Papers and Originals

CLINICAL CLUES IN VIRUS INFECTIONS*

BY

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Diseases like influenza and measles were recognized by clinicians long before the virus could be grown in the laboratory. It is still true that, for example, infection with the measles virus can be recognized as accurately by the clinician as by the laboratory, and far more quickly. However, other diseases, such as the acute virus infections of the upper respiratory tract, are caused by scores of different viruses, and in most cases the clinician cannot recognize the presence of these by any feature of the disease process. In such cases an exact diagnosis can be made only in the laboratory. For many years, however, there has been a recurring interaction between the clinician and the virus research worker, and on several occasions clinical observations indicated probable conclusions which laboratory work confirmed, and on others laboratory studies drew attention to clinical features which had previously been overlooked. In both cases there has been a valuable cross-fertilization of ideas. Some of these are reviewed in this paper. They should be regarded as the current instalment of a long serial story. The clues will not lead us inevitably to the solution of all the mysteries and certainly not to the apprehending of the villains.

Rashes and Enterovirus Infections

Aseptic meningitis may be due to many different viruses, although if paralysis develops this makes it probable, but not certain, that the infectious agent is one of the polioviruses. Late in the summer of 1956 some unusual illnesses were observed in many parts of Britain (see Tyrrell *et al.*, 1958). Cases of aseptic meningitis were seen which showed a rash reminiscent of rubella but with blotchy purplish lesions on the face (Fig. 1). Small ulcers were also seen in the mouth, and many patients had enlarged lymph nodes in the neck and elsewhere. Cases without meningitis, and with only rash or only fever were also recognized, especially in the families of typical cases. Some patients relapsed once or twice before recovering completely. Now it was possible to show that this disease was due to a virus (E.C.H.O. 9 or Coxsackie A23) which belongs, like poliovirus, to the enterovirus group and multiplies in the throat and lower alimentary tract.

It is known that, like poliovirus, E.C.H.O. 9 virus produces viraemia (Yoshioka and Horstmann, 1960), and it is probably in this way that virus reaches the central nervous system (Godtfredsen and von Magnus, 1957). The rash in E.C.H.O. 9 disease may therefore occur because virus is scattered by viraemia, lodges in the skin, and there produces local lesions. The literature revealed that a similar disease with a rash had been seen in cases infected with the same virus in earlier years. In other outbreaks of infection with an apparently identical virus which occurred particularly in Southern Europe only meningitis had been seen, and the reason for this difference is still quite obscure. The full range of illness due to the same virus, E.C.H.O. 9, has also been seen in North America in subsequent years (see, for example, Kibrick and Enders, 1958).

However, another epidemic disease had been seen in Boston (Neva *et al.*, 1954) and in Pittsburgh (Neva, 1956) and christened "Boston exanthem." In this epidemic the skin lesions were identical with those I have described, but there was no involvement of the central nervous system, and the disease was shown quite clearly to be due to another virus, E.C.H.O. 16, also belonging to the enterovirus family (Neva *et al.*, 1959).

Recently a further clinical type of enterovirus infection has been described under the name of "hand-foot-and-mouth" disease. This affected children in Toronto (Robinson *et al.*, 1958) and in Birmingham (England) (Alsop *et al.*, 1960), and in typical cases there were, in addition to a maculopapular skin rash on the trunk and limbs, vesicles or bullae on the palms and soles and in the mouth; in both towns the disease was shown to be due to Coxsackie A16. A similar syndrome has been seen in the U.S.A. (Magoffin *et al.*, 1961), and a vesicular eruption was found in other cases infected with Coxsackie B3 virus (Lerner *et al.*, 1960). Coxsackie virus and E.C.H.O. viruses are closely related, and the disease resembles both the E.C.H.O. 9 disease and herpangina, which is produced by certain types of Coxsackie A virus.

Relatively infrequently there have been other reports of a rash, usually rather like rubella, in association with infection with other enteroviruses. In these cases so few patients were studied that it was often impossible to prove that the viruses isolated caused the rash, but it is probable that they did. In conclusion, therefore, the simplest way of looking at the matter seems to be to

FIG. 1.—Rash due to an enterovirus infection. The blotchy purplish rash on face and the finer rash on trunk can be seen. The patient was 1 year old and E.C.H.O. 9 virus was isolated.

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recognize that many enteroviruses may cause a general infection of man with invasion of the blood, and that certain strains tend to attack the skin; others prefer to attack the tissues such as the central nervous system or muscles, while some can attack both the skin and the central nervous system. None of the skin diseases is serious but some of them have in the past no doubt been diagnosed as "sweat rash," "teething rash," or second or third attacks of German measles.

Chicken-pox and Herpes Zoster

There have in the past been differing opinions on whether these two diseases were due to infection with the same agent. The skin lesions are similar in kind though they differ in distribution, and there is epidemiological evidence that exposure to a patient with one illness may be followed by the other type of illness in the exposed person (Hope-Simpson, 1954). Some observers thought that the epidemiological evidence was weak and that it was unlikely that such differences between the diseases could be due to differing responses of the host. The unitary concept has now been supported by laboratory work, for it has become possible, by the use of tissue cultures, to isolate viruses from both conditions (Weller, 1953; Taylor-Robinson, 1959), and these viruses cause identical pathological changes in tissue culture (Figs. 2 and 3) and seem to bear identical antigens (Weller and Witton, 1958; Taylor-Robinson and Downie, 1959). Subjects with zoster do, however, have more antibody than those with chicken-pox, and this may be the host factor which accounts for the clinical difference between the diseases.

Herpes Simplex

The virus of herpes simplex is to the laboratory worker a well-known and long-studied organism and a creature very different from the chicken-pox-zoster virus. We

are all familiar with the way this virus emerges from its latent state to cause labial herpes. However, Stern *et al.* (1959) have shown that one type of acute whitlow may be due to herpes simplex virus. They studied an epidemic of the disease in nurses (Fig. 4), who apparently acquired the virus from neurosurgical patients who were excreting it silently. The nurses affected were apparently without antibody at the onset of illness, and this may therefore be an unusual form of primary herpetic infection distinct from the pharyngeal type which is so well known. However, it might be recognized more often than it is if clinicians were more aware of its existence.

Primary Atypical Pneumonia

When it became possible to control bacterial pneumonia with drugs such as penicillin and the sulphonamides it was realized that there were cases of pneumonia which did not respond to these drugs.

FIG. 2.—Effect of varicella virus on human amnion cells in tissue culture. There are giant cells and also shrunken rounded cells: intranuclear inclusions are common. (Haematoxylin and eosin. $\times 380$.)

FIG. 3.—Effect on human amnion cells of a virus from a case of herpes zoster. It shows exactly the same features as those in Fig. 2. (H. and E. $\times 380$.) (Figs. 2 and 3 by courtesy of Dr. D. Taylor-Robinson.)

FIG. 4.—Typical primary herpetic infection of finger. Confluent pustules on index finger of a nurse. The white areas consist of tenacious necrotic material, and the fluid contents were sterile on bacterial culture. The lesion resolved in three weeks. (Photograph and clinical details by courtesy of Mr. H. F. Anderson and Professor S. Elek.)

Primary atypical pneumonia was particularly clearly distinguished among these because of its clinical course, and also because a rising titre of cold agglutinins or of agglutinins against the streptococcus MG is often associated with the disease. A number of physicians had the impression that broad-spectrum antibiotics, such as the tetracyclines, had a therapeutic effect on primary atypical pneumonia. An infectious agent which behaved very much like a virus was recovered by Eaton *et al.* (1944), from cases of this disease. Since then others in the U.S.A. have developed easier methods of handling it and measuring antibodies (Liu, 1957). By these methods it has been shown that many, but not all, cases of primary atypical pneumonia are infected with the Eaton agent. Marmion and Goodburn (1961) brought forward evidence suggesting that the Eaton agent was not a virus at all but a mycoplasma or pleuropneumonia-like organism, and this suggestion has been confirmed by Chanock *et al.* (1962), who have cultured the organism on non-living medium.

We now come to two interesting clinical points. The first is that, in the U.S.A., volunteers were given a strain of Eaton organisms which had been cultivated in the laboratory (Rifkind *et al.*, 1962); three developed atypical pneumonia and 12 developed milder upper respiratory illness, as might have been expected from earlier epidemiological studies. In addition, however, 12 volunteers developed acute myringitis, which appeared to be due to the same Eaton agent. This has not attracted attention in reports of the naturally occurring chest disease, but it is possible that it has been overlooked. The organism may cause some cases of ear disease in children.

The second clinical point is that cases of atypical pneumonia were treated with a tetracycline drug, demethylchlortetracycline (0.9 g. daily for six days), in a properly controlled double-blind trial, and it was found that those due to Eaton agent were significantly improved by the drug (Kingston *et al.*, 1961). Those due to adenovirus and other virus infections were unaffected, and this probably accounts for the conflicting results of earlier reports.

Common Colds

From the clinical point of view colds are among the most difficult illnesses to understand as well as being the commonest to be met. If we exclude those cases in which the running nose is the result of allergy or psychological abnormalities we are left with numerous cases which occur most commonly in the cold season of the year and seem, therefore, to be the result in some way of the cold weather. Yet in many instances these colds seem to be transmitted from person to person round the home or in the wider community. Clinical impressions therefore suggest that the common cold is basically an infectious disease, the epidemic spread of which is encouraged by something in the environment in winter-time.

When washings are collected from the nose of a patient with a cold and given as nasal drops to volunteers, some of the volunteers usually develop colds after an incubation period of about two days, and this confirms the general conception that the disease is infectious (see Andrewes, 1953). Work in this country and in the United States shows that the exact type of cold produced by each washing may not be the same (Jackson *et al.*, 1960; Roden, 1963), the nasal discharge may be more or less, the average incubation period may vary

from one to three days, fever may appear in a proportion of cases, and so on; these experiments confirm the clinical impression, which is supported by epidemiological analysis (Lidwell and Williams, 1961), that when a cold "goes round" a family it tends to "breed true" in its main clinical features, such as the presence of a sore throat, cough, or fever.

In the past five years it has become possible to cultivate in the laboratory viruses found in washings from patients with colds. In the first place, viruses of the parainfluenza group and respiratory syncytial virus were recovered from infants and young children admitted to hospital with bronchitis, croup, or pneumonia (Chanock *et al.*, 1957, 1958). It was shown, however, that these viruses could also cause milder diseases classified as colds. Most children are infected with these viruses in the first few years of life, but in the case of parainfluenza 3 Chanock *et al.* (1961) showed that if the children had already been infected once and had developed a detectable amount of antibody they might be reinfected, but in this case only the mild cold-like illness occurred. Reinfection with parainfluenza and respiratory syncytial virus can also occur in adult life and similarly lead to colds. It seems, therefore, that some of the colds which adults catch represent reinfection with childhood viruses (Hamre and Procknow, 1961; Robinson *et al.*, 1962). Others may in fact be mild infections with influenza virus, adenoviruses, or other organisms which usually produce more severe disease. However, most colds in adults are not due to any of these viruses.

Viruses of another group, which we call rhinoviruses, can be isolated from a substantial proportion (20-30%) of washings taken from cases in the acute stage of illness (Hobson and Schild, 1960; Tyrrell and Bynoe, 1961; Hamre and Procknow, 1961). These viruses are biologically quite different from those mentioned earlier; in their basic physical properties they are more like enteroviruses, although they do not multiply in the gut. They usually fail to infect volunteers who have circulating antibodies, so they are less likely to reinfect than are parainfluenza viruses. The fact that colds are so common seems to be due to the existence of numerous serotypes with little or no antigenic relationship with each other (Taylor-Robinson and Tyrrell, 1962a). Adults have antibody against more serotypes of virus than do children, and this is the probable reason that, as has been shown repeatedly, they suffer from fewer colds than children do (Taylor-Robinson and Tyrrell, 1962b; Schild and Hobson, 1962).

When presented with the clinical fact that colds are so common we thought at first that this was either because there were a few "cold" viruses which could reinfect repeatedly, or else that there were many viruses of different serotypes to which we acquired specific immunity one at a time. It appears that either explanation can be true, depending on which particular "cold" virus we are discussing.

Conclusion

By exploiting the new methods of virus study more has been learned about the significance of clinical observations than one could have imagined possible say 10 or 15 years ago. Yet I feel that there are many clues yet to be followed up. For example, we cannot explain why certain individuals consistently have more colds than others. Perhaps the genetic approach will give answers here; people of blood group O seem to be relatively susceptible to influenza A2 (McDonald and Zuckerman, 1962). Then there are syndromes such as

the "winter vomiting disease" or epidemic gastroenteritis which seem to be due to virus infections and yet no agents have so far been cultivated from such cases; so we need more studies by virologists to find new methods for cultivating these. Finally, a group of compounds which was originally presented to virologists as a tool for studying the nucleic acid of the virus has just been shown to have a chemotherapeutic effect on herpetic infections of the eye of man. Perhaps specific virus chemotherapy is not so far off after all (Kaufman, 1962).

Summary

A combination of improved laboratory methods and clinical observation is rapidly advancing our understanding of virus infections of man. Some recent examples are given. Certain acute infections with a prominent rash and affecting children have been shown to be due to enteroviruses. Chicken-pox and herpes zoster are due to infections with the same virus. Herpes simplex virus may cause a whitlow. The Eaton agent is now known to be a mycoplasma (pleuropneumonia-like organism), and the pneumonia it produces can be effectively treated with demethylchlortetracycline. The common-cold syndrome can be produced by a variety of viruses, including parainfluenza viruses, respiratory syncytial viruses, and rhinoviruses.

Addendum

The REOViruses, once called E.C.H.O. 10 virus, are biologically quite distinct from the enteroviruses, but, like them, may be found in the throat and faeces. Lerner *et al.* (1962) have reported on patients infected with REOVirus type 2 and five of these had an itchy maculopapular rash, while one had a vesicular rash. Perhaps this is yet another virus which can cause a rash disease.

Large numbers of rhinoviruses have now been isolated in various laboratories from cases of the common-cold syndrome (Johnson *et al.*, 1962; Ketler *et al.*, 1962; Mogabgab, 1962; Reilly *et al.*, 1962). The position is confused, as names such as "coryza virus" and "entero-like virus" have been used, and all the strains have not yet been compared with each other, but there are probably scores of serotypes. Virus isolations from more severe types of acute respiratory illness have been reported, but it was not proved that the virus isolated caused the disease.

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EFFICIENCY OF ANTISEPTICS WHEN ACTING ON DRIED ORGANISMS

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Antiseptics are frequently employed to deal with organisms that are dry and adherent to textiles or impervious surfaces made of metal, glass, plastics, or paint. Unfortunately, the choice of an antiseptic for such purposes is rendered difficult because, other than the Rideal-Walker or Chick Martin coefficients, the only available information in regard to their efficiency is the highest dilution that will kill certain species of organisms suspended in broth, saline, or water within a specified time, which is seldom less than 10 minutes. Such information is virtually useless, because the antiseptic must generally be able to kill the organisms in a very much shorter time if it is to be of any practical value, and the organisms will not only be dry but will probably be embedded in films which, almost certainly containing protein, may delay its action considerably.

We have therefore tested a number of antiseptics by a method first suggested by our colleague Dr. W. D. Foster which is much more economical of time, glass-ware, and effort than the use of threads (Koch, 1881),