A Lecture

ON

ZOSTER, VARICELLA, AND ENCEPHALITIS*

BY

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Herpes zoster is now regarded as due to an infection with a virus which is quite distinct from that responsible for herpes febrilis. It is confusing to apply the term herpes to both, and it would be advantageous to confine this term to herpes febrilis and to speak of herpes zoster simply as zoster, on the analogy of the French "zona." The infective character of zoster is an inference from the following facts. The eruption is often preceded by a disturbance of the general health, and sometimes by fever, and causes enlargement of neighbouring lymph nodes. There is a seasonal incidence, most cases occurring in the early summer and late autumn. Small epidemics have been described, and the contagiousness of the condition is well established. There is also a relationship between zoster and varicella, which I shall discuss further below. A patient suffering from zoster may infect others with varicella. More rarely the opposite occurs. Immunity almost always follows the attack, and the histological changes in the skin and nervous system are inflammatory in character. In spite of the strong presumption that zoster is an infection, it is doubtful whether it has ever been transmitted to animals. Lipschütz¹⁵ and Grüter's⁷ experiments are not conclusive. Kundratitz¹¹ and others, however, appear to have transmitted it to children by direct cutaneous inoculation. The histological changes in the nervous system in zoster are now familiar. They were first described in 1861 by von Baresprünge, and have since been studied by many observers, especially by Head and Campbell⁸ and by Wohlwill.²⁴ In the acute stage there are haemorrhages, infiltration with mononuclear and occasional polymorphonuclear leucocytes, especially in the form of perivascular cuffs, and degenerative changes in the nerve cells. Fibrosis and secondary degeneration follow in severe cases. The changes occur in the first sensory neurone. The posterior root ganglion and its cranial equivalent, the Gasserian ganglion, are most frequently affected, but the spinal cord often exhibits a lesion at the base of the posterior horn, and the peripheral nerves may also suffer. These tissue reactions are clearly inflammatory, and led Head and Campbell, in 1900, to speak of zoster as "an acute specific disease of the nervous system" manifesting itself as "an acute posterior poliomyelitis."

"Symptomatic" and "Idiopathic" Zoster

It is very important for clinical purposes to distinguish two groups of cases of zoster—those with and those without a discoverable predisposing cause. The former are often called "symptomatic" as distinguished from "idiopathic" zoster. "Symptomatic" zoster may occur in the course of intoxications—for example, with arsenic, bismuth, carbon monoxide, and other poisons. Jonathan Hutchinson, in 1868, described cases of zoster arising during treatment with arsenic. It may also complicate infections such as pneumonia or tuberculosis, but is especially liable to occur when the first sensory neurone is itself damaged. Thus syphilitic radiculitis and spinal compression following carcinomatous deposits in the vertebrae are well-recognized causes. In the idiopathic

group no obvious predisposing event can be found. Clinical distinctions, however important to the physician, are sometimes biologically misleading, and we now know that "symptomatic" and "idiopathic" zoster are fundamentally identical. Head and Campbell observed thirty years ago that the histological changes of both were indistinguishable. Their etiological identity has been established by Netter¹⁹ by means of complement-fixation tests, which I shall describe later. What, then, is the relationship between zoster and a lesion of the first sensory neurone? This is most direct when a gross injury of the posterior root is followed by zoster. In such a case it is a legitimate inference that the primary lesion has lowered the resistance of the root ganglion to the zoster virus. Known exogenous or endogenous toxins presumably operate in the same way, and it is surely no unjustifiable leap to the conclusion that in idiopathic zoster an unknown factor, infective or toxic, may exercise the same predisposing effect, lowering what Levaditi¹⁴ calls the "tonus immuno-trophique" of the ectodermal tissues of the metamere. Once the virus has invaded the sensory neurone it proceeds peripherally towards the skin and centrally towards the neuraxis. Kundratitz has demonstrated the virus in the vesicles, hence the cutaneous lesions are a zoster dermatitis, and not, as was formerly supposed, "trophic" or primarily vasoparalytic in nature.

Some Clinical Aspects of Zoster

Besides the characteristics of zoster in its commonest form with a cutaneous eruption and sensory disturbance, there are manifestations of the infection which are interesting and important on account of the implication of other tissues. These are not very rare, and may be puzzling if one is not familiar with them.

1. *Ophthalmic Zoster.*—As we have seen, zoster may invade the Gasserian ganglion, in which case the eruption appears in some part of the trigeminal distribution. Usually only a part of the ganglion is involved; hence the eruption is usually confined to the distribution of one division of the nerve. Since the cornea receives its sensory supply from the ophthalmic division, it may be the site of the eruption when this division is attacked. Even so, it may escape, and, as Jonathan Hutchinson first pointed out, it usually does so unless the naso-ciliary branch is involved. Hence the absence of an eruption on the nose in zoster of the first division of the trigeminal usually means that the cornea will escape. According to Paton,²¹ in his excellent account of "The trigeminal and its ocular lesions," "the most frequent primary corneal lesion takes the form of small, round infiltrations in the more superficial layers of the substantia propria of the cornea." I must refer you to Paton's paper for the corneal complications of zoster, which are sometimes severe, and may even involve loss of the eye. Other orbital structures may be involved in the inflammation, and the most important complication, fortunately a rare one, is optic neuritis, followed by atrophy and leading to blindness. Oculomotor paralyzes sometimes occur, the third nerve being more often affected than the fourth and sixth. Trigeminal zoster, like zoster elsewhere, may be either "idiopathic" or "symptomatic." In the latter case it may follow any intracranial lesion of the fifth nerve, even alcoholic injection of the Gasserian ganglion. It must be distinguished from neuro-paralytic keratitis, a much commoner complication of this therapeutic measure, and from simple herpes of the cornea, which usually manifests itself as a dendritic ulcer.

2. *Geniculate Zoster.*—Zoster of the geniculate ganglion is interesting, not only anatomically, but also as a cause of facial paralysis. This tiny ganglion is the sensory ganglion of the facial nerve, corresponding to the Gasserian

* Delivered to the Glasgow University Medico-Chirurgical Society.

ganglion of the trigeminal and to the spinal posterior root ganglia. Its main sensory function is the reception of taste impulses from the anterior two-thirds of the tongue by the chorda tympani, but it also sends sensory fibres to a variable area of the external auditory meatus and concha, and to the anterior pillar of the fauces and soft palate. Geniculate zoster is associated with typical zoster vesicles in the auricle, less often on the fauces, and with pain in the ear and mastoid region, radiating to the anterior pillar of the fauces and to the vertex. The principal sensory loss in geniculate zoster is of taste in the anterior two-thirds of the tongue on the same side. Its most important clinical feature, however, is facial paralysis, which is almost invariably present (Ramsay Hunt¹⁰). Since the herpetic vesicles may be inconspicuous, the true cause of the paralysis is likely to be missed by anyone unfamiliar with the condition. The facial paralysis which may be associated with clonic facial spasm is doubtless due to the spread of inflammation from the geniculate ganglion to the facial nerve. Sometimes the eighth nerve is also involved, with resulting deafness or vestibular disturbances.

3. *Lower Motor Neurone Lesions in Zoster.*—We have just dealt with one example of a lower motor neurone lesion in zoster due to involvement of the facial nerve. Occasionally we meet with similar lesions corresponding to the muscular supply of spinal segments. Thus I have seen weakness and wasting of all the muscles supplied by the fifth cervical segment on one side associated with zoster of the same cutaneous distribution. Segmental paralysis of the abdominal wall is fairly common, and similar motor lesions may occur in other situations. It is more likely that they are due to a spread of the inflammation from the posterior to the anterior horns than to mutual involvement of the corresponding roots.

4. *Zoster Arthritis.*—Acute inflammation of the joints is a rare manifestation of zoster which has been little recognized in this country. Six cases have been reported in France, and I have seen two, one a patient of my colleague Dr. Anthony Feiling. In all eight cases the joints involved have been those of the fingers, and in one instance the wrist also. In some cases only one or two fingers have been involved, the joint changes corresponding to the segmental distribution of the eruption. In other cases, including my own patient, all the fingers of one hand were affected, though the eruption was limited to one root segment. In all the reported cases the onset of the arthritis has approximately coincided with the outbreak of the eruption. Pain and oedema have been severe, and in some instances oedema of the skin and subcutaneous tissues has persisted for months. Zoster arthritis seems always to be followed by great limitation of movement of the affected joints, probably due mainly to periarticular changes, since radiograms show few bony alterations, except rarefaction. French writers usually describe these disturbances as arthropathies, but the evidence points to their being, in fact, an arthritis. During the acute stage the clinical appearances are indistinguishable from an acute arthritis, and neither clinically nor radiologically does the condition resemble the familiar arthropathies. As we have seen, there is evidence that the zoster virus spreads along the nerves to the skin, and Paton believes that it reaches the cornea in a similar manner. It is not unreasonable to suppose that sometimes it may reach the joints also.

5. *Zoster Meningitis and Encephalitis.*—If, as there is reason to believe, zoster is primarily a posterior poliomyelitis or ganglionitis, it is not surprising that the infection should sometimes spread to other parts of the nervous system. That the meninges are often secondarily involved is indicated by the frequent occurrence of lymphocytosis

and raised protein content in the cerebro-spinal fluid. Chauffard and Froin³ first drew attention to this, and Chauffard and Rendu⁴ described it as "Meningite zonateuse." They pointed out that the evidence for meningitis might be not only cytological, but also clinical, and that cervical rigidity and Kernig's sign might be present. In some cases we find zoster associated not only with meningitis, but with evidence of involvement of the substance of the brain—that is, encephalitis. These cases are not easy to interpret, since we know that symptomatic zoster may follow a lesion of the nervous system, and the question arises whether the zoster is secondary to an encephalitis of different origin, or whether the encephalitis has been produced by the zoster virus. Schiff and Brain²² have recently reviewed the reported cases of this association and published a further example. They reached the conclusion that although in some instances the zoster was a complication of an independent encephalitis, there remained a group of cases in which an extension of the zoster infection had produced the clinical picture of encephalitis. In their own case this conclusion was supported by complement-fixation tests on the cerebro-spinal fluid, which were carried out by Bedson and Bland,¹ and which afforded evidence of the presence of the zoster virus therein. In the mildest cases, therefore, extension of the zoster infection to the meninges is indicated only by the appearance of inflammatory changes in the cerebro-spinal fluid. In more severe cases the clinical manifestations of meningitis are added, and a further extension may involve the substance of the neuraxis. In zoster meningo-myelitis myoclonus is not uncommon. At least two fatal cases of zoster meningo-encephalitis have been reported.

THE RELATIONSHIP BETWEEN ZOSTER AND VARICELLA

The existence of an association between zoster and varicella appears to have been first observed by Bokay² in 1888, and has since been very thoroughly investigated by clinical, bacteriological, and serological methods.

Clinical Observations

1. In Bokay's original instance zoster in one individual was followed after ten days by varicella in a contact. This is by far the most frequent sequence, and has now been recorded hundreds of times. Netter¹⁹ in 1928 had collected 174 examples published in France alone. The same author has investigated the incubation period in 102 cases and found that it ranged from seven to twenty-four days, but more than half of the cases of varicella occurred between the thirteenth and the sixteenth day after exposure. Varicella may thus follow not only so-called idiopathic zoster, but also zoster occurring in the course of arsenical treatment.¹⁹

2. Conversely, zoster may occur in an individual who has been in contact with varicella, though this is much less frequent. Netter has collected twenty-five cases in which the incubation periods were the same as in the preceding group. The sequence zoster-varicella is eight or ten times as frequent as the sequence varicella-zoster. Hill,⁹ recording epidemics of both in an institution, found nine of the former and one of the latter.

3. It is common enough for varicella to breed true and cause varicella in contacts. The same may occur with zoster.

4. All possible combinations of these associations have been recorded. Thus a case of zoster may be followed by zoster in one contact and varicella in others, and the same is true of varicella. In the case of either disorder the first generation of contacts may show the similar and the second the dissimilar illness, or vice versa.

5. The same individual may show both zoster and a scattered eruption resembling varicella. There may be only a few "aberrant vesicles" or a widespread vesicular eruption. The latter has been described by some authors as "zoster generalisatus." Others, struck with its resemblance to varicella, have written of "zoster and varicella in the same patient." Usually the generalized rash appears within three or four days of the outbreak of zoster, but the interval may be longer. Bokay² has investigated this point in twenty-nine recorded cases. He found that in ten cases both local and general eruptions appeared on the same day, and in twenty-one the latter was evident before the fifth day. It is sometimes, however, delayed even until the third week.

Epidemiology

Allusion has already been made to the occurrence of epidemics of zoster. Bokay has sought to discover whether these have any relation to varicella epidemics. He therefore obtained such data as were available concerning the incidence of the two disorders month by month in Budapest for the ten years 1915-24. These data are admittedly not complete, and are indices rather than totals. Nevertheless, there is a striking correspondence between the variations in the monthly prevalence of the two diseases. In nine out of the ten years there is an autumn peak, usually reaching its maximum for varicella in November, and in most years a smaller peak in June. A point of interest and importance to which Bokay does not draw attention is that the peak of the zoster curve usually occurs one month before that of varicella.

Bacteriology

Kundratitz¹¹ was the first worker to claim to have transmitted zoster by inoculation to children. In 1927 he reported twenty-six successful inoculations of children with the contents of zoster vesicles. The usual result was an eruption at the site of inoculation, but a few patients also exhibited a generalized vesicular rash. Children who came in contact with those successfully inoculated developed varicella. Kundratitz previously reported fourteen successful inoculations in twenty-two attempts. The inoculation period varied from nine to fourteen days. Only children who had not previously had zoster or varicella were found to be susceptible. A successful inoculation protected against a subsequent zoster inoculation and also against varicella. Netter¹⁹ quotes eight other workers, and Cleveland⁵ one, who obtained similar successful inoculations of zoster, often with transmission of varicella to contacts. It is uncertain whether the serum of patients who have recovered from zoster protects others against varicella. Kundratitz claims positive results. Sicard and Paraf²³ have failed to verify them. Netter, however, justly points out that negative results are not very strong evidence against the common nature of zoster and varicella, since several workers have found that serum from varicella convalescents fails to protect against varicella.

Complement-Fixation Tests

In 1923 de Lange¹² claimed to have demonstrated antibodies to varicella in the blood of a patient suffering from zoster. Netter and Urbain²⁰ thereupon set themselves to investigate this point by means of complement-fixation tests in a large series of patients. In 1926 they published the results in 100 cases of zoster, of which 84 had had no apparent contact with varicella. In 93 out of the 100 cases deviation of complement occurred when the crusts of vesicles either from varicella or from zoster were used as antigens against the blood serum of the zoster

patients. Exactly the same results were obtained with the same antigens and the blood serum of patients convalescent from varicella. Netter and Urbain have similarly demonstrated the presence of antibodies to varicella in the blood serum of nine patients in whom zoster followed arsenical treatment, of three in whom it was induced by injections of bismuth, and of two in whom mercury was apparently a precipitating factor. Lauda and Silberstein¹³ have failed to confirm Netter and Urbain's complement-fixation tests, but Bokay attributes their failure to a variation in technique. Netter quotes Pincherle and Vegni¹⁹ as having confirmed his findings.

Relation between Zoster and Varicella

What conclusion can we draw concerning the relation between zoster and varicella? It seems incontestable that some cases of zoster are due to a virus which may also produce in contacts a condition indistinguishable from varicella. It is not yet proved, however, that all cases of zoster and all cases of varicella are due to the same organism, though there is evidence which suggests that they may be. The indications that zoster arising in the course of treatment with arsenic, bismuth, and mercury may be of varicellar origin goes far to support the view that lesions of the first sensory neurone also operate only as predisposing causes. If so, the heterogeneous causation of zoster is not an argument against its being due to a single virus. Reports of varicella in contacts with zoster arising secondary to gross lesions of the posterior roots are lacking, and would be very valuable. Netter and Urbain's complement-fixation tests and Bokay's epidemiological investigation go far to link together at least a large proportion of cases of both zoster and varicella.

Let us leave open the question of how far we can generalize, and turn to the interesting problems which arise from the conclusion that at least some cases of both diseases are due to the same organism. Why do some infected persons develop zoster, others varicella, and some both? And why is it about ten times more common for zoster to give rise to varicella than vice versa? Answers to these questions must be largely speculative. Nevertheless, there are some indications as to the directions in which the explanations should be sought. There is a striking difference in the average age of the zoster-from-varicella and the varicella-from-zoster patients. In Netter's first group only eight out of twenty-five were children. The ages of the adults are not all given, but the average of five was 55, and among the remainder were a grandmother, a concierge, and two doctors. On the other hand, almost all the varicella-from-zoster patients are children, the average age of fifty cases reported by Netter being 6 years. These facts suggest that adults are relatively immune to the varicella virus, that immunity wanes as life goes on, and that the adult who becomes susceptible develops zoster rather than varicella. It is tempting to suppose that this hypothetical immunity is due to an early attack of varicella. The special susceptibility of the first sensory neurone in adults may be due to its possessing a tissue immunity feebler than that of other parts of the body, or to its immunity being temporarily diminished by a preceding lesion. Once the infection has established itself in the metamere it may disseminate itself in the blood stream, causing the generalized rash as in generalized vaccinia. From what we know of the effects of partial immunity upon the manifestations of an infection we may hazard a guess that the length of the interval between the outbreak of zoster and the occurrence of a generalized rash is an index of the degree of existing immunity to the virus. The shorter the interval the greater, probably, is the immunity.

Cranston Low¹⁷ has suggested that varicella is a haematogenous infection, while in zoster the virus reaches the posterior root from the cerebro-spinal fluid, to which it gains access from the nose. This may be true, but the significant difference in age incidence seems to require an explanation in terms of immunity.

VARICELLAR ENCEPHALITIS

Much attention has recently been directed to the occurrence of encephalitis as a complication of the acute specific "fevers," and a brief study of varicellar encephalitis and myelitis may prove not only interesting in itself but illuminative of the general relationship between "fevers" and their neural complications. I have been able to find in the literature thirty-two cases which can reasonably be included under this heading. Apart from two patients aged 32 and 23, all were children, the average age in twenty-seven cases being $4\frac{1}{2}$ years. Symptoms of involvement of the nervous system developed as a rule between the fifth and the twentieth day after the appearance of the rash, in most cases during the second week, usually between the seventh and tenth days. The onset was acute, and was generally associated with fever, headache, vomiting, and giddiness, and sometimes with delirium. In the following table I have arranged the thirty-two cases in groups according to their predominant symptoms.

Meningeal	2 cases
Ataxic and "cerebellar"	11 "
Tremor	3 "
Chorea and choreo-athetosis	2 "
Diplegia	1 "
Hemiplegia	1 "
Ophthalmoplegia	2 "
Spinal	8 "
Coma	1 "
(?) Polyneuritis	1 "

The distinction of "types" in dealing with so diffuse a process as encephalitis is of course artificial. Thus a pyramidal lesion may coexist with ataxia and meningeal symptoms with transverse myelitis. Nevertheless the classification is valuable as indicating the predilections of the disease for certain parts of the nervous system. It is striking that in half the cases disturbances of co-ordination with or without involuntary movements were the conspicuous feature. The ataxia was often so gross that the child was quite unable to walk. The spinal lesion usually produced the picture of a transverse myelitis at the dorsal level of the cord. In one case one upper and both lower limbs were paralysed. It is doubtful whether the diagnosis of "polyneuritis" is correct, since the patient thus diagnosed was not examined till five years after the onset, and was then found to have muscular wasting of all four limbs. In only a small number of cases is there a report on the cerebro-spinal fluid. In some this was normal; in others there was an excess of cells, up to 71 per c.mm. In one case these were polymorphonuclear; in the others their nature is not described, and it may perhaps be assumed that they were mononuclear. The prognosis is good both as to life and as to recovery of function. Of thirty-two patients, only two died—the two adults—one of ascending myelitis, the other in coma twenty-four hours after the onset of the nervous manifestations and on the third day of varicella. As this patient was pregnant, it is possible that the cause of death was related to the pregnancy rather than to the varicella. Only three of the remaining thirty cases appear to have failed to recover completely; even the grossest ataxia usually disappeared within a few weeks. In neither of the fatal cases was there a post-mortem examination, and I have been unable to find any record of a pathological examination in varicellar encephalitis.

Two views prevail as to the nature of post-vaccinal encephalitis: that it is due to the virus of vaccinia, and that it is produced by some other virus which invades the nervous system secondarily to vaccination. The same alternatives have been put forward to account for measles encephalitis, and it has been suggested, chiefly on pathological grounds, that both measles encephalitis and post-vaccinal encephalitis may result from the same secondary invader. Are we to regard varicellar encephalitis as due to the organism of varicella or to this hypothetical neurotropic virus? In this case we have no pathological findings to guide, or perhaps to mislead, us, and we must therefore turn for light to the clinical features. It is instructive to compare certain of the clinical characteristics of encephalitis complicating vaccination, measles, and chicken-pox, tabulated below:

	Post-vaccinal Encephalitis	Measles Encephalitis (Ford ⁶)	Varicellar Encephalitis
Cerebellar syndromes:			
Frequency	Rare	14 out of 125	11 out of 32
Recovery from	—	12 out of 14 incomplete	All complete
Mortality (all cases) ...	58%*	10%	6%
Recovery of function (all cases)	Good	25% complete 65% incom- plete	81% complete 9% incom- plete

* English epidemic, 1922-23.

We have here indications that the clinical pictures, mortality rates, and prognosis as to functional recovery are quite different in the three conditions. Those who regard them as due to the same virus will have to suppose that the action of this hypothetical organism is hypothetically modified by the influence of the different pre-existing infections. This may be true, but it seems less speculative to suppose that the differences are due to the encephalitis being produced by different organisms—namely, the viruses of vaccinia, measles, and chicken-pox. The solution of this problem, however, awaits a greater knowledge of these viruses and the discovery of better methods of detecting both the organisms themselves and the antibodies which they evoke in their hosts.

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