REFRESHER COURSE FOR GENERAL PRACTITIONERS

/THE TYPHUS GROUP OF FEVERS X

BY

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PART I

As recently as twenty-five years ago typhus fever was thought to be a single entity, an infectious fever that by repeated epidemics, usually associated with war and famine, had long decimated armies and populations. Traditionally attributed to contamination by vermin or vitiated air, it was only in 1909 that its transmission by body-lice was demonstrated, and in 1922 that rickettsiae were incriminated as the causal micro-organisms. Its occurrence in Great Britain was very rare, and few were familiar with it.

Since then the collaboration of serologist, virologist, and entomologist, intensified by the spur of war and aided by refinements of technique that brought precision, has shown that there are eight, possibly twelve, individual members of a comprehensive group of typhus-like fevers, some prevalent in each of the five continents. One, scrub typhus, had an incidence of 25,000 cases and a death rate of 10% in the Allied Armies in the second world war. Another, "Q" fever, first identified in Australia, is to-day being recognized increasingly in the Americas, Europe, and Great Britain. This recent elucidation and the mounting British military commitments overseas have made it incumbent on clinician and laboratory worker to acquire familiarity with it—an obligation enhanced by the notable success of treatment with the newer antibiotics and of prophylaxis by vaccines and insecticides.

Originally the typhus group comprised only those fevers in which the blood serum of the convalescent patient gave a positive Weil-Felix reaction. But inasmuch as in two recently discovered rickettsial fevers—Q fever and rickettsialpox—convalescent sera do not agglutinate any known strain of *Proteus* X, an alternative designation, "rickettsial fevers," or the "rickettsioses," has gained currency.

A classification of these fevers based on the vector, though not ideal, is the most lucid, and is as follows:

Louse-borne: epidemic typhus; trench fever; ? Brill's disease.

Flea-borne: murine or endemic typhus.

Tick-borne: Rocky Mountain spotted fever; fièvre boutonneuse; North Queensland tick typhus; Indian tick typhus; Q fever; South African and East African tick typhus; Siberian tick typhus.

Mite-borne: scrub typhus (tsutsugamushi disease); rickettsialpox.

All have much in common, especially the clinical syndrome, pathological changes, morphology of the causal rickettsiae, and the response to antibiotic therapy. It must suffice to describe these common features only once in as much detail as space allows, and in other members of the group to restrict detail to contrasting features.

Louse-borne Typhus

(*Synonyms*: typhus exanthematicus, classical typhus, epidemic typhus.) Epidemics of louse-borne typhus have been recorded through many centuries: the largest in Eastern Europe and the Balkans; others in South America, Mexico, Japan, and the mountainous regions of North Africa, India, and other parts of Asia. In Great Britain the disease has been almost unknown for a generation.

Clinical Syndrome.—The incubation period is usually 10–14 days. The abrupt onset of headache and fever, with generalized aches and pains, is the rule. The temperature rises quickly to the region of 104° F. (40° C.). Between the fourth and seventh days a rash appears; faint rose-spots, fading on pressure, become maculo-papular and occasionally purpuric. Deafness is a frequent and valuable sign in the second week. The pulse and respiration are accelerated. Albuminuria is slight. Complications of the pulmonary and nervous systems may supervene after the seventh day; the former as bronchitis, bronchopneumonia, or (more rarely) lobar pneumonia; the latter as active delirium or stupor. In the second week the clinical signs intensify. In the absence of complications the fever declines between the 14th and 18th days, usually by quick lysis, and improvement is rapid; in their presence fever may be prolonged into the fourth week. Other complications are: thrombosis of the internal saphenous vein, gangrene of the foot, parotitis, facial paralysis, and subdural haemorrhage with resultant hemiplegia have all been recorded. The mortality varies in different epidemics: usually between 10 and 20%, it increases with age.

Human Pathology.—At necropsy there is no pathognomonic sign. Usually petechial haemorrhages are found in the endocardium, gastric mucosa, renal pelvis, and sometimes in the brain. In the lung there is congestion, bronchopneumonia, or (more rarely) lobar pneumonia. The histological picture is that of an endarteritis of the smaller blood vessels, arterioles, and capillaries, which also show some degree of perivascular proliferation. In the myocardium the salient features are oedema, vascular dilatation, and a diffuse infiltration of plasma cells, monocytes, and lymphocytes between the muscle bundles, changes that dictate slow convalescence.

Aetiology.—The causal organisms of all the rickettsial fevers are rickettsiae, bipolar or diplobacillary organisms, easily visible under the 1/12-in. oil-immersion system. Most of them do not pass through bacteria-tight filters; all multiply only within living cells. Minor variations in morphology within the group occur. *Rickettsia prowazekii*, the causal organism of louse-borne typhus, is of the slender rod-shaped diplobacillary variety.

Transmission.—The vector is the body-louse, *Pediculus humanus*; it feeds only on man, so that the transmission is exclusively man-louse-man. *R. prowazekii* multiplies in the endothelial cells lining the gut, which ultimately rupture, so that the louse faeces become infective three to five days after an infective feed and, in the dried state, remain so for many months, thus being a vital factor in the epidemiology of the disease.

Laboratory Diagnosis.—For the routine laboratory two methods are suitable—the Weil-Felix reaction and the

The Weil-Felix Reaction. Usual Agglutination Results Obtained in the Rickettsial Diseases

Disease	Proteus		
	OX 19	OX 2	OX K
Epidemic typhus	++++	+	0
Murine	++++	+	0
Scrub	0	0	++++
Rocky Mountain spotted fever	++++	+	0
or occasionally	+	++++	0
Q fever	0	0	0
Rickettsialpox	0	0	0

isolation of *R. prowazeki*. In louse-borne typhus agglutination is of the OX 19 type. Except for tick-borne typhus most laboratories omit *Proteus* OX 2. The waxing and waning of successive titres is as significant as the height of titre attained. For the isolation of *R. prowazeki*, guinea-pigs are inoculated intraperitoneally with whole blood drawn during the first week of fever, or with macerated blood-clot if the blood is drawn later. Male guinea-pigs are preferred, since scrotal redness and swelling (the Neill-Mooser reaction) in the initial or later serial passages virtually exclude louse-borne typhus. A non-fatal febrile reaction of six to seven days' duration results. Inoculation of infected material into the yolk-sac of the fertile hen's egg has proved highly successful; smears of the yolk-sac membrane reveal endothelial cells laden with rickettsiae; but utilization of this technique is restricted to appropriately equipped laboratories.

Control Measures

Former cumbersome methods of delousing by the steaming of clothes and shaving of hair have been supplanted by the application of 10% D.D.T. powder by a hand-pump into the hair, down the neck, up each sleeve, and down the waist into the trousers, a procedure completed in a few seconds. For a period of three weeks all lice present, and those hatching from eggs or reintroduced, are destroyed. Impregnation of clothing by D.D.T. solutions is even more effective, but problems of supply, distribution, and application detract from its practicability in mass anti-lice campaigns.

Immunization.—Weigl's very effective vaccine, based on the anal inoculation of laboratory-bred lice, lacks practicability on the score of expense, and has been superseded by killed rickettsial suspensions prepared from yolk-sac material, a vaccine introduced by Cox, refined by Craigie and by Topping, and available commercially. Three injections of 1 ml. are given at weekly intervals, and a "booster" dose yearly. Used on a vast scale in the second world war, it reduced the incidence, length, and intensity of the infection, and the liability to complications; and virtually eliminated mortality.

Therapy.—Because of the success of the newer antibiotics in all the rickettsial fevers, treatment will be considered later in one composite section.

Flea-borne Typhus

(*Synonyms*: endemic typhus, urban typhus, murine typhus, shop typhus.) The introduction of the Weil-Felix reaction in 1915 placed this mild disease amongst the rickettsial fevers. World-wide in its distribution, in Great Britain it is rare. Clinically it simulates louse-borne typhus, but is milder and briefer, and complications are fewer. The death rate is less than 1%. The causal organism is *Rickettsia prowazeki mooseri*, demonstrable in smears stained by Giemsa's or Machiavello's method from the exudate in the tunica vaginalis of male guinea-pigs inoculated as described for louse-borne typhus. The Neill-Mooser reaction is usually present. Rats and rat-fleas (*Xenopsylla cheopis*) are the common reservoir and vector respectively. Faeces from infected fleas will cause

infection if inoculated by scarification. The life-span of the flea is not shortened; the faeces continue to contain rickettsiae until death of the flea. For laboratory diagnosis two tests suffice—isolation in male guinea-pigs and the Weil-Felix reaction. In laboratories appropriately equipped the complement-fixation and rickettsial-agglutination tests will distinguish louse-borne from flea-borne typhus.

Control measures are anti-rodent, anti-flea, and anti-rickettsial. Rodent control includes proper storage of food, disposal of garbage, and poisoning, trapping, fumigation, and rat-proofing. Rat-fleas are very vulnerable to the dusting of rat runs and burrows with 10% D.D.T. An effective vaccine prepared from *R. mooseri* by the yolk-sac technique is available commercially.

Mite-borne Typhus

(*Synonyms*: scrub typhus, Japanese river fever, pseudotuberculosis.) Long known as the tsutsugamushi disease of Japan and Formosa, a high incidence occurred throughout the Allied Armies in the South-east Asia and South-west Pacific theatres of war. It is an Eastern disease: an arc drawn on a map from Assam and Burma southward, eastward, and

Fully-fed larval mite on the head of a pin. By courtesy of N. J. Kramis, C. B. Philip, and the *Scientific Monthly*.

then northward to Japan, thus including Ceylon, Malaya, Indonesia, Queensland, the Philippines, and Formosa would broadly indicate its known incidence in 1941. It was then more interesting than menacing, but later when jungle warfare began the incidence soared.

Clinical Syndrome.—In its incubation period, abrupt onset, febrile reaction, headache, rash, deafness, and complications, the syndrome resembles that of louse-borne typhus. But there is an added sign, a dermal lesion at the site of the mite-bite; this is first macular, then papular, and in some cases (more often in Europeans than in Asiatics) progresses to become a necrotic ulcer, consisting of a black crust, about 5 mm. in diameter, surrounded by a contiguous hyperaemic areola. The commonest sites are the calf, upper arm, neck, axilla, scrotum, and ankle, determined partly by the brevity of tropical clothing, partly by the preference of the vector for moist areas of skin. The adjacent lymphatic nodes may be much enlarged and tender; but if no ulcer develops there is only a generalized moderate enlargement and a slight tenderness that nevertheless comprise a valuable diagnostic sign. An enlarged spleen is usual. The mortality rate varies with different endemic areas, reflecting marked strain differences; in Japan, 60% in one district, 30% in another; in Burma, 10-15% in the north, 1% in the south; in Malaya, about 10%. The morbid anatomy and histology resemble those of louse-borne typhus, but the lesions are fewer.

Aetiology and Transmission.—The causal organism is the *Rickettsia tsutsugamushi*, the term given by Ogata in 1929 to the short bipolar-staining bacilli; $0.8 \mu \times 0.4 \mu$, obtained by him from the testis of rabbits infected by the intratesticular route. They stain well by Giemsa's method. The vectors are the larvae of certain species of the family Trombiculidae (see Figure). In Japan and Formosa the species is *Trombicula akamushi*; in Malaya and Indonesia, *T. akamushi* and *T. deliensis*, which are closely akin. The common reservoirs are field voles in Japan and rats in Malaya, Indonesia, and Formosa. Wartime investigations extended the range of hosts to tree-shrews, bandicoots, civets, barking deer, and the mongoose. Larval mites have also been found on birds of many species, some of them migratory; most recently an American Army medical research unit in Malaya found infected mites on quail, in numbers far exceeding those on rats trapped in the same area. These data explain why in the late war the incidence of scrub typhus soared. The ebb and flow of jungle warfare increased human incursion into the haunts of this disease, essentially one of mites and rats. Increasingly, therefore, man supplanted the rat as a host of the infected mite, and, to his cost, became the indicator of hitherto "silent" areas.

Laboratory Diagnosis.—This is made by the isolation of strains in the laboratory mouse, and by the Weil-Felix reaction. In the former, 0.5 ml. of whole blood drawn from the patient during the first week of fever is inoculated intraperitoneally into mice; death occurs about 10 days later. Necropsy reveals three cardinal signs—namely, a sero-fibrinous peritoneal exudate, pleural effusion, and splenic enlargement. Smears from the visceral peritoneum, after staining by Giemsa's method and differentiation with acetone, reveal abundant intracellular rickettsiae, mostly as clusters near the nucleus of endothelial cells. In the Weil-Felix reaction agglutination is of the OXK type. Positive titres (1 in 125 or higher) are obtained from the eleventh day onward. The waxing and waning in titre in successive samples of blood drawn at weekly intervals is significant.

Control Measures

Anti-rat.—Attempts to reduce permanently the rat population of an area of countryside rarely succeed. The hunting of rats, encouraged by rewards, has proved the most practicable method on estates; but cessation is followed by rapid reversion to former conditions.

Anti-mite.—These measures are twofold, mite-avoidance and mite-poisoning. The former is secured by burning off surface scrub by flame-throwers, bull-dozing the surface soil, and repeated covering of the ground with diesel oil; the expense and techniques limit them to use by the armed Forces. The development of effective mite-poisons was one of the important advances of the late war. American and Australian investigations demonstrated that clothing impregnated with dibutyl phthalate and benzyl benzoate, separately or as a mixture, proved lethal to mites within the space of two minutes. The British used a simple hand-smearing technique; the Americans, mechanical processing plants; 75% of the incidence was thus averted.

Anti-rickettsial.—The development of vaccines was sought unremittingly by British and American scientists, but without any convincing success. Vaccines prepared from the fertile hen's egg, cotton-rat lung, rat-lung, rat-spleen, and agar tissue-cultures gave indications of efficacy in laboratory animals, but evidence of success in man was lacking.

[Part II will appear in our next issue.]

Refresher Course Book.—The first 55 articles of this series (fully revised) are available as a book, price 25s. including postage, from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1. A list of the contents of the book will be found at p. 839.

THE NEW ACADEMIC YEAR

KING'S COLLEGE HOSPITAL

The Congestion of the Curriculum

The opening of the 123rd winter session of the King's College Hospital Medical School took place on October 3, when Dr. F. M. R. WALSHE presented the prizes and delivered an address. It was close upon 50 years, he said, since he first entered a medical school. In those halcyon days the students were not stuffed with information from morning to night; they were allowed a reasonable amount of time for independent thinking. They received sufficient information to make them willing to learn afterwards in the hard school of responsible medical practice, which at least gave them experience and judgment. There was no complaint in those far-off days that they were not being taught what they would most need to know in their later career, nor that they were being taught things they would never need to know. All teachers knew that only certain facts and principles could be taught in school, and that all else they wanted to make a good doctor must be learned in the hard way as they went through life. "One cannot teach a man to be a doctor; one can only teach him to be a technician."

Dr. Walshe's submission was that the present intolerable congestion of the curriculum ignored the fact that some things could not be imparted by formal teaching. The student must be instructed to steer his course intelligently and to acquire a gift of understanding his fellow men and a capacity for dealing with them, sick or well. Grumbles were often heard that the student was not taught in hospital to deal effectively with the mass of minor ailments which were going to be his main task in later life. This was surely another field where experience alone could give what was needed. It could be acquired by himself only by direct responsibility and by learning from his mistakes. He besought them not to expect the impossible from their training in hospital. A selective appetite must be encouraged.

In apologizing for the iconoclasm of his address, Dr. Walshe said that there was a well-established tradition in domestic life that an occasional breaking of china cleared the air. He had been breaking a few idols that afternoon, but he desired to end with something constructive. There were things that could not have a place in the student's training, and about which his examiners would never ask him, except indirectly. One of these things was the student's acquaintance with literature. Medical student life left less time than ever for general reading. We grew more scientific and at the same time less civilized. Yet they were still members of a learned profession and should try to remain civilized persons with some capacity for expression. A Spanish writer had said that what marked the superiority of a man was not what he asked for himself but what he asked from himself. To that minority he would like to see the profession continue to belong, and with that in mind he begged the students to give some part of their scanty leisure to general reading.

ROYAL FREE HOSPITAL SCHOOL OF MEDICINE

Medicine and Experimental Science

The inaugural address at the Royal Free Hospital School of Medicine on October 3 was given by Sir HENRY DALE, and the prizes and certificates were presented by Lady Dale. In speaking of the place of research in medical education and practice, Sir Henry Dale said that the range of knowledge which the medical student was now expected to acquire was changing and expanding at a rate which might well be exhilarating, but which from the point of view of the examinee—or even of the examiner—might even appear alarming. He could see no sign that this rate of progress had reached its climax. When he was a student there were two stages in a medical student's education—the pre-clinical and the clinical—and the general assumption was