REFRESHER COURSE FOR GENERAL PRACTITIONERS

THE TYPHUS GROUP OF FEVERS

BY

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PART II

Q Fever

Q fever was first described by Derrick in Queensland in 1937. Burnet and Freeman identified the causal organism as one of the rickettsiae, later to be named *R. burneti*. Philip has proposed an alternative term, *Coxiella burnetii* Derrick. About the same time a similar organism was isolated by Davis and Cox from the tick *Dermacentor andersoni*, in the Western United States. Laboratory comparison of the Australian and American strains proved their identity. Elsewhere it remained a medical curiosity until the second world war, when troop movements served as indicators of "silent areas" of the disease, particularly in the Mediterranean littoral. More recently outbreaks among stockyard workers have stimulated intensive study by epidemiologists and experimental pathologists, and reports of its identification in Europe, the Americas, and North Africa have been frequent. In Great Britain cases have been recorded from several counties.

Clinical Syndrome.—This is of variable duration and severity. Preceded by an incubation period of 14–26 days, the onset is usually abrupt, with headache, myalgia, fever, chills, and sweating. Fever, ranging between 101 and 104° F. (38.3 and 40° C.), with pronounced daily fluctuations, and a relatively slow pulse persist usually for four to seven days. Lung symptoms become prominent about the fifth day, with the development of a dry cough and pain; and radiography reveals pulmonary involvement, consisting typically of patchy areas of increased density of ground-glass appearance, usually in the periphery of the lower lobes. Resolution takes about two weeks. Occasionally the pulmonary signs may occur without fever, and vice versa. Pleural effusion is rare. In most instances the clinical course is mild, complications are uncommon, and convalescence is rapid. During the past three or four years, however, it has become clear that the syndrome, once thought to be uniformly mild and brief, may occasionally be of much greater duration and severity. Thus Lennette and his associates, investigating a series of 180 unusually severe cases in California, found the duration of fever to average 13 days, and to exceed 28 days in 30 patients aged 40 years or over, with prolongation of the residual weakness and fatigue for several weeks. Fatal cases are rare.

Morbid Anatomy and Laboratory Diagnosis.—The two or three necropsy reports recorded in the literature indicate that the essential findings are in the lung and spleen. In the former there is congestion, oedema, and lobar pneumonia or broncho-pneumonia. The latter resembles an acute splenic tumour. Laboratory diagnosis has an enhanced importance, since until the pulmonary lesion becomes evident the clinical diagnosis may be in doubt. The Weil-Felix reaction is negative. Isolation of the organism in guinea-pigs is simple. Complement-fixing and agglutinating antibodies appear in the patient's serum; the former are highly specific and persist for at least four years.

Epidemiology.—Australian and American workers have found certain species of tick to be heavily infected in nature; as also are sheep and goats. The disease is transmitted to sheep, goats, and dairy cattle by infected ticks;

man is usually infected by the inhalation of dust-laden air contaminated by tick-faeces or excretions from infected cattle. The causal organism has often been recovered from the placenta, milk, and udder of these animals. The infection is thus an occupational hazard in certain groups of workers—for example, those engaged in abattoirs, packing-houses, and dairies, and in the preparation of hides.

Control Measures.—The differing methods of transmission indicate that these measures can be most profitably devised in relation to the known or suspected circumstances of transmission in any particular outbreak. They would thus variously include the sterilization of the excreta and sputum of patients, the suppression of dust, and the very thorough pasteurization of raw milk, to which latter process the organism seems to be more resistant than is the tubercle bacillus. Egg-vaccines have given promising results in America, and may well find application for laboratory workers handling *R. burneti* and for abattoir and dairy workers.

Rocky Mountain Spotted Fever

This tick-borne disease occurs only in North and South America. Closely akin to it, however, are boutonniuse fever, endemic in the Mediterranean littoral, and the tick-borne fevers of South Africa, and perhaps those of Equatorial Africa, India, North Queensland, and Siberia. Therefore, to maintain perspective, it deserves brief mention. It is an acute endemic infectious disease, the causal organism being *Rickettsia rickettsi*, and the principal vector is the wood-tick, *Dermacentor andersoni*, in the Rocky Mountain region, and other ticks elsewhere. Clinically it resembles other rickettsial fevers; but the rash is more profuse, intense, and petechial, and gangrene of the scrotum more frequent. Man is an incidental victim when he intrudes into the tick-rodent-tick cycle of transmission. The Weil-Felix reaction is positive and of the OX19 type, although occasionally agglutination of the OX2 strain of *Proteus* predominates. Protection tests are much used. The complement-fixation test differentiates the disease from louse-borne, flea-borne, and mite-borne fevers, and from Q fever and boutonniuse fever. The use of D.D.T. powder on dogs and cats, and immunization by vaccines prepared from infected ticks or yolk-sac material, are effective methods of control.

Boutonniuse Fever

(**Synonyms:** fièvre boutonniuse, Marseilles fever, eruption fever.) This acute tick-borne febrile disease, first described in 1910 in Tunis, is prevalent in the Mediterranean littoral and perhaps further afield in Africa. It is a variety of Rocky Mountain spotted fever. A dermal lesion with attendant bubo, identical with that of scrub typhus, usually marks the tick-bite. This apart, it resembles Rocky Mountain spotted fever clinically, but is milder; cerebral symptoms are rare; the death rate is about 5%. The causal organism is the *Rickettsia conori*, which is transmitted by the dog-tick, *Rhipicephalus sanguineus*. Conclusive evidence concerning the reservoir is lacking. Epidemiological studies point to an association with dogs, but no canine strain has yet been recovered in nature. The role of the dog may be indirect only; transovarian passage in the tick and the longevity of the organism in the tick and its faeces may alone be adequate to maintain the cycle of trans-

mission. In the guinea-pig there is reciprocal cross-immunity between boutonneuse fever and Rocky Mountain spotted fever. The two diseases may be differentiated by the failure of spotted fever vaccine to immunize against boutonneuse fever and by the complement-fixation test. Kenya typhus and South African tick typhus are closely related to it. The Weil-Felix reaction is positive in early convalescence; titres with the OX2 strain of *Proteus* may equal those of the OX19 strain. The anti-tick measures described for spotted fever are applicable.

Other Tick-borne Typhus Fevers

These merit only passing mention in this brief account. South African tick-bite fever, the tick typhus of Equatorial Africa, and the tick typhus of India and of North Queensland all bear resemblance to boutonneuse fever. The first- and last-named are, however, thought to be distinct entities.

Rickettsialpox

This most recent addition to the rickettsial fevers, first identified in 1946 in New York City, and later in Boston, has certain clinical resemblances to scrub typhus and to chicken-pox. The abrupt onset, fever, and headache are typically those of the typhus group, though mild and brief; but the maculo-papular lesions of the rash develop vesicles that dry to form a black crust which falls off within seven days, leaving no scar. The Weil-Felix reaction is negative. Strains may be isolated and maintained in the guinea-pig and mouse. The causal organism is the *Rickettsia akari*, resembling *R. prowazeki*. Strains have been recovered from house-mice (*Mus musculus*) and from rodent mites (*Allo-dermanyssus sanguineus*). Early results of immunological tests suggest that the disease is related to the spotted fever group.

Therapy

During the past five years the problem of the treatment of all rickettsial diseases has been essentially solved by the discovery of three wide-range antibiotics—chloramphenicol, aureomycin, and terramycin—all of low toxicity in the recognized therapeutic doses and readily absorbed from the gastro-intestinal tract. In those rickettsial diseases most thoroughly investigated, amongst them those of the gravest prognosis—namely, typhus exanthematicus, scrub typhus, and Rocky Mountain spotted fever—these antibiotics have proved to be a veritable therapeutic scythe. The clinical manifestations are abolished within two to three days. Relapses are very uncommon, and invariably respond to re-treatment; the development of any degree of drug-resistance that might interfere with this has not occurred. The antibiotics are effective even when given quite late in the course of the disease, although defervescence may then take a day longer and require longer therapy. Their efficacy will be exemplified by the use of chloramphenicol in scrub typhus, since this has been extensive and the results differ little from those obtained in other members of the rickettsial group. In Q fever and rickettsialpox some reservation about their specificity must be made: in the former because of its variable severity; in the latter for lack of sufficient data.

In 1947 Smadel and his associates at the United States Army Medical Research and Graduate School, working with eggs and mice, showed that chloramphenicol acted powerfully on experimental scrub typhus. Trial in the human disease was clearly warranted, and collaborative studies were speedily instituted in Malaya, where the occupational nature of the disease ensured a succession of patients among estate labour and military personnel. Of some 150 cases treated, all responded promptly.

The drug is given orally in gelatin capsules, usually as an initial dose of 3 to 4 g., calculated on a basis of 60 mg. per kg. of body weight, followed by 0.25 g. at three-hourly intervals for 24 hours. For ill-nourished patients some prefer a smaller initial dose, or to split it into three and to give 1 g. hourly. Giles and Symington used with success

only a single dose of 3 g. For about 12 hours the clinical condition remains unchanged. Thereafter toxicity declines sharply, and within 48 hours the patient is afebrile, placid, and clamant for food. This success prompted Smadel and his colleagues to make prophylactic trials in volunteers exposed to infection in hyperendemic areas. They showed that, in one such trial, a weekly dose of 4 g. of chloramphenicol given for six weeks was so effective that only 1 of 31 volunteers developed typical scrub typhus, in contrast with an incidence of 13 cases amongst the 18 volunteers of the control group. These trials continue.

From these trials has emerged an unexpected finding. Those who have contracted the disease occupationally rarely come under treatment before the seventh day; in these, relapse never occurs. In contrast, in volunteers in the field trials close observation enabled chloramphenicol treatment to begin on the second or third day of illness; clinical signs promptly yielded, but in one-half of the cases reappeared after about seven days. This recrudescence at once responded to further chloramphenicol therapy. In some cases a second relapse occurred. Correlation of these facts with laboratory data from *in vivo* and *in vitro* tests led to the conclusion that chloramphenicol is rickettsiostatic, not rickettsiocidal, and that it suppresses the growth of the organism for about one week, during which time the patient develops his protective mechanism, under the stimulus of rickettsial antigen. But only in those treated late has this mechanism progressed enough for the added suppressive effect of the antibiotic to ensure an overwhelming immunity.

Aureomycin gives similar results in the therapy of scrub typhus, including relapses in cases treated very early and the prompt response to further treatment. Terramycin lacks extensive trial; but Smadel and his colleagues found it effective in eight patients, though less prompt (by 12–24 hours) in securing defervescence. For the treatment of scrub typhus their order of preference is chloramphenicol, aureomycin, and terramycin, based on slight differences in occasional and mild side-effects—namely, nausea and vomiting, looseness of stools, and a glossitis and thrush—none of them serious. During the treatment with chloramphenicol of some 300 patients suffering from scrub typhus or typhoid in Malaya no side-effects of note were observed. Drug-levels in blood or urine, however interesting to the experimental pathologist, are no longer necessary for the administration of any of the three antibiotics in the recognized therapeutic doses.

In the other members of the rickettsial group the recorded numbers of human cases thus treated are fewer. Although occasionally a clinician may express a preference for one or other of the three antibiotics, the results with all are essentially identical with those described above. Q fever, however, is occasionally an exception. Whereas in the experimental disease and in the earliest recorded human cases chloramphenicol and aureomycin seem to have been as consistently successful as in the other rickettsial fevers, Lennette and his co-workers, using aureomycin in 45 severe cases, found it useful but not invariably effective. In 22 defervescence was complete within three days, and in 32 within five days. But in nine it took longer; although within three days a subjective improvement and a sharp drop in temperature did occur, there followed several days of low-grade fever. In four cases improvement was minimal or absent. However, Smadel, Jackson, and Ley have shown that terramycin is much more active than chloramphenicol and aureomycin in experimental Q fever; its use in human cases will therefore be awaited with great interest.

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