No redness, swelling, or tenderness is observable in the painful joints. The spleen may just be palpable, but more often is not. Meningococcal endocarditis has been described, and may complicate the septicaemia, but more frequently the valves are not affected. A necropsy on Case III after remittent pyrexia for twelve months revealed no endocarditis. Cases with metastases in joints, pleura, and conjunctivae have also been described.

Occurrence of Meningitis

Meningococcaemia may persist for many weeks or months after an attack of meningitis, but in the cases to which we more especially wish to call attention there is (i) an absence of all signs of meningeal involvement, (ii) transient signs of meningeal irritation at the onset, shown by headache, pain in the back of the neck, and perhaps some neck rigidity, the cerebro-spinal fluid in these cases remaining unchanged, or (iii) a terminal onset of meningitis, as happened in Case III after nine months' illness.

The blood count may show a leucocytosis of 12,000 to 25,000 white cells, or may be normal. There is never a leucopenia. The chronic forms of meningococcaemia are not peculiar to any group of meningococci, Types I, II, and IV being found in the present series. The organism can sometimes only be isolated from the blood with difficulty, or not at all, and a negative blood culture does not exclude the condition.

Duration and Prognosis

The pyrexia may last for many weeks or months. In our cases the pyrexial period extended over nine, eleven, twelve, fifteen, and fifty weeks respectively. Several cases continuing for five to nine months are recorded in the literature, but no reference has been found to an instance lasting for twelve months, as did Case III.

The prognosis is good. Four out of the present five cases and over 75 per cent. of those previously published have completely recovered after many weeks' or months' pyrexia. Endocarditis or the late development of meningitis, usually both, occur in almost all fatal cases. Definite endocarditis probably renders the prognosis hopeless.

Conclusions

Subacute and chronic forms of meningococcal septicaemia may last for a few weeks, or for longer periods up to nine or twelve months, signs of meningeal involvement being absent, or only transient at the onset. They are characterized by irregular pyrexia, with occasional rigors but with little elevation of the pulse rate, leucocytosis, pains in the limbs, and peculiar skin eruptions. Over 75 per cent. of these cases recover completely, but endocarditis or terminal meningitis may be a fatal complication.

The condition is seldom diagnosed in the absence of meningeal symptoms. The organism is sometimes difficult or impossible to isolate, and negative blood cultures and a negative complement-deviation test are not necessarily conclusive. This was shown by Case III, in which repeated blood cultures were negative during the whole period of twelve months of pyrexia and rigors, the meningococcus only being recovered from the cerebro-spinal fluid at the terminal stage after meningitis had eventually set in, and only thus was the diagnosis established.

It is thought that this condition probably occurs more frequently than is generally recognized, and that some cases pass undiagnosed. The skin lesions may so closely resemble erythema nodosum that perhaps some cases at present diagnosed as erythema nodosum may really be examples of meningococcal septicaemia. More particularly is this so in those cases in which the pyrexia persists for several weeks, with recurrent crops of the nodes, especially if the lesions are also present on the arms, chest, or face. In a case of long-continued and obscure pyrexia a meningococcal origin should be considered as a possibility. Inquiries should be made for any of the characteristic symptoms and signs, and the appropriate laboratory investigations should be undertaken, bearing in mind that a negative blood culture is not necessarily conclusive.

I wish to express my thanks to Drs. Hutchison, Leyton, and Rowlands for their kind permission to publish their cases, and to acknowledge with gratitude Dr. Lawson Stote's previous publication of the two earlier cases from the London Hospital, the case records of which I have also referred to in the discussion of the clinical picture.

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VIRUSES IN THE AETIOLOGY OF SKIN DISEASES*

BY

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Lesions of the skin produced by filterable viruses present a variety of types. There are such lesions as warts and molluscum contagiosum in which cellular proliferation and tumour-like formation are the dominant features, anything in the nature of an inflammatory reaction being absent. There is, again, the type of lesion presented by herpes, zoster, and varicella, characterized by swelling and ballooning of the affected epidermal cells with considerable leucocytic infiltration of the epidermis, and the presence of a serous exudate, which dissociates the epidermal cells and collects beneath the stratum corneum in the form of a vesicle. In some cases, as in the pock diseases, the leucocytic infiltration reaches such dimensions that the vesicle fluid becomes frankly purulent and the fully developed lesion is a pustule.

In addition to these two main types of lesion—the hypertrophic tumour-like lesion and the vesicular or pustular—there are others. The exanthem of measles is essentially an urticarial papule in which vesicle formation is so little in evidence as to be only detectable by means of the microscope ; the erythematous macule of typhus constitutes yet another type. Thus there is nothing either in the naked-eye appearance or the gross histology which can be said to be a common feature of virus lesions of the skin ; further than this, similar types of lesion are produced by agents other than viruses.

Pathological Manifestations

This does not mean that histological study of a lesion is of no value, for the affected cells may present changes which are peculiar to virus lesions. These are the inclusion bodies, homogeneous or granular acidophilic masses of varying size situated either in the cytoplasm or in the nucleus. Although inclusion bodies have not been demonstrated in the case of all viruses, available evidence suggests that they are not produced by any other type of infective agent. The nuclear inclusions produced by the viruses of herpes, zoster, and varicella, and the cytoplasmic inclusions seen in molluscum contagiosum, are good examples of this type of change.

In addition to this it may be possible to demonstrate the virus itself in smears made with material from the

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lesion, for it is now recognized that quite a number of these agents come within the limits of visibility with the microscope. Here, however, special staining methods are required, and considerable experience is essential for the correct interpretation of the findings. Even the largest viruses are only about 0.25 μ in size, and such small bodies are only too readily confused with cell granules and artefacts by the inexperienced observer. In the fluid from the vesicles of herpes, zoster, and varicella the virus particles, or elementary bodies as they are often called, are present, and can be demonstrated by suitable staining methods ; smears made from molluscum bodies are rich in elementary bodies. Thus it is clear that, although the appearance and gross histology of a skin lesion are of little help in deciding whether its causal agent is a filter-passing virus, suggestive evidence of this may be provided by the finer histological detail.

Aetiological Considerations

Proof of the virus aetiology of such a lesion is another matter. The first thing is to attempt to establish the presence of an infective agent in material from the lesion by animal inoculation, using, if possible, a number of different animal species, and introducing the material by a variety of routes. When, as in herpes, one or more of the ordinary laboratory animals is found to be susceptible, the matter is simple. Serial passage and filtration experiments, together with the inability to cultivate the causal agent on a lifeless medium, furnish the necessary evidence.

But many of the viruses are strictly species-specific in their infectivity, and the inability to demonstrate the presence of a virus in a human lesion by animal inoculation may be due to this fact. The viruses of molluscum contagiosum and human warts appear to be capable of infecting man only, and although there is some evidence that varicella virus can produce a lesion in the testicle of vervet monkeys (Rivers and Eldridge, 1929), man alone would seem to be readily susceptible to this virus and its close relative zoster virus. Human transmission experiments may be carried out, and it is by this means that the evidence of the virus aetiology of warts and molluscum contagiosum has been obtained.

Several investigators, among them Kundratitz (1926) and Bruusgaard (1932), have also used man as their experimental animal in their investigations of zoster and varicella, and so obtained valuable evidence as to the presence of virus in the fluid of the vesicles which appear on the skin in these two conditions. Such work has also contributed to our knowledge of the close relationship which exists between these two viruses, but it is obvious that investigation entailing the use of man as the experimental animal can never be undertaken on a very lavish scale, and quite frequently would be unjustifiable owing to the risk involved. Fortunately this is not the limit of the possible lines of investigation.

In virus infections, as in diseases due to cultivable bacteria, specific antibodies are developed which can be demonstrated by the various antigen-antibody reactions. Thus elementary bodies (virus) present in the lesions of a given condition can be agglutinated by the sera of those convalescent from the disease, or be shown to fix complement in its presence. It was by means of the former reaction that Amies (1933–4) showed that the minute bodies present in the fluid of the vesicles of zoster and varicella were in all probability the virus, and Netter and Urbain (1931) made use of the complement-fixation reaction in demonstrating the close relationship between these two viruses. These immunity reactions can therefore be of great value, and provide us with circumstantial evidence which will help in establishing the virus aetiology of a skin condition of unknown causation.

Experimental Work

During the last five years I have carried out investigations on the four skin diseases of known virus origin: herpes, zoster, varicella, and molluscum contagiosum. This has been done not only to attempt to add to our knowledge of these viruses and the diseases they cause, but also to familiarize myself with the technique of virus work with a view to investigating some of those skin conditions whose aetiology remains unsolved. Several strains of herpes virus have been isolated by the inoculation of guinea-pigs in the plantar skin of the hind feet, and maintained by serial passage in this animal. Filtration experiments have confirmed the findings of previous workers that this virus filters with difficulty through any of the ordinary filters, but passes readily through collodion filters of an appropriate pore size.

In the serum of animals which have recovered from experimental infection specific antibody can be demonstrated by the neutralization test (Bedson and Crawford, 1927), or by the complement-fixation reaction (Bedson and Bland, 1929). It is interesting to note that, using the neutralization test, Bedson and Bland (1928) were unable to confirm the claim of Gildermeister and Herzberg (1925 ; 1927) that the viruses of vaccinia and herpes were related and gave a certain degree of cross-immunity. Using the complement-fixation reaction I was able to show that specific herpetic antibody was present in the serum of human sufferers but absent from those who had never had herpes (Brain, 1932).

In the case of zoster, reference has already been made to the absence of a suitable susceptible experimental animal. My own attempts to establish this virus in animals have met with the same lack of success as that of previous workers. The presence of specific antibody in the serum of zoster convalescents has been demonstrated by Netter and his colleagues by the complement-fixation reaction, and in addition they have obtained evidence of the unity of idiopathic and symptomatic zoster and of the close relationship which exists between this virus and the virus of varicella (Netter and Urbain, 1931). They made use of suspensions of crusts from the skin lesions as antigens in their investigations. My experience leads me to the conclusion that the vesicle fluid is superior. Using this antigen I have obtained results in conformity with those of the French workers, and furnished further evidence of the close relationship between the viruses of zoster and varicella (Brain, 1933).

Clinical Evidence

The infectivity of human warts and molluscum contagiosum has already been demonstrated by experiments in man, and is in accord with clinical observations. Attempts were therefore made to demonstrate the presence of antibodies in the sera of patients with multiple lesions. Using an antigen prepared by grinding up curetted wart material with saline solution, sera from five cases of multiple warts were examined by the complement-fixation reaction, the technique of Bedson and Bland (1929) being employed. No specific fixation was obtained, and precipitin tests with both heated and unheated antigens were negative.

Suspensions of elementary bodies in a relatively pure state are easily prepared from molluscum lesions, and with such an antigen I carried out some complement-fixation tests. Sera from six patients with multiple mollusca and from one individual who had been given a series of inoculations with formolized molluscum material were tested ; in only two cases were positive results obtained. Precipitin and agglutination tests were also made, and here again the results were negative, though it would be rash to conclude from these few experiments that specific antibody is not developed in these conditions.

Transmission experiments have also been performed with material from cases of dermatitis herpetiformis. Bullae do not occur in certain chronic phases of this condition, and out of ten cases examined fresh bullous fluid was obtained in only four. The undiluted fluid was inoculated intradermally in the shaven skin of the flanks and the plantar skin of the hind feet of guinea-pigs. Two of these specimens were bacteriologically sterile, and the animals inoculated with these developed no lesions. The other two fluids contained staphylococci and streptococci and, with these, herpetiform lesions were produced in the plantar skin of the inoculated animals ; no lesions appeared in the hairy skin. Brief notes regarding the investigation of these two cases follow.

Case 8.—A girl aged 9 had a six-weeks history of bullous eruption, clinically dermatitis herpetiformis. Inoculation of a guinea-pig in the plantar skin with a vesicle fluid produced a pustulo-vesicular reaction in two days. The animal was killed, and the " pads " were removed and ground up with saline solution to give a 1 in 10 suspension, which contained staphylococci and streptococci. A " gradocol " (Elford, 1932) filtrate made from this suspension was sterile, and proved non-infective for the guinea-pig. The unfiltered suspension produced a similar reaction to that obtained with the primary material, and from this and from a sterile gradocol filtrate a further animal passage was obtained. A suspension made from the lesions in this last guinea-pig proved sterile bacteriologically and non-infective on inoculation. Control inoculations made with broth cultures and saline suspensions of agar cultures of the bacteria grown from this bullous material produced no lesions in the guinea-pig. Fresh bullous fluid collected from this case two weeks later was sterile culturally and non-infective in the guinea-pig. Intradermal inoculations of the patient with the streptococcal vaccine and a filtrate of it produced bullous reactions ; a control test with a staphylococcal vaccine produced no reaction.

Case 10.—A man aged 64 had a three-months history of an eruption which was thought to be dermatitis herpetiformis. A guinea-pig was inoculated as in Case 8 with undiluted bullous fluid ; a pustulo-vesicular reaction appeared in the skin of the hind feet after six days. A suspension made from these lesions was found to contain streptococci ; further passage was unsuccessful.

Transmission experiments were conducted with different material from two other cases—namely, saliva from one case with many ulcerative lesions in the mouth ; in the other case, showing many erythematous plaques, the fluid obtained by blistering with liquor epispasticus over the lesions was used. In both cases the material proved non-infective for the guinea-pig.

Bedson (1935) reported successful transmission to guinea-pigs with vesicle fluids from three out of six cases of dermatitis herpetiformis ; passage to the third and eleventh generations was realized with two of these strains. Although this demonstration of an infective agent in the bullous fluid from some cases of dermatitis herpetiformis supports the observations of Urbach and Reiss (1931), Urbach and Wolfram (1933), and Taniguchi (1934), as Bedson points out, the presence of a streptococcus in the material used in our series of experiments may be of significance. In only one instance was a bacteriologically sterile filtrate found to be infective, although it should be added that attempts to produce lesions in the guinea-pig's skin with the streptococci obtained from the human lesions were unsuccessful. Using bullous fluid as antigen, I have attempted to demonstrate antigen-antibody reaction by complement-fixation and precipitin tests without any specific result, and it has to be admitted that our evidence to date of the virus aetiology of dermatitis herpetiformis is conflicting and far from complete.

Sterile bullous fluid from a case of pemphigus vegetans was inoculated into a guinea-pig, a rabbit, and mice without result. I have also to record the unsuccessful inoculations of guinea-pigs with material from five other cases of bullous eruption, urticarial or erythema multiforme in type, kindly referred by Dr. W. J. O'Donovan. One of these bullous fluids contained staphylococci and streptococci ; the other four were sterile. The sera from eight cases of psoriasis have been tested with various antigens prepared from psoriatic scales, but complement-fixation and precipitation reactions were entirely negative. It was thought that artefact bullae superimposed upon recent lesions of psoriasis or lichen planus might contain the hypothetical virus, but no specific antigenic reactions were obtained with such material.

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FURTHER INVESTIGATION OF A NEW ANTI-CHOLERA SERUM

BY

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Since our preliminary note on the " Treatment of Cholera with a New Anti-cholera Serum "[1] attempts have been made to increase further the potency of the serum. Several modifications of the original method of toxin production as discussed in our paper on the preparation of cholera toxin and its experimental pathogenic action[2] were made in order to enhance the titre of toxin. At the same time serum was also prepared by injecting agar culture to compare the therapeutic value of the serum prepared with our original toxin and that prepared by injecting agar culture. The therapeutic effect of serum obtained by immunizing horses with agar culture only was hardly noticeable, though tried both intraperitoneally and subcutaneously. We showed in our note that the agglutinating titre of the serum obtained by immunizing horses with the toxin was 1 in 8,000.

It may be possible that both exotoxin and endotoxin of cholera vibrio play important parts in the disease, and that by our method of toxin preparation both exotoxin and endotoxin are available in fair amount for the immunization of the horse. It is a common experience to those working in cholera hospitals to find that there are two distinct groups of cholera—namely, (1) with excessive purgation and a high specific gravity of the blood, and (2) with early onset of vasomotor paralysis, lower specific gravity of the blood, and absence of pro-