THE POSITION OF RICKETTSIA AS AN ÄETIOLOGICAL FACTOR IN DISEASE.

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No notable progress has been made in the study of typhus fever during the last few years comparable with such discoveries as the part played by lice in the natural transmission of the disease, the transmissibility to guinea-pigs, the establishment of the association of the disease with rickettsia in lice or the agglutination of the Bacillus proteus X by the serum of patients. Nevertheless, much work has been done, and a number of important accessory facts have been learned while these four discoveries have been almost universally confirmed.

The natural desire to form a more complete picture of the infective cycle in man and the louse has led to what perhaps have been somewhat hasty interpretations of incomplete observations and the formation of rather unbalanced hypotheses. The only two other diseases besides typhus with which rickettsia is known to be concerned, namely, Rocky Mountain spotted fever and trench fever, have not been open to examination by so many workers. The former is confined geographically to a rather limited area and the latter, though possibly widespread, is as a rule unrecognized during times of peace, and the observations made on it during the war can therefore scarcely be repeated at the present day, and are in the main only open to re-examination by means of control observations on normal men or those suffering from other diseases and on healthy uninfected lice.

Rocky Mountain spotted fever has been further investigated, both as regards the transmission by the tick and the infection of wild animals. The aetiology of this disease and the relation of the virus to the invertebrate host do not run exactly parallel with these factors in typhus and trench fevers, since the tick has a very different anatomy and physiology to the louse, is not confined to one mammalian host and has a much longer and more complicated life history. The facts at present known and the appearances in the tick associated with infection, however, strongly support the view that Dermacentroxenus rickettsi, the minute form found in infected ticks, is of a similar nature to Rickettsia prowazeki and R. quintana.

The critical cytological study by Nicholson [1] of the staining properties of the rickettsia of Rocky Mountain fever as compared with other granular forms met with in the vertebrate and invertebrate hosts has a direct bearing on the present subject. This writer finds that rickettsia in tick and guinea-pig tissues is easily distinguished from mitochondria, which stain with aniline fuchsin and methyl green, and from other granules—remains of
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nuclei and red blood corpuscles—which stain with iron-hematoxylin. The more recent views and speculations concerning rickettsia bodies and their nature which have appeared of late years have taken mainly three directions.

(1) The occurrence of rickettsia as intracellular parasites in the tissues of mammals suffering from Rocky Mountain fever has been described by Wolbach, and corroborated by Nicholson. As regards typhus in man and the guinea-pig similar claims have been made by Jaffé and Kuczinski, and with much greater detail and apparently with a higher proportion of successful attempts by Wolbach, Todd and Palfrey [2]. Other workers have often failed to confirm these observations, or at any rate to completely satisfy themselves as to the nature of bodies called R. prowazeki which have been found in mammalian tissues. The exhaustive and careful work of Wolbach and his colleagues, however, at present holds the field.

(2) Several claims to have cultured R. prowazeki in artificial media have been put forward by different workers, who believe that they have shown in this way that rickettsia is a microbe belonging to a special, though at present not very well defined group of organisms. For instance, Kuczinski stated that he had obtained cultures on a special medium. Barykin and Kritsch described cultures in mammalian tissues of their Microbion typhi-exanthematici which these writers considered possibly identical with rickettsia.

More recently Wolbach and Schlesinger [3] have reported the survival in cultures of mammalian tissues both of the virus of Rocky Mountain spotted fever and of typhus for twenty-eight days, accompanied by what they consider conclusive evidence of multiplication of the rickettsia inside tissue cells. They, however, obtained no evidence of an increase free in the plasma, nor of passage from one cell to another in the cultures.

In this connexion may be mentioned Nöller's detailed account of the culture of R. melophagi from the leucocytes of sheep's blood, which, however, needs confirmation.

(3) Another result of the attempts to simplify and comb out the tangled claims of divergent opinions has been the rather unexpected capitulation by several Continental writers to the view of Friedberger that R. prowazeki is merely the form which B. proteus X assumes in the louse. The attraction of this hypothesis is that when combined with the view that the B. proteus X is the cause of typhus fever, the curious association of typhus with agglutinins in the blood for B. proteus X and the occurrence of the same bacillus in the stools, urine or blood, at any rate of some patients, are explained and brought under a single unifying idea. The additional evidence advanced by Weil, that rabbits which have received a dose of typhus guinea-pig virus can be shown also to have agglutinins for the X bacillus in their blood, would also be rendered intelligible. Weil himself appears to have subscribed to this view, indeed he took a prominent part in developing it, though he usually made a reservation to the effect that
the relation of the typhus virus to the *B. proteus* X might be one of constant association rather than of identity.

A later form of the view that the typhus virus is thus bacillary in nature has been espoused by Weigl, who has done such remarkable work in studying the artificial feeding and infecting of lice *per anum*. This author now appears to regard *R. prowazeki*, *B. proteus X* and *B. typhi-exanthematici* of Plotz as essentially identical, but as adaptations to different environments. Rabinowitsch has recently written adopting this hypothesis as an extension of his claim in 1909 to have found the causative micro-organism in a diplococcus present in the blood of patients.

It seems hardly likely that these views will on the existing evidence find general acceptance by bacteriologists.

(4) The latest additions to the literature of the subject have been by Woodcock [4, 5], who adopts a view in accordance with his comprehensive scheme of "haemataboloy" in relation to disease. He maintains that rickettsia bodies are not really independent living micro-organisms, but are merely a stage in the breaking down of previous formed elements, especially of mammalian red blood corpuscles and the nuclei of mammalian leucocytes, but also of the nuclei of the cells of the gut and other cells of the insect host.

This view, except in so far as the chromatin and haemoglobin are held by him to play a predominant or almost exclusive part, is essentially that which has of necessity met at the outset every investigator who has sought for microscopic evidence of the presence of virus in the louse, whether in connexion with typhus or trench fever.

The questions which were posed to the present writer and his colleagues when investigating these two diseases; as they have no doubt confronted previous and contemporary workers such as Sergent, Rocha-Lima, Otto, Topfer, etc., as well as the critics Nicolle, Brumpt and others, have been the following: Are there any bodies in the excreta or contents of infected lice which can be distinguished from the numerous granules of cell debris, pigment and bacteria which occur in similar preparations from normal lice? If so, what is the range of their size and shape; how constantly can they be found, and at what stage of the disease, or at what period after the louse has fed on a patient? These questions required careful and detailed study of many lice at different periods after feeding, and only by prolonged observation could definite criteria be set up and the above questions satisfactorily answered.

The conclusions arrived at with considerable details of the research can be found in the papers already published on the subject.

Plates illustrating the appearances found in lice are at best unsatisfactory evidence, though useful to indicate the forms to be sought in actual specimens. The only convincing evidence to any one wishing to decide for himself the value of the conclusions and the criticisms directed to them, is the examination of stained films or sections. Fortunately, many of
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those made by the late Mr. Bacot, my other colleagues and myself are still extant, especially those made from lice taken in series at different periods after an infecting feed on trench fever patients. These can be examined at the Lister Institute by any one interested in the subject. The criticism of Woodcock is really directed against two distinct elements in the rickettsia theory: (1) the exclusive association of certain forms of rickettsia with disease; and (2) the nature of rickettsia.

(1) He denies that rickettsia found in association with lice from cases of typhus and trench fevers are different in kind from bodies found in normal lice, and states that when examining films of admittedly normal lice he finds forms which he calls rickettsia. These forms may be much larger or smaller or of similar size to the typical rickettsia of lice from cases of disease. He says that he finds microscopic evidence that these are derived from broken-down mammalian red corpuscles and leucocytes, and also from spermatozoa and other cells of the louse. He also quotes with approval the forms from normal lice called rickettsia by di Mello, many of which are, judging from the description, indistinguishable from bacteria of ordinary size, as indeed are some of the forms figured by Woodcock himself.

The question is really whether amongst the debris and bacteria in smears of lice and louse excreta, other forms—true "rickettsia"—cannot be distinguished, which are really distinctive of disease-bearing lice as opposed to the objects seen in films from normal lice which are free from these particular bodies.

Those who, like the present writer, believe in the intimate association of rickettsia in lice with typhus and trench fevers in man have satisfied themselves that with due care and precaution this distinction can as a rule readily be made, whilst Dr. Woodcock professes himself unable to see any dividing line. In addition to this they believe that in most cases it is not very difficult by examining infected lice to distinguish between those containing the virus of typhus and those infected with trench fever, and that this can be done (1) most readily in some cases by the position of the rickettsia inside the gut cells in typhus and in the lumen of the gut in trench fever, and (2) by the different range of morphology of the rickettsia in the two diseases (Arkwright and Bacot [6]). Woodcock gives a certain support to this latter thesis, for he admits that in examining films of infected trench fever lice made a few days after the infecting feed, the appearance of immense numbers of uniform rickettsia is so striking that the picture is quite different from that found at an earlier date. He also does not deny that the location and shapes of R. prowazeki are different from those of R. quintana. He, however, believes that these peculiar features are due to the presence of different viruses in the two cases and their different action on the digestive apparatus of the louse and its pabulum. He suggests that the invisible mammalian virus in each disease has a different effect on the louse. It is true that the typhus virus causes the
cells of the gut of the louse to be shed and may cause the death of the louse, but this is generally regarded as the result of the multiplication of rickettsia inside the cells, whereas Woodcock believes that the digestive and metabolic processes of the louse are upset by an invisible specific virus, which by a process of hematoboly or chromatinoboly manufactures rickettsia which simulate micro-organisms. In any case the concurrence of a special kind of rickettsia with each of the two diseases is acknowledged. The association of each specific virus with a distinctive and recognizable form of rickettsia in the louse is the first and most important thesis which it is desired to maintain.

The intimate association of rickettsia with typhus virus has been further confirmed by showing that if the virus is transferred from man to the guinea-pig or monkey either by means of blood or the louse and then again lice are infected from the mammal, even after several passages in guinea-pigs, the characteristic rickettsia again appears in the louse gut (Atkin and Bacot [7]).

(2) The interpretation of the appearances met with in normal and infected lice and the nature of the rickettsia seen rests on a different basis to the claim for constant association with disease, since rickettsia cannot with any certainty be cultivated in artificial media. Whether rickettsia bodies really represent living organisms or special forms of digested cell débris is of necessity an inference based largely on analogy with other micro-organisms both as regards their morphology and apparent growth and multiplication in the louse gut, and on the nature of the infection of mammals.

A strong additional argument in favour of the rickettsia being a micro-organism is the demonstration by Ledingham [8] that rabbits inoculated with the excreta of lice infected with trench fever virus develop agglutinins for R. quintana, whereas the excreta of normal lice do not cause the production of any such antibodies. Observations on the agglutination of R. prowazekii from infected lice by the serum of typhus fever patients were recorded by Otto and Dietrich in 1917, and Ricketts also obtained results of the same kind with the similar bodies from infected ticks and the serum of patients suffering from Rocky Mountain fever.

That rickettsia is an independent micro-organism certainly seems the most probable and the simplest explanation, but the matter cannot be regarded at present as entirely beyond the region of controversy, and it rests on a different foundation to the surely established facts of the association of rickettsia with disease.

REFERENCES.

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References to most of the other publications quoted will be found with Dr. Woodcock's papers, or with the present writer's previous papers.