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PRIMARY ATYPICAL PNEUMONIA*

BY

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As my remarks will be concerned with the aetiology of this condition and its laboratory diagnosis I shall begin by defining what I understand by the term "primary atypical pneumonia," because not all, apparently, think alike on this point. For me this term refers to a clinical syndrome produced by a variety of infective agents, among which certain viruses, a rickettsia (*R. burneti*), and a fungus (*Coccidioides immitis*) have already been identified. Others would remove from this group those cases due to the psittacosis viruses, *R. burneti*, and *C. immitis*, and reserve the name primary atypical pneumonia for cases caused by the somewhat ill-defined virus of Eaton *et al.* (1942) and possibly, in addition, some as yet unidentified virus. While approving this endeavour to break down the conglomerate mass of atypical pneumonias into a number of aetiological entities, it seems to me that it would be most unfortunate if it resulted in the definition of a disease entity named "primary atypical pneumonia."

In my opinion the term should be used to describe a train of symptoms or cease to be employed. And although the name primary atypical pneumonia for this syndrome has little to recommend it I have no alternative to suggest.

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Certainly the term "virus pneumonia," which some would put in its place, strikes me as most unsuitable, for, apart from the fact that a rickettsia and a fungus figure among the causal agents of this syndrome, it is by no means every virus pneumonia which qualifies for inclusion in the group. Pneumonia due to the influenza viruses, for instance, does not, in my opinion, conform either in clinical pattern or in histological change to the pneumonia which we label "primary atypical"; and the giant-cell pneumonia of Hecht and the virus pneumonitis of infants described by Adams (1941) are further examples, though admittedly the virus aetiology of these two last conditions rests only on histological evidence.

I mention giant-cell pneumonia because I have had the opportunity of examining material from two cases which occurred at the London Hospital. Both occurred in infants in early convalescence from varicella, and death was due to a bacterial bronchopneumonia, but the histological changes of this terminal condition did not obscure the presumably earlier ones characterized by the formation of giant cells, often draped around the alveolar walls. Nuclear and cytoplasmic acidophil inclusions were numerous in these cells, and one is tempted to conclude that they represent parasitism by the varicella virus, a varicella pneumonia which had preceded and predisposed to the secondary bacterial infection. A similar giant-cell pneumonia has, however, been described in measles.

Primary atypical pneumonia might be described as an infective process of various aetiology, often with an indefinite onset, and characterized clinically by moderate fever, malaise, and a cough which is harassing though largely unproductive, at any rate during the first week of disease. Characteristically, there is a paucity of physical signs in the chest and the pneumonic changes might be overlooked were it not for x-ray examination; the shadows thus revealed are lacking in density owing to the incompleteness of the consolidation. Those cases which have come to post-mortem examination have shown histological lung changes which have been very similar whether the cause has been a virus of the psittacosis group, some other virus, or Q fever.

These changes, usually described as interstitial pneumonia, consist in a thickening of the alveolar walls due to congestion and infiltration with mononuclear cells and an exudate into the alveoli composed of serum, fibrin, red blood corpuscles, mononuclear cells, desquamated alveolar cells, and occasional polymorphonuclear leucocytes. Characteristically the exudate varies considerably from one part of the lung to another. It is usual to say that a failure to respond to sulphonamides is a distinctive feature of primary atypical pneumonia, but it must not be forgotten that a few strains of psittacosis virus are sulphonamide-sensitive. I have seen three human cases which undoubtedly responded to this treatment, and others have been described (Hinshaw, 1940).

Aetiology: Viruses of the Psittacosis Group

Turning now to the causation of this syndrome, the first group of agents that I would like to consider is the psittacosis viruses, and I mention them first, not because they play a preponderant part in the production of this condition, but because psittacosis virus was the first recognized cause of atypical pneumonia. I should perhaps point out for the benefit of those who have not followed the literature of this subject that psittacosis is not just one virus as at first believed, but a group of closely related viruses. And the primary hosts of these viruses are not

confined to psittacine birds, but extend to many other avian species—various finches, sea birds, the pigeon, duck, and domestic fowl.

The name of ornithosis virus is used by some authorities for those avian strains which differ in minor ways from the original psittacosis virus. There is also evidence that the primary host range of this group of viruses may include mammals, for the virus of cat pneumonia described by Baker (1942) seems to belong to the group, and, more recently, Roca-Garcia (1949) has described naturally occurring infection of opossums in South America. There is even a suggestion that some strains of psittacosis virus have become adapted to man, using him as their only natural host: the S.F. virus of Eaton, Beck, and Pearson (1941) and the Louisiana pneumonitis virus (Larson and Olson, 1946) are examples in point; the readiness with which they pass from man to man is an important and striking feature of these strains.

The practical importance of all this recent work on the ecology of the psittacosis viruses is, of course, that the chance of man's contracting psittacosis is very much greater than was at one time believed. As already mentioned, some authorities would exclude psittacosis from the group of primary atypical pneumonias, and, while it must be admitted that the severe case of psittacosis, with its attendant toxæmia and typhoid state, presents a picture unlike that of primary atypical pneumonia, this is not true of the milder cases which constitute the majority of human infections with the psittacosis viruses. Human psittacosis, like any other infectious disease, can vary considerably in severity, and it is not by any means all cases of psittacosis that develop signs of pneumonic involvement; some of these infections may even be inapparent (Bedson, 1939).

Serological Investigation

Many of the milder cases with pneumonitis would have remained indistinguishable from the mass of primary atypical pneumonia had they not been picked up by the laboratory in the course of routine serological investigation. The diagnosis of psittacosis is essentially a matter for the laboratory, and though isolation of the virus is undoubtedly the most satisfactory evidence which can be adduced in support of this diagnosis it is not always practicable. The virus is best sought in the sputum, but this material is usually scanty or may even be absent, and the alternative procedure for obtaining material from the pneumonic foci by lung puncture can hardly be recommended as a routine. So the laboratory has to rely on the indirect evidence afforded by the complement-fixation test.

In this connexion it has to be observed that the antigen used as a routine in the psittacosis complement-fixation test is the heat-stable group antigen which is not only common to the viruses of the psittacosis group but also to lymphogranuloma venereum (L.G.V.) virus and other viruses belonging to the psittacosis-lymphogranuloma group. This means that a positive result indicates no more than infection with a virus of the psittacosis-lymphogranuloma group, and its correct interpretation can be made only in the light of the clinical findings. And, as in the case of any diagnostic serological tests, the demonstration of a rising titre of antibodies is much better evidence of active infection than the finding of even a high titre on a single occasion. There is evidence (Bedson *et al.*, 1949) that absorption of the serum with the group antigen discloses a specific antibody which can then be detected by complement fixation, the fresh unheated virus being used as antigen, but technical difficulties make it unsuitable as a routine procedure.

Skin Test

The question of whether a skin test might be of service in the diagnosis of psittacosis is worth investigation, though there is already a suggestion that infection with these viruses does not lead to the development of skin sensitivity to the same extent as in L.G.V. In the latter condition the percentage of reactors to the Frei test is high, approximately 95, and, since the active antigen in this test is the heat-stable group component which L.G.V. virus shares with psittacosis virus, one might expect that a heated preparation of psittacosis virus would successfully replace the orthodox Frei antigen, and that cases of psittacosis would give a positive Frei reaction. The former conjecture is more or less true: though there are some divergences between the skin reactions given by cases of L.G.V. to heated psittacosis and L.G.V. virus, the concordance is high (Bedson *et al.*, 1949). And, as Eaton, Beck, and Pearson (1941) have shown, the Frei test may be positive in psittacosis: they obtained five positive results in eight cases. I think it would be worth while skin-testing all cases of human psittacosis, using in parallel the orthodox Frei antigen and a similar preparation made from psittacosis virus. Those that reacted positively to one or both might then be tested with the acid extracts of the two viruses, which preliminary findings suggest contain the species-specific antigens (Barwell, 1949; Bedson *et al.*, 1949).

Incidence

Before leaving the question of the relationship of the psittacosis viruses to primary atypical pneumonia it might be useful to attempt some estimate of the proportion of cases with this aetiology. Where this rests on the demonstration of the virus in morbid material we are on sure ground, but extensive investigations on this point are few. Meiklejohn, Beck, and Eaton (1944) isolated viruses belonging to the psittacosis group from sputum and lung-puncture material in 10 out of 250 cases, and in a smaller group of 33 cases Glover and his colleagues (1948) obtained one positive result. As might be expected, serological evidence of infection with these viruses in atypical pneumonia is not only more abundant but places the incidence higher.

Smadel (1943), using the psittacosis complement-fixation test, demonstrated a rising titre of antibodies in 10 out of 45 sporadic cases of primary atypical pneumonia in eastern States of the U.S.A., and Eaton (1945), in reviewing the work done on this problem during the war, concludes that some 10% of the cases of this syndrome are due to viruses of the psittacosis group. My own experience during the war led me to a somewhat similar estimate. Relying alone on the demonstration of antibody by means of the psittacosis complement-fixation test, 9 out of 120 cases were diagnosed as psittacosis. The incidence of primary atypical pneumonia has returned to its pre-war sporadic level, but the investigations now being made by the Virus Reference Laboratory of the Public Health Laboratory Service should, in time, give us further and more conclusive evidence on this point.

The Virus of Eaton

It is not my intention to make more than a passing mention of those cases of this syndrome which are due to *C. immitis*, since infection with this fungus is confined to certain localities in North America. Nor shall I do more than refer to the virus of lymphocytic choriomeningitis as a possible cause of an occasional case. I propose now to pass to a consideration of the virus described in 1942

by Eaton, Meiklejohn, van Herick, and Talbot. Earlier I referred to it as ill-defined, but in doing so I was not questioning its existence so much as registering the doubt which, to my mind, still exists concerning its relationship to respiratory disease in man.

This virus was first isolated by the intranasal inoculation of cotton-rats with sputum obtained early in the disease. Difficulty was experienced in adapting it to the cotton-rat, and there seems to have been some doubt concerning the six strains finally established. In the end it was concluded (Eaton, 1945) that they were in all probability a latent virus of the cotton-rat. However, Eaton and his colleagues (1944) have shown that a virus can be obtained from cases of primary atypical pneumonia by the inoculation of 12-day eggs with filtered sputum by the amniotic route.

Presumably this virus is the same as that with which they started in their earlier experiments; it can be maintained in eggs but, unfortunately, produces little or no visible change in the embryo, and one has to rely on subinoculation of hamsters and cotton-rats to demonstrate its presence. Nasal inoculation of these animals produces lung lesions in some 75%, and neutralizing antibodies for this virus are found in human convalescent sera. Whether or not Eaton's virus is responsible for those cases of primary atypical pneumonia not caused by known infective agents—the psittacosis viruses, *R. burneti*, *C. immitis*, and lymphocytic choriomeningitis—the vast majority in fact, remains to be shown, but there is good evidence that they are of virus aetiology. The absence of a demonstrable bacterial cause, the histological findings in the few cases that have come to necropsy, and the transmission of the condition to human volunteers by means of filtered sputum (Commission on Acute Respiratory Disease, 1945, 1946) all support such a conclusion.

The literature on primary atypical pneumonia during the recent war contains a number of claims that viruses have been obtained from this condition; but some of these claims were subsequently withdrawn, and in other instances the virus was lost before it could be characterized and its relation to the human disease established. The virus of feline pneumonia of Blake, Howard, and Tatlock (1942) possibly merits consideration, but, apart from this, Eaton's virus holds the field, though I should be surprised if his virus alone was responsible for this large group of atypical pneumonias.

Cold Agglutinins

It was hoped at one time that the occurrence in the serum of abnormal concentrations of cold agglutinins for human group erythrocytes might be of assistance in defining this group of primary atypical pneumonias, of which Eaton's virus is the possible cause. The original and independent observations of Peterson, Ham, and Finland (1943) and of Turner (1943) suggested that an increase in these antibodies was peculiar to primary atypical pneumonia among respiratory infections, and subsequent work by these and other investigators largely confirmed this.

When Eaton (1945) observed that this increase in cold agglutinins did not occur in cases of atypical pneumonia due to the psittacosis viruses—a finding in line with my more limited experience—and the same was said to be true of Q fever (Caughey and Dudgeon, 1947), it looked as though the development of cold agglutinins might be of service in defining the group of atypical pneumonias in which Eaton's virus was supposedly concerned. The development of agglutinins for the M.G. streptococcus had apparently the same significance; the development of these two kinds of antibody, though entirely distinct, occurred

very largely in parallel. But more recent work has shown (Finland, Jolliffe, and Parker, 1948; Morgan and Finland, 1948) that an increase in the titre of cold agglutinins can undoubtedly occur in psittacosis pneumonia, and, though there is no suggestion that this is more than an occasional happening, that it occurs at all seems to rob this test of much of its value.

It may be that the development of agglutinins for the M.G. streptococcus will prove a more useful test for the identification of atypical pneumonia not due to the psittacosis viruses or *R. burneti*. Further work on this point and on the usefulness of cold agglutination is required: the survey being made by the P.H.L.S. will no doubt supply the answers to these questions. But more important, obviously, is the provision of precise information concerning the causation of the large number of cases of primary atypical pneumonia which still remains unknown.

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The December issue of *The Practitioner* (price 4s.) contains an important symposium on the medical aspects of atomic warfare, in which, in addition to orthodox and straightforward simple articles on such subjects as nuclear physics and the pathology of radiation injuries, a Home Office adviser describes and illustrates how to assess the probable casualties and damage from an atomic-bomb explosion in a built-up area; and the adviser in surgery to the Ministry of Health sketches the proposed first-aid and hospital organization in the event of war. In industrial areas the central hospitals will become lightly manned casualty transit centres, while most medical and nursing staff will move out to peripheral cushion hospitals situated on main roads and close to railways. Base hospitals will contain special centres and be either for acute or for "recovering" patients (continuous specialist supervision no longer needed), who will be transferred from the cushion hospitals by ambulance train or coach as soon as their primary treatment has been completed. The hospital service will be controlled from Whitehall through the regional hospital boards and through medical officers of the Ministry of Health posted at Army Command and Civil Defence Region headquarters. The First Aid service will be an integral part of the hospital service, and first-aid stations will be based on selected cushion and base hospitals. Each station will comprise a fixed first-aid post at the parent hospital, together with three mobile first-aid sections and a mobile gas cleansing unit, for each of which two light cars and a van will be provided, with a motor-cyclist as messenger. Ambulances will be the responsibility of the local health authority.