evidence that the larva of *Trombicula deliensis* was

the responsible vector in Queensland, and the natural reservoir of infective *rickettsiae* was in native animals such as bush rats and bandicoots. The geographical distribution of these mites in North Queensland corresponded with that of the disease. This distribution was distinctly patchy. Over a period of two years Heaslip reported over 50 cases of scrub typhus originating in 20 different places, widely separated over two hundred miles of coastal districts in North Queensland. Gunther had also studied the disease in New Guinea and produced proof that it was identical in nature with the mite-borne typhus endemic in tropical areas from Malaya to Japan. In Queensland the position was hardly so well defined, for there it seemed likely that several different infections had been included under the general title of "coastal fever". However, there was no doubt that scrub typhus existed there, and it was not material whether "coastal fever" or "Mossman fever" were terms strictly scientific or not. But it was not possible to transfer epidemiological information direct to New Guinea. It had not been possible to make any wide surveys in the extensive forest and jungle areas of Queensland, and though the nature of the problem was clear in 1942, its solution was not so clear. Some uncertainty was felt whether a vector other than the mite was concerned. The discovery of Q fever by Derrick had aroused interest in Australian ticks as vectors, as it seemed likely that *Ixodes* ticks transmitted the *Rickettsia burneti* from native host to cattle, from which *Boophilus* ticks imbibed the virus and excreted it, thus giving opportunity for human beings to acquire it through scratching or inhalation. Q fever was a possible variant of tick-borne typhus, but even if unrelated its method of transmission aroused some reflection. The typhus problem, too, was complicated by the skin irritation known as "scrub itch". This condition had been recognised for a long time as due to multiple bites of mites, such as occurred in many parts of the world. The use of the term "mokka bites" common in New Guinea did not give any entomological enlightenment, as it might refer to irritable and perhaps infected bites due either to mites or to ticks. However, in 1942 it was not generally considered likely that ticks played any part in endemic typhus transmission in Australia or New Guinea, though, as will be seen, the question was raised later, and the problem of prevention correctly centred round the larval mite. There were, however, peculiar inconsistencies. The existence of scrub itch in a locality bore no relation to the incidence of scrub typhus, as the former might abound in areas where typhus was rare. But it was thought curious that the mite caused no apparent irritation to its native animal hosts, and also that scrub itch occurred only in some 30 per cent of patients with mite typhus. The eschar of the latter was usually single and was devoid of pain or irritation.

It was known that there were between 20 to 30 varieties of trombiculid mite in New Guinea, and it was uncertain whether more than one variety could transmit typhus. Further, the life history of these tiny creatures remained obscure. Even study of the larval mites responsible for irritable skin rashes in certain urban districts of Australia where investigations had been made had not shed light on their life cycle. The wide dispersion of

some varieties of mites and of supposed carriers, such as rats, the painlessness of the bite which causes the eschar, and the observed occurrence of typhus in areas where mites were hard to find were other difficulties to be reconciled in explaining the transmission of scrub typhus. There was no likelihood of an epidemic of mite typhus in New Guinea, but it was important to try to control a disease with so high a morbidity. The most fruitful methods appeared to be recognition of heavily infested areas, measures taken to reduce exposures to bites and the discovery of an efficient mite repellent.

At the end of 1942 some advance had been made in these aims. In the study of localities several methods of approach were possible—comparison of the topography of the areas where infection occurred, and the density of infection therein, observation of vectors in relation to outbreaks of the disease, and of animals which might be possible reservoirs.

The need for a suitable area on the Australian mainland in which troops from the islands could be trained and rested led to the selection of the Atherton Tableland in North Queensland. Though this was admirable in point of climate and location, and offered country well adapted to training in jungle warfare, it contained foci of infection by scrub typhus. The number, location and density of these areas were not known, since before the war very few people had moved about this heavily timbered country and made such intimate contacts with it as troops would under training. The possible hazard of typhus on the Atherton Tableland was realised from the beginning, but with the concentration of several divisions there it became evident that close local study of the epidemiology was essential. Thus the epidemiological experience gained during the first and second campaigns in New Guinea and during the training periods in Australia produced valuable information. The patchy distribution of scrub typhus was illustrated in all areas. Further, the foci of disease were sometimes extraordinarily limited. For example, early in 1943 it was observed that of a group of cases occurring at Wau practically all arose on the west side of the airfield and within half a mile of it. By comparison troops working in the jungle were scarcely affected. One company had 15 per cent of its men affected within a little over two weeks of occupying an area by the side of a road where they were working. Numbers of such happenings could be cited. One which attracted some notice was an outbreak which occurred in the 2/31st Battalion training in the Edmonton area. This series, though small, was marked by its severity, and drew attention to the need for taking precautions in the northern parts of Australia.

The need for caution in forming generalisations about the relative dangers of different types of country was illustrated in three outbreaks described by Cook. The first occurred in heavily timbered country in the cool elevation of the Atherton Tableland. Scrub itch, due to *Trombicula hirsti,* was troublesome here, particularly in one divisional area. A sudden outbreak of 45 cases of typhus in 4 weeks affected only platoons of companies patrolling one delimited locality. The second occurred near Palm Beach, north of Cairns, 28 out of 37 men affected in a brigade group

belonging to those companies of one battalion which had camped in one particular spot. The third instance was near Dumpu in the Ramu Valley, near the northern coast of New Guinea. Units camped near streams closely fringed by jungle were attacked by typhus, others in kunai grass or in the foothills except in certain localities escaped. These are good examples of the intensity of infection within limited foci, though it should be pointed out that the danger of such foci waxed and waned. Cook thought that an important common factor was the presence of streams emerging from close vegetation, such as strips of jungle, and suggested that carrier animals and insect vectors made contact in these areas. In view of some inconsistencies in the epidemiology he further suggested that alternative vectors might be worth considering, such as a larval ixodid tick. However, such suggestions did not affect the position of larval *trombiculid* mites as the vectors of this distinctive variety of typhus.

The generalisations relating to the types of country were also fallacious, as later work showed. Likewise, observations of scrub itch were illusory, as there was no essential connection between this and scrub typhus. Much of the information on which beliefs were based before the war, was based on the incidence of scrub itch, and had a popular rather than a scientific background. Mites were supposed to abound in rotting vegetation, particularly in dense rain forests. R. N. McCulloch from investigations on the Atherton Tableland concluded that these generalisations were incorrect: mites were rarely found either in the extremes of dense scrub or cleared grass country, or in decaying leaves or timber. More typically their habitat was in narrow belts along the edge of scrub, or clearings in the scrub with little or no grass, or in the shade of trees where grass was sparse. Though it was thought that mites could be brushed off bushes by the clothing of passers by, they were found chiefly to reside in the soil and rarely to climb higher than a few inches from the ground. Mites were proved to reach the trunk by travelling up from the feet. The contrast between the irritation caused by the mites responsible for scrub itch and the completely unaffected skin of the animals which acted as their normal hosts was striking. This was probably an indication that man is not a natural host for the mite.

Mites were collected in various areas and it was found that many unnamed species existed. Womersley and Heaslip previously described twenty-four species in New Guinea alone and these have been added to considerably. This work proved that a light population of mites might exist in an area known to be bad for typhus, but in some such areas mites were recognised that were proved later to be vectors, such as *T. fletcheri* and *T. walchi.* Some of the apparent inconsistencies could thus be explained. Further study showed that the habitat of a given species in Australia was often different in New Guinea. In most of the surveyed country in New Guinea no forecast could be made as to where mites would probably be most numerous. In New Guinea McCulloch found some species only in grass, others in both grass and jungle, and noted no clearly marked belts along the edges of the scrub. By 1943 much more

was known of the factors governing the incidence of scrub itch and of typhus, but little help could be gained from this knowledge in selecting camp sites. Trained men could detect heavy mite concentrations in a new locality, but only in selecting settled areas would this be of value; it was not practicable with a fighting force on the move. Cutting and burning kunai grass round tents or huts reduced the number of mites, but never abolished them, even for a short time. There was little risk to men marching through mite-infested country, but if the men sat, lay down or stood still, the mites were able to establish themselves on their new hosts. There was not much opportunity for work on the relation between mite-borne typhus and animals, birds and reptiles. Heaslip in Queensland and others during the war in New Guinea had found evidence of the native mammals acting as carriers. Southcott also made some observations on birds, since the distribution of *tsutsugamushi* fever through the eastern tropical zones is consistent with bird migration. Only very limited work was possible, but one bird, the pied currawong (*Streptera graculina*) was found to have a high titre of agglutination to *Proteus OXK*. Larval trombiculid mites have been found on birds both in North Queensland and New Guinea. They also infest snakes and lizards, but no opportunities offered for testing the blood of reptiles for agglutinins. One curious observation was reported in 1945 by the A.D.M.S. of the 3rd Division at Torokina that mites had been observed to drop from mosquitoes on to the skin. Even if confirmed this could not lessen the importance of contact with the earth, the natural habitat of *trombiculae,* in the chain of infection.

The species of *Trombiculae* were studied both as to their habits and their capacity to carry typhus. Though most of the eschars were found in the vicinity of the trunk rather than on the distal parts of the limbs, some varieties such as *Schöngastia* habitually bit around the ankles. The capacity of mites to detect new stationary objects introduced into their environment was hard to explain, especially as such local curiosity was only transitory. Most of the identification of species was done by Womersley in Adelaide; he considered that type *walchi* and type *fletcheri* were included in the species *T. deliensis* and *T. akamushi.* They were found in nearly all areas in New Guinea and were established as vectors by the United States Typhus Commission. *Schöngastia* was a common cause of itch in New Guinea, inhabiting jungle and kunai grass.

The work of the American Typhus Research Commission established the identity of scrub typhus in New Guinea with the *tsutsugamushi* fever found elsewhere. The *Rickettsia orientalis* was isolated in a number of strains from ground-up mites, the material being injected into experimental animals. Identification was made by local injection of the anterior chamber of the eye of rabbits. In this way similarity was demonstrated to the strains known elsewhere in the world. Identical mites have been shown to inhabit limited ground areas and to prefer certain body sites in animals, but no means of proving beforehand the capacity of mites in a given area to produce typhus has been found. *Rattus concolor* was proved to act as a carrier.

Work on the *Rickettsia orientalis* was also pursued in Australia. Fielding described a modification of Breinl's method of staining *Rickettsia*. J. L. O'Connor in investigating methods of assessing the potency of suspensions of *Rickettsia,* showed that the haemagglutination phenomenon described by Hirst in influenza virus was also demonstrable in the *Rickettsia orientalis.*

PREVENTIVE MEASURES

While these observations were being made intensive work was carried out on repellents. At the end of 1942 favourable reports were received from U.S.A. on the value of dimethyl phthalate; it was found that when applied to clothing it gave five days' protection under field conditions. This substance had just been selected as a mosquito repellent for use by Australian troops, and contemporaneous work had been done in Australia on its repellent properties. Field research was carried out by a mobile entomological section under McCulloch, and dimethyl and dibutyl phthalate were tested, first in areas in Australia where harmless mites abounded, and later in areas where scrub typhus was endemic, including Queensland, New Guinea and Borneo. Volunteers tested the behaviour of mites in thickly infested areas wearing clothing treated and untreated with repellent. In typhus areas men were selected who had had scrub typhus six months before, and were presumably relatively immune. It was at once apparent that dimethyl phthalate gave remarkable protection against mites: indeed apparent inconsistencies in early results were found to be due to traces of the repellent persisting in the clothing after washing. Treated bands round the limbs were less effective than complete treatment of the clothes. One millilitre per square foot of shirt and trousers, and 1.25 per square foot for socks protected men sitting or lying among mites for at least two days. Rubbing the drug lightly into the material was sufficient to impregnate it effectively. Trial of dibutyl phthalate showed that this was superior to the dimethyl preparation, particularly in its power to withstand washing of clothes, though the latter was more rapid in action at first. Even after being soaked and agitated vigorously in cold water twice in five minutes, treated clothing continued to give protection for eight days. As dimethyl phthalate was then on issue as a mosquito repellent and supplies might be insufficient for a dual purpose, the dibutyl phthalate was preferred. Further, the troops feared malaria much less than typhus, and it was thought that issues of dimethyl phthalate designed for anti-malarial use might be extravagantly used for scrub typhus. As malaria was the much greater military risk this might have been distinctly detrimental to the forces. In 1943 methanol was difficult to obtain in Australia, but there was no shortage of butanol, and therefore adequate supplies of dibutyl phthalate were more likely to be maintained.

In 1943 DDT was on experimental trial, and this substance was assayed as a mite repellent at Dobadura, which was known to be infested with mites and a centre for scrub typhus. Two Australian hospitals were then setting up in a kunai flat ringed by jungle. Volunteers from one of these units offered to perform ordinary duties, clearing grass and scrub from

the area and, in addition, deliberately exposed themselves to mites by sitting or lying about for defined periods. The results of these field tests showed that DDT was inferior to both dimethyl and dibutyl phthalate, while the last mentioned was much superior to the other test substances, particularly in its resistance to washing of impregnated clothing. These experiments were continued only long enough to yield trustworthy results, owing to the risks involved. Methods were then evolved for testing the toxicity to mites of cloth treated with the test substances. The investigators collected mites for these tests by standing still till mites began to run over their boots, when they lifted them with a camel hair brush on to the test cloth. Where mites were abundant a sufficient number would soon collect on any inert object placed on the ground. Mites have surprising mobility for such tiny creatures, some species covering an inch in three or four seconds. Their "stopping time" was observed on treated cloth, and thus a standard could be applied. "Mite watching squads" of men wearing treated clothing were provided by A.A.M.C. units; they worked either with magnifying spectacles, or unaided eyesight. Mechanical means were also used to confine the mites within treated cloth, counts of those stopped being made after a selected interval. The species of the mites was determined by subsequent examination. Many of these tests were carried out at Atherton. Care was taken to control the longevity and activity of mites under varying conditions of climate and temperature. Cloth tests enabled further observations to be made on methods of washing. It was found that little adverse effect was caused by any method of washing or laundering, and as a practical outcome it was established that treatment of clothing with one ounce of dibutyl phthalate per set was sufficient to retain the power of protection for at least a fortnight as breakdown occurred only between the tenth and sixteenth wash. Exigencies of military operations prevented complete tests from being made on some aspects of the repellent powers of various other drugs under trial. Some variation was found in the reaction of different species of mites to repellents. Actually dimethyl and dibutyl phthalate were killing agents rather than simple repellents. "Staway" and "612", American mosquito repellents, were tested at the request of Major Ahern of the U.S. forces; both gave protection against mites, but this did not survive washing of fabric.

As a result of this field work a standard method was worked out by which each soldier treated his own clothing by rubbing in repellent by hand. Official instructions were circulated, and each formation and unit was responsible for seeing that they were carried out. The method was simple. The finger tips were dipped in the fluid, and the hands thus smeared rubbed it evenly into each part of each garment. One ounce of fluid allowed about 70 "smears", which would impregnate the clothing sufficiently to withstand 7 washings in cold soapy water or 3 boilings. A parade lasting fifteen minutes a fortnight was found adequate if properly supervised, to supply protection to each man. More elaborate methods were tried but discarded, and, owing to the local conditions in combat areas, bulk treatment of clothing was not found practicable, nor so satis-

factory as individual application. Blankets were treated in field laundries or in the units, by dipping in a 5 per cent emulsion of dibutyl phthalate. One dipping was effective for three months if the blankets were not laundered within that period.

Field experiences as well as copious experiment proved that the phthalates were not irritating to the body surface with the exception of the scrotal skin and the eyes and then only in concentrated form. Dibutyl phthalate after prolonged trial proved not only effective but harmless provided that the undiluted substance itself was kept away from contact with the eye.

Wading in streams was thought at first to lower the concentration of repellent in socks, as for instance in the Ramu Valley where it was often necessary for men to wade knee deep. Investigation showed that patchy application of the repellent was rather responsible; in any case re-treatment of socks each week with a little dimethyl phthalate prevented mites from biting. Blankets were treated also as soon as supplies were sufficient, and in the latter part of 1944 this precaution was generally applied. The blankets were either treated by hand, with 1½ ounces of fluid for each, or dipped in soap emulsions of the fluid at army laundries. From November 1943 the method of individual protection was coming into general use in the field, and thus began a new phase in the epidemiology and prevention of scrub typhus.

Attempts were made in various areas to disinfect localities known to be densely populated with trombiculid larvae. Sulphur, recommended before the war, was not found to be very effective. DDT was also ineffective. In Queensland in October 1944 dinitro-ortho-cresol was tried in a watery spray. The mites could be thinned out but not abolished. Tidying the areas of surplus vegetation, as previously mentioned, was useful in reducing mite populations for a time. Curiously, even the inhabitation of an infected area, though it might produce a wave of scrub itch and typhus, would be followed after some weeks by a decline in these manifestations of mite activity. This did not hold for all heavily infected areas: at Dobadura, for example, a well known stronghold of mites, recurrences of infection occurred, owing apparently to the springing up of freshly introduced mite generations.

Work was also carried out by Lewthwaite, O'Connor and Williams on the production of a prophylactic vaccine from egg cultures of *rickettsiae*. It was hoped that the yolk-sac method might yield organisms of greater antigenetic capacity. Had this method proved fruitful, it might perhaps have supplemented the huge British project of large scale vaccine production by the cotton-rat-lung method. By the latter great quantities of vaccine were prepared: its protective capacity was doubtful, but the end of the war came before the clinical value of this could be assessed. Unfortunately the Australian experiment failed, as satisfactory active immunisation was not produced in animals with the egg vaccine, and satisfactory suspension of *rickettsiae* suitable for immunological work could not be made. Yet another of the many tragedies occurred in connection with research on typhus fever when Miss Dora Lush, a brilliant worker in the Walter and

Eliza Hall Institute in Melbourne, contracted a fatal attack of scrub typhus in the course of her work.

The epidemiological studies so far recounted left many aspects of mite-borne typhus without adequate exploration, but much was done to bring the disease under control. It should be observed that in this infectious disease as in many others constant surveillance and careful organisation are constantly necessary to prevent outbreaks. Quite apart from the occurrence of mite-borne typhus, some useful applications of the knowledge gained of mites, their habits and control may be made to problems of civil life. The "grass itch" troublesome in some suburban areas of Sydney, "ti-tree itch" of South Australia, "black soil itch" of Queensland, and "scrub itch" of Queensland and New Guinea are all due to mites. Gunther has pointed out too that there is a danger of typhus in overgrown and deserted plantations.

THE RESULTS OF PROPHYLAXIS

It was of course important to determine what would be the effects of the use of an effective repellent in reducing the incidence of mite-borne typhus. The figures are of interest for the forces in New Guinea from the end of 1943 onwards. Twelve weekly periods showed the following numbers of cases of scrub typhus reported:

Period ended	Cases reported
31 Dec 1943	859 (peak incidence)
24 Mar 1944	402
16 Jun 1944	102
8 Sep 1944	56
1 Dec 1944	13
23 Feb 1945	21

A proportion of this decline was due perhaps to changes in the strength and distribution of the Australian forces, but in the main reductions of strength affected areas where scrub typhus was very rare. At the same time the incidence of scrub itch in the troops was markedly reduced. This practical proof of the lethal effect of dibutyl phthalate on mites also helped considerably in establishing faith in the method among the soldiers, always an aid even to the best of discipline.

In order to assess accurately the part played by mite-repelling methods in the regional incidence of a disease so irregular in its distribution as scrub typhus, it is necessary to examine military movements in relation to the incidence of typhus, and in addition such local outbreaks as occurred in the later years of the war. The former study concerns more the operational history, where it will be considered in greater detail. Here it is sufficient to say that analysis shows that a low typhus rate was in general found in those formations whose organisation for instruction of troops and distribution of anti-mite fluid was most efficient, and that in proportion as such organisations improved case rates fell. Such comparisons can of

course only be made between formations carrying out similar military tasks in country known to have foci of infection.

Further study of local outbreaks shed light on other features of scrub typhus, such as its incubation period and the importance of correct technique in the use of the mite repellent. Southcott analysed an outbreak which occurred at Bramston Beach in Queensland following a large scale amphibious exercise. Over seventy cases were recorded in this series. Data obtained by Southcott and Andrew established the incubation period for mite-borne typhus at twelve days, which agrees with the figure obtained by Cook at Palm Beach near Cairns. At Bramston Beach 29 out of 34 carefully studied patients were almost certainly infected within a single day, and the incubation period of these fell between 11 and 18 days, with a calculated mean of 13.06 days and a standard deviation of 1.89 days.

In this exercise 3,000 troops were in the vicinity of the beach for 24 to 36 hours: they had previously been in areas where no typhus had been encountered, and their movements during the period of the exercise were known. Enquiry showed that at least three areas were infected, particularly those in outcrops of vegetation near the beach. Thirty of the thirty-four men had used mite repellent, but in most instances an incorrect method was used, such as application with a fly spray. Despite this and faulty supervision it appeared that some protection was afforded. Most of the affected men had eschars in the axillary or inguinal folds, illustrating the need for special protection in these regions: Williams and his colleagues had already found that they were frequent sites of eschars. Other examples may be quoted of outbreaks connected with failure to use the protection given by dibutyl phthalate.

In June and July 1944 increased numbers of attacks were noted along the coast of New Guinea north-west of Alexishafen. One brigade was concerned, and most of the cases came from two battalions. All the men had been in the neighbourhood of one area at the probable time of infection. Investigation showed that anti-mite fluid was available but that its distribution and application were defective until the occurrence of cases of typhus gave point to the need for stricter organisation and supervision, after which the incidence rapidly diminished.

An outbreak also occurred in the Aitape-Wewak sector along the north-western coast of New Guinea. During the second quarter of 1945 sixty-seven cases were reported compared with seventeen from other forward Pacific areas. Investigation showed in part at least that this rise in incidence was related to a failure to follow instructions accurately. Before this the same force had penetrated areas known by American experience to comprise endemic foci, and had not then had men affected.

Bat Island afforded another example of the value of wearing protected clothing. In May 1944 this uninhabited coral atoll, north of Madang, was abandoned to its animal occupants after twenty-nine men out of forty-seven had contracted typhus within less than two months, with five deaths. Four men who slept in hammocks in a hut on the beach were not infected. Two different research parties later visited the island, several of the U.S.A.

Typhus Research Commission, and a R.A.A.F. research unit. Both these parties were engaged in recovering strains of *Rickettsia orientalis* from mites of the *Trombicula deliensis* species on the local rats. Protected clothing was worn and tent floors were sterilised with creosote. In no instance did infection occur.

Experiences in Borneo during and after the landings there reinforced these lessons. Tarakan and British North Borneo were apparently free of infection and there no cases occurred. At Balikpapan over twenty cases were notified, most of the infections being mild. Here again the affected men came chiefly from one brigade and were infected during one period, July 1945. The infested areas were in neglected plantations. The cessation of hostilities put an end to further research here, but it was interesting that investigations up to that point had discovered very few mites.

TREATMENT

Concerning the treatment of mite-borne typhus, there is nothing specific to write, but a great deal of value to do. There are also a number of things not to do. The importance of speedy evacuation of patients suffering from suspected typhus to medical units where good nursing conditions prevail was early emphasised. The swiftness with which severe typhus may prostrate men is often dramatic. It has been well said that the man seriously ill with typhus fever is as ill at the end of the first week as most men severely ill with typhoid fever at the end of the second week or later. The bodily affairs of a man with severe typhus should be confined to the most automatic acts of living; skill and devotion can regulate this, and there is no doubt that the unremitting personal attention of skilled nurses is here of the highest value. Conscientious and well-trained male orderlies undoubtedly produced some of their best medical work in this disease, but experienced nurses are really needed for the worst cases. On occasion extra nurses have been flown to areas where the demands of typhus were heavy. Sedation was essential for many of the patients with disordered mental states. The respiratory complications produced a great deal of controversy. The occurrence of pneumonic consolidations suggested the use of sulphonamides. Pathological and radiological evidence indicated that bronchopneumonia was common, that both infarcts and lobar consolidation occurred, but the latter was not often due to secondary bacterial infection. The question was raised whether the exhibition of a sulphonamide drug was advisable for the pulmonary condition, and whether it might even do harm unless clearly indicated by the co-existence of a specific bacterial infection. The official position about this was made clear in a technical instruction. This pointed out that extensive trials with sulphamerazine (which was the drug of choice, because it was made in Australia) had shown that its use had not lowered the death rate from scrub typhus. There was no evidence that this or any other sulphonamide drug exerted any influence upon *rickettsiae* as a class. Therefore a direction was given that sulphonamides were not to be given to patients with typhus except for bacterial complications due to organisms likely to be combated by these

drugs. The existence of a lobar consolidation with muco-purulent sputum would justify their use, but the early pulmonary congestive changes which are so well known a part of the picture of typhus fever would not. The usual dosage was advised if the drug was used, and the usual precautions to avoid dehydration and to maintain a positive fluid balance were enjoined. It was also advised that the urine be kept alkaline, though it might perhaps be thought unnecessary to follow this direction rigidly.

Another question which was raised early was that of coincident antimalarial treatment. Many, in fact, perhaps most patients received antimalarial drugs in the early stages when diagnosis was in doubt. But even when the diagnosis was beyond question, it was thought by some physicians that it would be wise to preclude the possibility of an attack of malaria during the illness. Was suppressive treatment to continue? And in 1942 when quinine was still being used as a suppressive, did it have any influence on producing the deafness so often seen? The answer to the latter question was emphatically in the negative. With regard to suppression, there was no general rule, but it was usually discontinued for patients with established typhus. In practice malarial paroxysms did not occur at the height of the fever, though sometimes during convalescence. Indeed in a disease with so profound a reactive effect on the reticulo-endothelial system it would seem unlikely that a patient in the middle of typhus would have a malarial attack. Reports were published stating that atebrin and plasmoquine had a beneficial therapeutic effect in typhus. No evidence supporting this statement could be produced from Australian experience.

Both controversy and difficulty arose over the circulatory phenomena in typhus. On the one hand the disease was known to produce in its severest manifestations cellular infiltrations in the substance of the heart. On the other hand substantial falls in blood pressure occurred, and the concentrations of protein, calcium and sodium chloride in the blood were lowered. Too much was made of these. The first finding was after all based on post-mortem investigation, and similar damage occurs in other severe febrile diseases. There was, however, no evidence that degenerative sequels followed in the heart. Electrocardiographic evidence of damage was so slender as to be negligible. The other circulatory phenomena suggested the possibility of therapeutic action. Attempts were made to restore the lowered content of calcium and sodium chloride by intravenous infusions, and to provide additional protein by injection of serum, either convalescent or pooled serum or plasma. Little evidence could be adduced of the value of such procedures. Some physicians believed that small transfusions, given with cautious deliberation, did good. Too much zeal in this direction did no good, and may on occasion have done harm. The difference between a healthy but ensanguined man whose depleted circulation called for parenteral administration of fluid and a sufferer from a highly toxic disease with known predilection for vascular affection could hardly be greater. Great care was enjoined in the treatment of severely ill patients. Even slow drip transfusions may carry risk. All physicians could quote their surprising recoveries: so can all with experi-

ence of typhus. The middle way between undue zeal and undue conservatism is probably right. The best guide is an understanding of the curious pathological features of rickettsial infections.

Attempts were also made to raise the lowered salt levels in the blood by increasing the intake of salt. No definite results could be proved. The preservation of a positive fluid balance by avoidance of undue fluid loss was probably more important.

A definite risk incurred in the care of a patient with scrub typhus was the production of a circulatory and particularly of a cardiac neurosis. It is curious that this has been observed all over the world, no doubt because of the striking circulatory phenomena and the known histological changes seen in fatal cases. Where undue caution has been observed in regulating the patient's activities in the early days of convalescence, for example, where graduated exercise after severe illness has been apportioned too meticulously, the result has been to produce some variant of the effort syndrome. At the same time the length of convalescence must sometimes be considerable, and will depend as much upon the grade of the patient's illness as upon its duration. There has been no reason to doubt the capacity of an average healthy man or woman to make complete recovery after typhus fever. If the patient is allowed and encouraged to find his own level within the limits of ordinary discretion, there is no reason why he should suffer any circulatory disability, least of all one which may easily be iatrogenic in origin.

The nervous complications of typhus likewise may be over emphasised. Where motor weakness is a conspicuous local or general feature a correct form of occupational therapy is early advisable. Too much diversional treatment and non-purposive movements may only do harm. Drugs have not been found of special value. In occasional instances of muscular weakness prostigmin has been found to be of temporary value. Thiamin has been tried for localised palsies or myasthenic states, without convincing results. Para-aminobenzoic acid has been found of value experimentally, and favourable reports have been made of its use in severe typhus, especially in spotted fever and the epidemic variety. Good results are also recorded from its use in scrub typhus. High dosage was employed so as to maintain high blood levels, up to 30 to 60 milligrammes per 100 millilitres. Australian experiences are limited; it was thought that some benefit might have accrued to the patients to whom it was given, but no parallel series were studied.

TICK-BORNE TYPHUS

Before leaving the subject of epidemiology the work done on tick-borne typhus should be described. Rickettsial disease has been of great importance during this war, as it has in every war, and all knowledge of its nature and transmission is of value. The possibility that tick typhus might be the cause of a relatively mild short-term fever was raised during the siege of Tobruk. This is described in greater detail in Volume II. The

serological investigations of Major G. V. Rudd at the 2/4th A.G.H. failed to give any convincing proof of its existence there. Andrew, Bonnin and Williams described a series of twelve patients suffering from tick typhus all treated in Australian military hospitals on the Atherton Tableland. The importance of ticks as vectors of Q fever and possibly of members of the general groups of fevers known as "coastal" or "Mossman" fevers has been pointed out above. Tick-borne typhus had not been previously described in Australia, though widely distributed through the world. The 2,000 feet high tableland where these infections were recognised is clothed by light timber interspersed with belts of densely growing hardwood forests with thick undergrowth. There is a thick population of native marsupials and rodents which are infested with ectoparasites, mites and ticks. The housing and training of large bodies of troops have thrown into relief instances of disease that otherwise might pass unnoticed among the small bands of timber workers who alone have moved about these areas in the past. The general clinical features of the disease were similar to those of mild mite typhus. The onset was rapid, malaise and headache were intense, an eschar was usually found, the regional glands were enlarged and slightly tender. Other glands were often painlessly enlarged. Continuous or remittent fever yielded to lysis after a brief illness. The febrile period averaged a little over a week. A maculo-papular rash occurred in almost every instance. Mildness was a conspicuous feature of the illness. *Rickettsiae* were demonstrated in the blood of two patients by animal inoculation. White mice were used for these experiments specially prepared by being kept on a diet deficient in vitamins. Inclusion bodies resembling *R. Mooseri* were found in the mice in serous exudates, which when inoculated into the peritoneal cavity of guinea pigs caused fever and scrotal reaction. Intra-cellular but not intra-nuclear *rickettsiae* were found in the tunical exudates. Further work on these strains was carried out at the Walter and Eliza Hall Institute in Melbourne. In the differential diagnosis the occurrence of adenopathy and an eschar help to distinguish the condition from murine typhus, while the consistent mildness of the attacks and freedom from complications mark them out from scrub typhus. No joint involvement as in epidemic polyarthritis was seen. One patient in the series gave a history of having had a tick removed from his back ten days before the onset. Agglutination tests on the serum were made. The Weil Felix test as carried out in these hospitals were considered to be diagnostic only if the titre reached 1/320, or if it rose from 1/160 during the course of an illness. In 274 tests scrub typhus was found consistently to produce a higher titre with *Proteus OXK,* and murine typhus with *OX*19. Agglutination with *OX*2 in these forms of typhus was unusual. The patients with tick typhus all showed a Weil Felix reaction; a titre of 1/160 or higher was found for *OX*2 in every case, and in 9 cases a titre of 1/320 or higher for *OX*19. The most probable insect vector was the *Ixodes holocyclus.* This tick is one of four man-biting ticks found by army entomologists in the area. It is stronger in its preferences for the human host and is the only one which has been found on the troops.



(Australian War Memorial)

Wounded soldier on Tarakan receiving penicillin by drip apparatus.



(A. O. Watson)

Patient awaiting transport—New Guinea.



(Australian War Memorial)

Operation in Main Dressing Station 2/4th Field Ambulance at Soputa.

Funder and Jackson made a study of the *rickettsia* isolated, comparing it with that of murine typhus by animal inoculation and culture experiments. Different features were observed in the behaviour of these strains from that observed in murine strains. Partial immunity was conferred by them for murine strains. Tests of the serum of the patients gave specific complement fixation with an antigen prepared from one of the strains, and it was established that serologically the tick and flea strains were distinct.

Material was also examined by Major Harry Plotz of the U.S.A. Typhus Commission and his colleagues in Washington. They agreed that the Queensland strains were not serologically related to the agents of epidemic or murine typhus or to cognate rickettsial infections. They produced different pathological changes in animals to those caused by scrub typhus, and did not confer immunity to the *R. orientalis*. Certain features of intranuclear growth of these strains resembled those of the agents of the spotted fever group. These and other immunological considerations suggested that the North Queensland tick was caused by a hitherto undescribed *Rickettsia*.

Andrew and his associates excluded from their series any but cases they considered solidly proved, but it is probable that mild varieties of tick typhus are more common in North Queensland than hitherto suspected. Southcott described an undoubted case in which the infection arose at some point on the Queensland coast near Trinity Beach. Brody also described a case in a woman aged 50 years, arising in North Queensland. G. E. W. Streeten and others have since described three cases from South Queensland. Fenner carried out an investigation on mammalian hosts. Ectoparasites were collected from kangaroo rats, opossums and bandicoots, and the animals were bled. Ground-up ticks were used to inoculate guinea-pigs. By complement fixation methods, with the use of an antigen prepared from one of the Atherton rickettsial strains tested with the animal sera, evidence was produced of presumed infection of the animals at some previous time by *rickettsiae* of the North Queensland tick typhus. Tick typhus was not an important chapter in military medicine, but may well be one in the general history of typhus fever.

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