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CLASSIC PAPER

The Pathology of Herpes Zoster and its Bearing on Sensory Localisation†

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INTRODUCTION

This famous paper in the journal *Brain* was written at the turn of the century by a neurologist and a pathologist—Henry Head and A. W. Campbell respectively. The significance of the paper's seminal observations and deductions therefore has to be assessed in the context of what was known about the nervous system and about virology around 1900. Although the foundations for advances in clinical neurology and neuropathology had already been firmly established at this time, especially in Europe, the field of microbiology was in its relative infancy. Despite the major advances in microbiology and vaccination pioneered by such scientists as Koch and Pasteur in the latter half of the 19th century, the nature of viruses had yet to be established when these observations on herpes zoster (HZ) or 'shingles' were made. It was to be about 30 years later before the physico-chemical nature of viruses began to be established, prior to which animal transmission studies of virus diseases were prominent,[1] and it was not until the early 1950s that cell culture systems were developed for growing and studying viruses.[1] This was followed by the revolution in molecular biology which has led to our current sophisticated state of virological knowledge. While clinical neurology has, of course, also advanced over the last century, meticulous clinical observation of patients has remained until this day a critical part of the neurological assessment.

Head and Campbell did not know the cause of HZ, although they made some interesting suggestions. In 1909 Von Bokay noted the development of chickenpox (varicella) in children who had been exposed to individuals with shingles, and therefore suggested that the two conditions were caused by the same agent.[2] But it was not until 1965 that Hope- Simpson's theory of the pathogenesis of HZ was proposed,[3] and this is generally regarded now as correct. The theory states that following varicella infection a viraemia occurs and Varicella-Zoster virus (VZV) is transported from the skin along sensory nerve fibres to the sensory ganglia where it becomes latent. Reactivation of latent virus causing HZ may then occur spontaneously with no obvious precipitating events or following specific triggering stimuli such as trauma, sunlight, infection or malignancy. VZV then spreads antidromically along the involved sensory nerve to produce the HZ skin eruption in the corresponding dermatome.[3]

It should be appreciated that Head and Campbell's paper is primarily a neuropathological study with detailed and precise clinico-pathological correlations which allowed the mapping of the sensory dermatomes. It is not primarily an anatomical or a virological study except in the sense that the condition is now known to be caused by a virus. The paper is very long indeed, as were many of the neurological papers of this kind at the time, and there are immensely detailed pathological descriptions of many of the cases which they had studied over a period of at least four years. The editor has spared the reader much of the more tortuous parts of the paper, and only a limited number of sections are reprinted here. Nevertheless they are sufficient to provide you with a strong flavour of both the depths of their insights and the characteristic elegance of the writing style of this period. The reader is therefore asked to imagine himself or herself cast back almost 100 years to a time when neurovirology was embryonic.

Editor's note:
This article occupied 170 pages of *Brain*. We have chosen to reprint here selected parts of the text.

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THE PATHOLOGY OF HERPES ZOSTER AND ITS BEARING ON SENSORY LOCALISATION.

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INTRODUCTION.

It would be useless to attempt a review of all the literature that has grown up around the subject of '' Herpes Zoster,'' for from 1895 to the present time alone over seventy papers have been written on this subject, very few of which have any bearing on the matter of the present communication.

Moreover, our work deals with herpes zoster from two aspects. Firstly, we have determined the pathological lesion which underlies this disease, and, secondly, we have attempted thereby to determine the cutaneous distribution of certain fibres that enter each posterior root ganglion. We shall, therefore, only allude to such communications as throw light on the pathological lesions in herpes zoster, or on the distribution of the fibres which enter the posterior root ganglia.

It was not until the appearance of von Bärensprung's classical paper (23) in 1861 that herpes zoster was stated to be definitely of nervous origin ; and when von Bärensprung crowned his long series of admirably reported observations by a *post-mortem* examination (1), its association with a lesion of the posterior root ganglion was universally accepted. But as his conclusions in their passage from book to book have undergone modification, and as the position of the question he set himself to answer has been widened by our increased knowledge of the structure of the nervous system, it will be well to consider this first successful *post-mortem* examination more carefully. Moreover, we must remember that although von Bärensprung rightly placed the position of the lesion in the posterior root ganglion, he thought this structure stood in no connection with the fibres of the posterior root or peripheral nerve, but had special nerve-fibres of its own.

The eruption seems to have occupied the area we have called dorsal 7 ; for it ran in the form of a girdle over 2 inches in breadth between the 6th and the 9th ribs, passing the middle line behind for one or two lines at the level of the 5th to the 8th spines, to end beneath the xyphoid process. Death followed from tuberculosis forty days after the first appearance of the eruption.

The spinal cord and both anterior and posterior roots were stated to have been normal ; but '' Nachdem die Intervertebralkanäle geöffnet und die Intercostalnerven vom 5ten bis zum 9ten freigelegt waren fiel sogleich eine grössere Dicke und vermehrte Röthung des 6ten, 7ten und 8ten am meisten aber des 7ten auf, die von einer Auschwellung des mit erweiterten stark geschlängelten Gefässen durchzogenen Neurilems vorzugsweise abzuhängen schien. Der Durchmesser des 7ten Nerve übertraf fast um die Hälfte den des 5ten und des 9ten Intercostalnerven .... Den 6ten und 8ten Nerv zeigten die nämliche Röthung und Anschwellung aber etwas weniger stark und auf eine kürzere Erstreekung als den des 7ten.'' He then states that he found the remains of extravasated blood in the ganglion, without mentioning to which of the three ganglia he alludes.

This case seems to have borne a close resemblance to No. 2 and No. 4 of our series, in both of which cases the swelling of the affected ganglion and nerve was obvious to the naked eye. Thus by little more than a naked-eye examination von Bärensprung was enabled to prove that the ganglion was affected in herpes zoster.

The next report of a *post-mortem* examination was made by Charcot and Cotard in 1865 (4). A woman suffering from cancer of the breast developed zoster over what appears to have been the 3rd and 4th cervical areas. At the autopsy secondary growths were found to have invaded many of the vertebrł, especially in the cervical region. The 4th cervical vertebra was found to be profoundly affected. The only change found in the nervous system consisted in an active injection of the capillaries of the ganglia and nerves, a '' veritable neuritis '' without concomitant alteration of the ganglion cells or nerve-tubes.

This case is so poorly reported that even from the point of view of a naked-eye examination it is valueless, either to elucidate the pathology or localisation of the lesion of herpes zoster. It would seem to have closely resembled case 14 of our series, where examination, even by the simple methods of that day, would have revealed marked changes in the affected ganglion.

The next case was reported by Weidner in 1870 (18). In a paper on three cases of zoster he reported two autopsies with negative results. This is not surprising, since in his first case, although the eruption lay over what we have called cervical 4, he only examined the cord ganglia and nerves between cervical 7 and dorsal 2 ; and in his second case the patient died five years after the eruption.

In the same year E. Wagner (17) reported the result of an autopsy on a tuberculous patient who had developed an attack of zoster over the 9th and 10th ribs seven days before death. The six lower dorsal and the 1st and 2nd lumber vertebræ were laid bare by tubercular caries, and the dura mater was lined with a thick layer of cheesy pus. Only the ganglia were examined microscopically, and the 9th, 10th, and 11th dorsal were said to have been affected. But it is obvious that an incomplete examination of so complicated a case could add little to the knowledge of either pathology or localisation.

In 1871, Oscar Wyss (19) reported a case of zoster of the whole first division of the trigeminal nerve, where death occurred seven days after the appearance of the eruption. The ophthalmic vein was thrombosed and the eye-muscles contained small abscesses, and the connective tissue of the eyeball was infiltrated with pus. From the point where the first or ophthalmic division leaves the Gasserian ganglion to enter the eyeball it was surround by extravasated blood. The second and third divisions were unaffected ; but attached to the inner side of the Gasserian ganglion lay a red mass 1 cm. broad, apparently consisting of extravasated blood. Microscopically, there was an extravasation of blood into the inner aspect of the ganglion and

into the first division of the trigeminal nerve. There is also said to have been '' purulent inflammation '' of the ganglion, pushing the ganglion cells apart.

In 1875, Sattler (16) also reported a case of herpes ophthalmicus, extremely well worked out according to the methods then known. A man of 85 was poisoned by carbonic oxide gas. Four days later neuralgia came on over the right half of the forehead, and in a few days the forehead, the side of the nose, and the eyelids, became covered with an eruption of herpes zoster. Death occurred fourteen days afterwards. The Gasserian ganglion was found to be infiltrated with small round cells, and there was marked destruction of the ganglion cells. The ophthalmic division of the nerve was degenerated. The other two divisions were normal.

By this time it had come to be recognised that the ganglion was affected in cases of zoster, and in 1876 Kaposi (1) reported a case in which he arrived at a very odd result. A man of 54 died seven days after the appearance of an eruption that had the following distribution : '' Auf der allgemeinen Decke des Unterleibes rechts über den Darmbeinkamm und mit diesem parallel laufend eine continuirliche Folge von Herpes-gruppen welche etwa $1\frac{1}{2}$ bis etwa 1 Zoll vor und über der Symphyse sich erstrecken.'' The area affected seems to have corresponded with our dorsal 11. But he only examined the ganglia of dorsal 12 and lumbar 1 to 5, and states that hæmorrhages were present in the periganglionic fat of dorsal 12, lumbar 1, 2 and 3, and that the protoplasm of lumbar 2, the most affected ganglion, was pale and retracted. In the light of our present knowledge it is impossible that these changes could have been associated directly with the eruption over the area he describes.

In his text-book Kaposi again alludes to this case, and states that he also examined a case of herpes frontalis and found hæmorrhage and destruction in the Gasserian ganglion. We have not, however, been able to find any further account of this second case, and the first case, though frequently quoted, is valueless as a contribution to the pathology of herpes zoster.

In 1879, Chaudelux (3) reported the case of a woman who died of phthisis many months after an attack of zoster. He says the remains of the eruption lay over the 2nd and 3rd intercostal spaces on the left side, but gives no further details of its distribution. The 2nd and 3rd dorsal ganglia of the left side are said to have been double the normal size, and certain zones in these ganglia were completely transformed, ganglion cells and nerve-tubes were destroyed, and their place taken by dense connective tissue. From the figure he gives he evidently saw the condition figured by us on plate 1, fig. 2B. The spinal cord was destroyed in extraction, and the nerves, having been hardened in alcohol, gave no positive result.

In 1881, Lesser (12) published the first two satisfactory *post-mortem* examinations of cases of zoster of the trunk, and followed up his first communication by a second in 1883 (13), in which he reported a third case. In the first of these three cases the eruption lay over the right side of the neck, bounded in front and behind by the middle line, above by the lower jaw, and below by a line passing round the shoulder roughly to join the spine of the 2nd dorsal vertebra behind, with the third costal cartilage in front. This lower border dipped in front to occupy the extreme upper part of the anterior surface of the right arm. Death occurred twenty-six days after the eruption first appeared. The 4th cervical ganglion of the right side contained a focus visible to the naked eye, and situated on that side of the ganglion opposed to the anterior root. Microscopically, this focus consisted of a mass of cells surrounding what appeared to be the remains of a hæmorrhage. The remaining ganglia, the posterior roots, the nerves, and the spinal cord were stated to be normal ; but at that date no method existed by which the acute degenerative changes that probably existed could have been demonstrated.

In Lesser's second case the eruption appears to have occupied the area that we should call dorsal 8, and death took place about nine days after it first appearance. To the naked eye the 8th dorsal ganglion was very red, but not swollen. On microscopical examination this reddened area was seen to consist of hæmorrhage containing broken-down ganglion cells, and surrounded by a mass of inflammatory tissue. The case seems closely to have resembled Nos. 2, 4, and 5 of our series. Lesser thought that there was a similar though less pronounced change in the 9th dorsal ganglion, but he carefully states that there was no hæmorrhage or breaking-down of nerve elements, and our experience leads us to suspect that he was mislead by the hyperæmia not infrequently present in normal ganglia ; for he was evidently unwilling to believe that one ganglion could supply the whole of the area occupied by the eruption. The other ganglia, peripheral nerves, and spinal cord showed no change. Admirable figures accompany this paper, which is the first serious contribution to the pathology and localisation of zoster of the trunk.

Lesser's third case (13) died three weeks after an eruption that lay over the mamma and occupied the area we have called dorsal 5. On microscopical examination the 5th dorsal ganglion was found to be markedly altered. The nervous elements of the upper half of the ganglion were replaced by connective tissue, and the sheath of the ganglion over this area was thickened. The peripheral nerve of this ganglion also showed changes, for the normal fibres were in places widely separated by fields of granular tissue. He states that the 4th ganglion also was altered, but that the 4th nerve was normal. As, however, he gives no figures in this paper, it is difficult to gather the extent of these changes, and he admits that the 4th ganglion was not so carefully examined as the 5th.

In 1883, Pitres and Vaillard (15) reported the *post-mortem* on a curious case. After mentioning a number of cases in which they had examined the nerves in the neighbourhood of bed-sores, they mention a case in which there were scars of zoster in the 6th intercostal space on the right side, and an eruption that they thought was zoster in the 11th intercostal space of the same side. On microscopical examination they state that in the 6th dorsal ganglion nerve-fibres were destroyed but the cells were perfect, that there was parenchymatous degeneration and some sclerosis of the 6th dorsal peripheral nerve and degeneration of the posterior roots of the 6th dorsal. They also state that the posterior roots of the 6th dorsal. They also state that the 11th dorsal peripheral nerve was degenerated and sclerosed, but that the ganglion and roots were normal. The cord was everywhere normal. In the light of subsequent experience it would seem that the scars in the 6th intercostal space were probably due to an old zoster, but that the eruption in the 11th space cannot be classed under the heading of true zoster. However, the case is so poorly reported that it can add but little to our knowledge.

In 1884, Curschmann and Eisenlohr (5) published two cases in which an eruption of zoster was followed by the development of small nodular swellings on the peripheral nerves. In the first case several of these swellings were removed by operation. Microscopically they were found to consist of healthy nerve-fibres surrounded by small hæmorrhages, exudation of inflammatory cells and engorged capillaries, in fact, a condition of '' perineuritis acuta nodosa.'' This case died a year and nine months afterwards, and they found no change in nerves, ganglia, or cervical cord.

They also report a third case in which zoster appeared two days before death over the 11th rib and last intercostal space. On *post-mortem* examination the back muscles on the same side as the eruption were found to be infiltrated with blood, and through this infiltration passed the branches of the 10th and 11th dorsal nerves. The nerve-fibres in these branches were, however, unaltered, and the 10th, 11th and 12th dorsal ganglia and the dorsal and lumbar cord were normal. But it is not improbable that these observers, like Pitres and Vaillard, were misled by their idea that zoster was due to changes in the peripheral nerves. Thus the fact that the anterior divisions of the 10th and 11th dorsal nerves passed through the broken-down muscles, caused them to imagine that these nerves must have been the seat of the lesion in spite of the fact that their peripheral branches do not supply the area over which the eruption lay (*vide* our plate 17). Probably the seat of the lesion in this case was the 9th dorsal ganglion, which they neglected to examine.

In 1884, Dubler (7) published the results of an examination of two cases. Of these we will consider the second and more straightforward case first. The distribution of the eruption, which occurred 103 days before death, was as follows :— '' Rechts über den unteren Rippen und über der unteren Bauchgegend eine von oben hinten nach vorn unter verlaufende 5 cm. breite gürtelförmige Hautpartie .... Diese Hautveränderung beginnt hinten an der Wirbelsaüle, reicht vorn bis zur Mittellinie wo sie 4 Querfinger oberhalb der Symphyse endet. Seitlich bleibt sie 3 Querfinger von der Spina Anterior Superior entfernt.''

Microscopically the spinal cord was normal. The 9th dorsal ganglion showed interstitial changes, degeneration of nerve-bundles and small pin-point hæmorrhages and dots. The 8th and 10th dorsal ganglia were normal. The 9th intercostal nerve and 9th dorsal roots were degenerated, and there was a small amount of degeneration in the 10th intercostal nerve.

Dubler's first case is less clear owing to the fact that the patient had tubercular necrosis of several ribs. The eruption seems to have occupied the area we have called the 8th dorsal, and the patient died 144 days after its first appearance. On the 7th, 8th and 9th ribs were caseous masses, due to necrosis of the bone. The 6th, 7th, 8th and 9th intercostal nerves passed through these swellings. A few nerve-fibres were degenerated in the anterior division of the 7th intercostal nerve ; there were marked degeneration in the posterior and anterior primary divisions of the 8th intercostal nerve, and slighter degeneration in the anterior division of the 9th intercostal. Ganglia, cord and posterior roots were said to be normal at the level of the 6th, 7th, 8th and 9th dorsal.

In 1887, Leudet (14) published a somewhat superficial paper in which he mentions a case of herpes frontalis where he found an old inflammatory process in the frontal nerve, and a degenerative condition of the Gasserian ganglion.

Thus up till the time we began to investigate the pathology of herpes zoster there had been two well reported autopsies on cases of zoster ophthalmicus [Sattler (16), Wyss (19)], and five satisfactory reports on zoster of the trunk [Lesser, three excellent cases (12 and 13), Chaudelux, one fairly reported case (3), Dubler, one excellently reported case (7)].

To these we now add twenty-one cases at all stages after the eruption.

Chapter 9.

§ 1. *Herpes zoster, an acute specific disease of the nervous system*.—A typical attack of zoster arises without any obvious peripheral or central cause, and must be considered an acute specific disease of the nervous system, for it starts with a prodromal period of varying length, during which the temperature is raised. During this period the patient feels ill and has more or less pain ; but it is then impossible to make a diagnosis. If the patient is a child, he may be supposed to be sickening for one of the ordinary acute specific diseases. Suddenly, however, after a variable period, the rash comes out and the disease declares itself. The febrile period lasts from three to five days and this may be considered the duration of the acute disease. The rash may appear a few hours after the onset of the disease or may tarry till the fall of temperature. This, if the rash taken to represent the physical signs, an attack of zoster may be compared in these characteristics with an attack of acute lobar pneumonia. For as is well known the signs in the lungs in this disease may be present very shortly after the initial rigor, or may not make their appearance until the crisis is reached. The rash in herpes zoster most commonly makes its appearance on the third or fourth day of the disease, just as the physical signs of acute lobar pneumonia usually become evident on the third or fourth day after the initial rigour.

If zoster be an acute specific disease, second attacks should be uncommon, and we find as a fact that second attacks are less common than second attacks of measles. We have met with only four such instances in over four hundred cases. Again, the disease should tend to occur more at certain periods than at others or even appear in actual epidemics. This is now recognised to be the case. The records kept by one of us at the London Hospital tend to bear out this statement; for, although sporadic cases occur throughout the year, at certain seasons there is a large increase in the number of cases. Thus, in 1896, 1897 and 1898, there was an epidemic in the middle of March. In 1897 and 1898 there was an outbreak from the middle to the end of May. In 1897 a large number of cases appeared during the long drought that lasted from the end of July until the beginning of November ; and during this period of four months fifty-eight cases were seen, or one half the cases of that year. In 1898 several cases appeared together in June, and there was a marked outbreak from the middle of July to the end of August, during which period twenty-two cases were seen in less than six weeks. In the same year another outbreak occurred in the middle of October. Thus there can be little doubt that the occurrence of epidemics of herpes zoster is associated with some atmospheric influence or conjunction of which we are as yet ignorant.

But if herpes zoster is an acute specific disease of the nervous system we find an exactly analogous disease in acute anterior

poliomyelitis. This disease begins with malaise and fever. The temperature may remain raised for from three days to a week, and at a variable time during this febrile period, or it may not be until the fever has subsided, paralysis is noticed.

On comparing the pathological condition discovered on microscopical examination in the two diseases their likeness becomes still closer. The following summary of the conditions found in those cases that have died at varying periods in the few months, given by Allan Starr (45), exactly corresponds to what can be seen in two cases of this disease we have had the opportunity of examining.[1]

'' On microscopical examination there is found a marked hyperæmia of the tissue ; all the blood-vessels are engorged and surrounded by exudation alike of serum, of leucocytes, and of small cells. The serum fills the lymph spaces about the vessels and about the nerve-cells. The leucocytes infiltrate the tissues about the cells and cluster around them. There is a great increase of small cells and nuclei in the neuroglia. . . This infiltration of the tissue with leucocytes may be so intense as to obscure all other elements. Ruptured capillaries and small hæmorrhages are seen here and there. It is thus evident that the supporting substance (neuroglia) of the grey matter and the blood-vessels are involved in the inflammatory process.

'' The changes in the ganglion cells of the cord are equally characteristic. These cells show great varieties of degenerative changes depending partly upon the severity of the case and partly upon the length of time the process has been going on in any one cell. The earliest change in the cell is the cloudy appearance of its protoplasm, and increased granular appearance obscuring the nucleus and leading to its deeper staining by reagents. In the next stage the cell absorbs stains no longer ; the nucleus is faint and the cell has lost its sharp outline and some of its prolongations. Later still the cell appears changed into a swollen, shapeless or spherical ball of matter, and its protoplasm is altered into a homogeneous unstained mass with vacuoles, or has become distinctly granular, in which case it stains deeply. . . The last stage is one of shrinkage, the cell body being changed into a small, deeply-stained mass hardly larger than its original nucleus. . . . . If the case be examined some weeks or months after the onset the vascular changes are no longer evident ; the serious exudation has been absorbed, there are no longer leucocytes and cells within the interstitial tissues. . . In some parts the anterior horn may be changed even into true sclerotic tissue.''

If for anterior horn we read posterior root ganglion, and for motor cell posterior ganglion cell; this statement would be an exact description of the changes we have described in Chapter I.

Moreover, the posterior root ganglion is the exact equivalent of the anterior horn. For whereas on the motor side the cells of the neurons of the lowest level lie in the anterior horn, on the afferent side, they happen to lie collected together outside the spinal cord in the posterior root ganglion. Thus zoster might justly be spoken of as acute posterior poliomyelitis.

§ 2. *The nature of the changes that produce herpes zoster*.—The changes which we have described above in the posterior root ganglion, closely resembling as they do those found in the grey matter of the anterior horn in cute anterior poliomyelitis, are typical of a pathological process in the nervous system that has of years been too much neglected. It is usually dismissed by the statement that it is '' of vascular origin.'' Now if by '' vascular '' is meant that the disease is directly secondary to occlusion or interference with a vessel, we deny its correctness ; if, on the other hand, it is simply meant that the vessels play an important part in the general inflammatory process, it is a platitude.

Many observers have occluded the vessels of the spinal cord for varying periods, and examined the changes so produced in the cells. Such occlusion of the arteries produces marked chromatolytic changes in the cells of the spinal cord, but is not followed by inflammatory changes or hæmorrhages. Leonard Hill ligatured the cerebral arteries in monkeys, and the brains of these animals were examined by Mott (34) at varying periods after the operation. Here, again, extreme chromatolysis of the cortical cells was found, but no inflammatory changes and no hæmorrhages.

Now the universal characteristic of the changes we have described in the affected ganglion is the presence of inflammation in every degree, from scattered collections of small round cells to profound hæmorrahages in the centre of inflammatory foci. On the other hand, our cases of spontaneous zoster did not show marked chromatolytic changes of the type seen when either the vessels of the spinal cord or of the brain were experimentally occluded. A certain number of ganglion cells seem to be killed outright, and others to be so injured that they quickly die. The remainder, however they may have been changed at the onset of the disease, rapidly recover. Very few, if any, of the ganglion cells appear to be undergoing that steady process of disintegration which we have learnt to associate with the appearances known as chromatolysis.

It is therefore peculiarly interesting to notice that in the two cases of secondary zoster, where we have every reason to suppose that the blood supply of the ganglion was profoundly affected, chromatolytic changes were well marked. In one of these (Case 14), the ganglion was completely surrounded by malignant growth, and in the other (Case 15), the spine had been fractured.

Moreover, secondary degeneration makes its appearance within eleven days of the appearance of the eruption over the whole central projection of the fibres, large and small, in connection with the cells of the posterior root ganglion. This looks far more as if the process were one of acute destruction of ganglion cells than of damage by a poison leading to degeneration and death of the nerve-cell.

Thus it would appear that the changes in the posterior root ganglion consist of an acute interstitial inflammation accompanied by necrosis of the ganglion cells.

Of the nature of the agent which is responsible for this process we are completely ignorant. Microscopically, we have not been able to find any signs of bacterial infection, but have not attempted to make cultivations for fear of spoiling our material for other purposes.

But this agent, whatever it may be, seems to have a specific attraction for the posterior root ganglion exactly as the equally unknown cause of acute anterior poliomyelitis attacks the substance of the anterior horns. Moreover, it is particularly liable to attack the dorsal part of the ganglion, *i.e.*, the portion opposite to the anterior root.

[1]We owe the opportunity of studying one of these cases to the kindness of Dr Mott, who has incorporated it in his Croonian Lectures (34). Sections of the other case were kindly given us by Dr Bulloch.

Each posterior root ganglion is supplied by a branch of the arteries in front of the spine (intercostal, &c.). This twig passes in with the peripheral nerve, and courses through the ganglion to meet the branch of either the anterior or posterior spinal arteries. In the ganglion this artery gives off branches towards the periphery, and it is around the terminations of these small branches that hæmorrhages are most often found. Owing to the anastomosis between the arteries of the spinal cord and the branches on the anterior surface of the spine, the ganglion can be injected with colouring material from both directions. If the hæmorrhage is severe it may transgress the territory of the ganglion and occupy the centre of the peripheral nerve (Cases 2 and 4).

It is probable that two ganglia are occasionally affected together. From clinical observation this seems particularly liable to occur with the 2nd, 3rd, and 4th cervical. Unfortunately, no such case is included in our series of *post-mortem* examinations. One case has come under our notice where a true zoster was present at the level of the 8th dorsal on one side and of the 10th dorsal on the other at the same time. Such cases are, however, excessively rare ; a similar one has been reported by Kaposi.

Thus the unknown agent responsible for the inflammation in the ganglion not only shows a specific attraction for the posterior root ganglia but commonly attacks one ganglion only. This selection of one group of cells is also partly characteristic of the poison that causes auto anterior poliomyelitis, but as the gray matter of the anterior horns forms a continuous column the inflammatory process has more opportunity of spreading upwards and downwards than in the case of the segmented groups of posterior nerve-cells collected as they are into separate and distinct ganglia.

But we have also to deal with the curious fact that some ganglia seem to be more prone to attack than others, as is shown by the following table compiled from records of 392 cases. No cases are included in which an area was seen in combination with one above or below it.

2nd	Cervical	. .	1	3rd	Dorsal	. .	34
3rd	,,	. .	15	4th	,,	. .	38
4th	,,	. .	21	5th	,,	. .	38
5th	,,	. .	2	6th	,,	. .	20
6th	,,	. .	3	7th	,,	. .	19
7th	,,	. .	5	8th	,,	. .	36
8th	,,	. .	0	9th	,,	. .	19
1st	Dorsal	. .	5	10th	,,	. .	26
2nd	,,	. .	9	11th	,,	. .	22

12th	Dorsal	. .	18
1st	Lumbar	. .	27
2nd	,,	. .	22
3rd	,,	. .	5
4th	,,	. .	1
5th	,,	. .	2
1st	Sacral	. .	0
2nd	,,	. .	1
3rd	,,	. .	5

It will be seen from this table that the ganglia most commonly affected are those which receive afferent impulses from the viscera through the white ramus of the sympathetic (*cf.* Head 30).

Now if any posterior root ganglion is carefully examined it will be found to contain two main groups of cells, large coarsely granular nerve-cells and smaller more pear-shaped cells that stain with methylene blue in a more uniform manner.[1] But the proportion of these two types of cell in any one ganglion varies according to its position. Thus the 6th, 7th, and 8th cervical contain a much larger proportion of large cells than of small ones, whilst from the 3rd dorsal to the 1st lumbar the small cells preponderate. In the 2nd, 3rd, and 4th cervical there is a great preponderance of small cells over large.

Thus the ganglia which receive fibres from the limbs, especially those which receive theirs from the hand (cervical 8) and foot (sacral 1) show a preponderance of cells of the large coarsely granular type. Now, these areas are exactly those which give rise to the long fibres of the posterior columns. For as many observers have pointed out from experiments on animals, and as our observations confirm for man (*vide* p. 374) the postero-internal column in the cervical region is mainly formed by fibres from the leg area, the postero-external by fibres from the arm.

Thus, it would appear that the toxic agent that produces herpes zoster not only has an affinity for the posterior root ganglia, but more particularly for those which contain a preponderance of the smaller type of ganglion cells that vie rise to the shorter fibres of the posterior columns.

But when once a ganglion is attacked all the cells within the area of inflammation suffer, whether they be of the large or small-celled type.

Now these small cells amongst other functions probably subserve that of pain, for Münzer (36) has shown that the long tracts of the posterior columns do not conduct pain impressions to the cerebrum. Hence the intense pain which accompanies an attack of zoster.

But if the case be seen before the rash appears it is sometimes possible to map out the area subsequently occupied by the eruption by means of the hyperalgesia that is present. This hyperalgesia, which closely resembles that so frequently seen as the concomitant of visceral referred pain, is followed by erythema. then, on the erythematous surface, vesicles appear.

Thus we are inclined to think that the trophic disturbance of the skin is an extreme form of activity of the same cells, disturbance of which by afferent impulses along the white ramus produces the hyperalgesia that accompanies visceral referred pain.

We do not imagine that the eruption of herpes zoster is produced by disturbance of special trophic nerves, but by intense irritation of cells in the ganglion which normally subserve the function of pain, and more particularly that form of pain produced by afferent visceral impulses.

Part II. The Bearing of the Distribution of the Eruption in Herpes Zoster on Sensory Localisation.

Introduction.

Before this research began one of us had collected a large number of cases of herpes zoster and had constructed a

[1]There is also probably a difference in the processes of these two types of cell, but this will form the subject of a further communication.

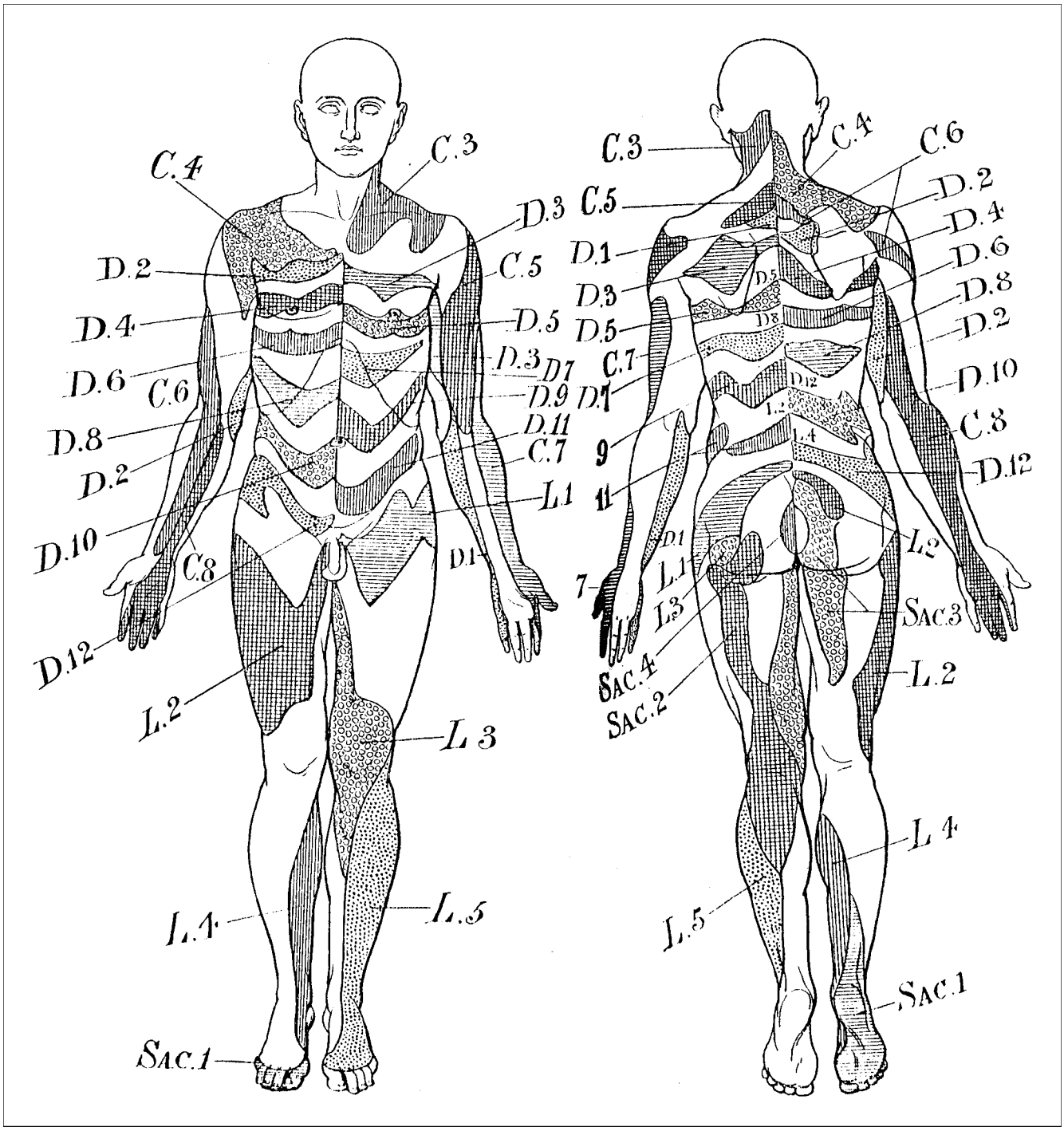

diagram to show the relation that the areas occupied by the eruption bore to one another. A series of segments was thus mapped out upon the surface of the body, and to each segment was given a hypothetical number which was supposed to represent its numerical localisation in the central nervous system. This numerical localisation met with universal disbelief, alike from anatomists and clinicians, and it was therefore felt that if a *post-mortem* examination could be obtained on a case of herpes zoster in which the distribution of the eruption had been carefully drawn or photographed, the question might be settled one way or the other.

But herpes zoster is not a fatal disease, and we felt that the only method by which we could obtain the material we desired was by the study of patients in asylums or infirmaries, a considerable proportion of whom remain in the institution until their death. By this means we have obtained fourteen outof the twenty-one cases we have examined ; of the remaining seven cases, we owe three to the kindness of the physicians of Guy's Hospital and four were collected by one of us at the London Hospital. At the same time one of us has collected drawings or photographs of 450 cases that have come under his personal observation.

This material enables us now to deal with the question of numerical localisation in a complete manner. But we wish it to be clearly understood that the segmental areas to which we refer in this paper are those marked out on the skin of the body by the eruption of herpes zoster, and when we speak of an area as, *e.g.*, '' the 4th dorsal,'' we mean that that area corresponds

with disturbance of the 4th dorsal ganglion. The question of the identity in position and constitution of these areas with the areas of hyperalgesia that accompany the referred pain of visceral disease, and the relation of these areas to the territory supplied by each posterior spinal root, will be dealt with subsequently by one of us in a separate paper.

On plate 17 we have attempted to combine the typical distribution of each area on a single diagram. Such an attempt is in itself fallacious, for no such combined figure can be absolutely accurate ; for on the trunk each area is a band cooled round one half of a rough cylinder, and must therefore vary in each case according to the shape of the trunk. Thus one of these areas extended around the abdomen of a baby will have a completely different appearance from the same area around the waist of a woman who wears stays. An eruption produced by a lesion of the 6th dorsal ganglion will differ considerably when extended on the narrow sloping chest of the phthisical or on the barrel-shaped high shouldered thorax of the emphysematous. Bony points are thus almost useless : skin points only are trustworthy, and of these we unfortunately possess only the nipple and the umbilicus.

We are also confronted with another difficulty which must always make such a combined diagram incomplete ; for the supply of the afferent ganglionic fibres is subject to variation, and any one portion of skin may be supplied in the one patient by the fibres that enter one ganglion, in another by those that enter the ganglion above or below. We hope, however, to be able to show that extent to which this variation may occur and the laws by which it is governed.

Lastly, we shall deal with the question of interdigitation and overlap in as far as it affects the areas mapped out on the body by the eruption of herpes zoster.

§1.–*The numerical localisation of the areas marked out by the eruption of herpes zoster.*—When the original diagram of the areas on the surface of the body was published by one of us (27), Thane (46) summed up the criticism of the anatomists in the following passage :—'' It may be pointed out that the areas as designated do not always agree with the distribution of the corresponding nerves as determined anatomically. Thus the area marked D3 of the inner side of the arm corresponds rather to the brachial distribution of the 2nd dorsal nerve through its intercosto-humeral branch and the communication with the nerve of Wrisberg, while the third dorsal nerve does not usually contribute largely to the supply of the arm. Similarly the areas marked D11, D12 and L1, would seem on anatomical grounds to correspond more nearly to the 12th dorsal and 1st and 2nd lumbar nerves.''

Thorburn (48), is equally definite : ''. . . If we trace Head's areas downwards we find other evidences of a tendency to describe them as being a segment or part of a segment too high. . . . If, however, we turn to the lower part of the diagram there appears to be a tendency in an opposite direction, that is, the areas are depicted too low. Thus it will be seen that his 1st lumbar region corresponds more closely to that which Starr and others besides myself assign to the 2nd lumbar, and anatomical dissection shows that the 1st lumbar nerve is mainly distributed above the line of Pompart's ligament where Head has the 12th dorsal . . . and finally, the umbilicus probably lies, not as Head places it at the junction of the 9th and 10th dorsal fields, but certainly no higher than the lowest part of the 10th.''[1]

The combined diagram we give differs somewhat from that on which these criticisms were written, but the differences lie in the form of the areas and not in their general position. A greatly increased number of cases has enabled us to bring the form of the various bands more nearly to that which we consider normal. But we still maintain that the 3rd dorsal usually supplies part of the inner side of the arm, that the 5th dorsal sends fibres to the lower part of the breast, that the umbilicus lies between the 9th and 10th dorsal areas, and that the 12th dorsal supplies the skin partly above and partly below Poupart's ligament.

The following table of the segments from the 3rd cervical to the 1st lumbar shows those we have examined :—

Cervical 3.—Examined twice. Case 6, fig. 6, and case 17, fig. 17.
Cervical 4.—Case 10, fig. 10.
Cervical 5.
Cervical 6.
Cervical 7.
Cervical 8.
Dorsal 1.
Dorsal 2—Case 7, fig. 7.
Dorsal 3.
Dorsal 4.—Examined twice. Case 11, fig. 11, and Case 14, fig. 14.
Dorsal 5.
Dorsal 6—Examined twice. Case 3, fig 3, and Case 13, fig 13.
Dorsal 7—Examined twice. Case 2, fig. 2, and Case 9, fig. 9.
Dorsal 8—Case 16, fig. 16.
Dorsal 9.
Dorsal 10.
Dorsal 11—Case 5, fig 5.
Dorsal 12.—Examined three times. Case 4, fig. 4 ; Case 8, fig. 8 ; and Case 12, fig. 12.
Lumbar 1—Case 1, fig. 1.

Thus out of nineteen consecutive areas we have examined ten, and of these ten we have examined five more than once.

Amongst these cases we are fortunate in having several that include the disputed points. Thus Case 11 and Case 14 show how the 4th dorsal lies above the nipple, supplying in a woman with large breasts, the upper half of the mammæ and sending a branch to innervate the upper half of the areola.

The 11th dorsal, and not the 12th, supplies the groin just above Poupart's ligament (Case 5), and thus it is certain that the umbilicus lies between the 9th and 10th dorsal areas.

Again, we are fortunate in having examined in three cases the 12th dorsal area, upon which universal doubt has been thrown (Case 4, Case 8, Case 12). The extent of the eruption varied in each of these cases, and the conditions of this variation will be considered in the next section. But in all these cases the eruption lay below the crest of the ilium, and extended on to the outer side of the thigh below Poupart's ligament. Moreover, as additional proof, we have examined one case of the first lumbar area, which, though the rash had not developed in front, it was sufficiently well marked, posteriorly and laterally, to confirm the numerical localisation.

[1]The interesting monograph by Wichman, ''Die Rückenmarksnerven und ihre Segmentbezüge,'' did not reach us until our paper was already in print. As far as the trunk is concerned, his figure of the sensory segments more closely resembles that of Head (30) than any other scheme. However, he places the umbilicus in the centre of the 10th dorsal field.

Thus if ten out of nineteen consecutive areas have been found by *post-mortem* examination to be correctly numbered, it is unlikely that there is any serious error in the numbering of the remainder.

§2. *Variation in form without variation in nerve supply*.—The primitive form of these segmental areas is a band passing around the body from mid-dorsum to mid-venter. The 6th dorsal still retains this primitive character in an almost unaltered form. It starts from the mid-dorsum opposite the 7th and 8th dorsal spines, and passes forward beneath the angle of the scapula. It dips a little in the axilla and swings forward beneath the lower border of the mamma to end in front over the fifth interspace. In its course it passes over the eighth, seventh and sixth intercostal spaces.

If the eruption over this band-like area is examined carefully it is seen to be made up of three main outbursts. The most posterior of these extends from the middle line of the back to about the line of the angle of the scapula, and obviously represents the supply of the posterior primary division. A second outburst takes place in the axilla, and from this point the eruption streams backwards and forwards, representing the lateral cutaneous branch of the anterior primary division. Lastly, over the fifth space in front of the nipple line is a third small outburst corresponding to the terminal twigs of the anterior primary division.

Thus in its complete and primitive form each of these segmental areas consists of a dorsal, a lateral and an anterior division. It is by the changes in the relative proportions of these three constituents that the areas in different regions arrive at their peculiar shape. Passing upwards from the 6th dorsal, we find a tendency for the lateral outburst to be pulled upwards towards the apex of the axilla. This tendency to lateral extension is still more marked in the 3rd and 2nd dorsal, where the lateral flap extends on to the ulnar surface of the arm and reaches its culmination in the detached lateral flap of the 1st dorsal, with its minute anterior and posterior flaps.

Below the 6th dorsal the posterior flap tends to extend downwards on the back, so that its ventral apex may lie below the dorsal apex of the lateral portion of this area. At the same time the lateral and anterior branches of the anterior primary division tend to form a rough triangle on the abdomen. The lower border of every area below the 6th is pulled somewhat downwards towards Poupart's ligament, but rises again towards the middle line of the abdomen. Thus the 9th dorsal area does not touch the middle line of the abdomen at any point below the umbilicus, but its lower border frequently lies considerably below the horizontal level of the umbilicus.

With the 1st lumbar on the front of the thigh and on the buttock, this tendency for the lower border to become dragged downwards becomes well-marked, reaching its culmination in the extraordinary shape of the 3rd lumbar. Below the knee the 4th and 5th lumbar and 1st sacral have entirely lost their anterior and posterior attachments, and consist of the remains of the lateral flap only.

Now it is at once obvious that such a condition offers many opportunities for variation apart from any change in the actual nerve supply. For such an area as the 10th dorsal spread round the abdomen of an infant is a broad almost horizontal band ; but on the waist of a woman, especially if she belong to the long-chested type, this area comes to resemble two triangles, in each of which the widest angle is directed towards the leg. The trunk of an infant so much more nearly resembles a cylinder that all the areas, from the 3rd dorsal to the 1st lumbar, tend to become horizontal bands, whereas in the adult they more nearly resemble a couple of obtuse-angled triangles.

Then, again, the trunk of an infant forms a proportionately much larger part of the whole body than in an adult. Thus the areas on the front of the thigh of a young child appear to be smaller and more band-like than those of an adult.

The distribution of these segmental areas on the breast requires special consideration. We will begin with the chest of a young male where the nipple is situated over the lower border of the 4th rib. In such a case the anterior limb of the 3rd dorsal will send a minute downward tag that almost reaches the inner side of the base of the nipple. The anterior axillary branch of the 4th dorsal sends a tag that runs upwards and forwards to end on the outer side of the nipple, whilst the small anterior flap supplies the upper and anterior portion of this structure (fig. 14, Case 14). Thus at least one-quarter of the nipple lies below the lower border of the 4th dorsal area. The 5th dorsal sends an upward projection from its upper border to envelop this portion of the nipple.

This description also applies to the undeveloped breast of a young girl ; but as soon as the breast of a woman increases in size, the appearance of these three areas alters profoundly, although on analysis their relations to one another are seen to remain unaltered. The downward tag from the 3rd dorsal becomes of much greater importance, covering a considerable portion of the upper surface of the breast. The forward branch of the lateral flap and the termination of the anterior primary division now become a very prominent feature of the 4th dorsal area, and supply the whole outer and the whole inner quadrant of the mammæ (fig. 11, Case 11). The 5th dorsal supplies the whole under surface of the mammæ, except that when it is considerably enlarged as in a suckling woman, the upper border of the 6th dorsal laps onto that part which lies over the fifth space and sixth rib.

Into this category we are inclined to place the different appearances presented by the eruption in the three cases where the 12th dorsal ganglion was found to be affected. We regard fig. 8 (Case 8) as the most usual appearance of this area, for it corresponds with the majority of the cases where this area was represented amongst the 450 of our collection. In fig. 12 (Case 12) the downward projection on to the thigh is much less marked, whilst in fig. 4 (Case 4) two long streamers occupy much more of the outer side of the front of the thigh. Yet in all these cases the superior border occupied the same position and the point reached by all three cases in the mid-ventral line was identical.

Thus in conclusion we wish to point out that these areas may differ markedly in different individuals owing to variations in the surface of which the skin is stretched without any necessary alterations in nerve-supply.

§3. *Variation in nerve-supply*.—In order to investigate to what extent these areas were liable to true variation, it became necessary to select one of them and to examine as many cases as possible where the eruption lay over that area.

The area selected for this purpose must be easily localised, have well marked anterior, posterior and lateral flaps, and occur with sufficient frequency in a complete form. These conditions are best fulfilled by the 3rd dorsal.

The form assumed by this area, which we consider to be normal, is characterised as follows : The upper border of the posterior flap starts at the 3rd dorsal spine, slopes slightly downwards and then rises to cover the spin of the scapula. From this point it slopes downwards towards the arm to be continued into the posterior border of the lateral flap. The lower border starts behind, about an inch below the upper border, but then slopes rapidly downwards over the scapula, rising again with the external border of that bone to enclose a triangular patch somewhat resembling in shape the lower part of the scapula itself.

The lateral flap covers the upper half or two-thirds of the post-axial border of the arm. Thus, when the arm is raised to a vertical position, with the ulnar border of the forearm and the little finger facing the observer, the lateral flap should appear in its entirely extending one-half or two-thirds of the distance towards the elbow.

The upper border of the anterior flap touches the lower border of the second rib, and the lower border dips on to the region of the mamma to reach a point just above the areola of the nipple. From this point it rises to end over the third rib cartilage.

Out of twenty complete cases in which the eruption lay over the 3rd dorsal, twelve followed exactly this course.

Now if this area were prefixed, *i.e.*, moved up somewhat nearer the head end of the nervous system, we should expect it to show a closer resemblance to the 2nd dorsal than when it assumes what we have called the normal form. That is to say, the upper border of the posterior flap would lie along or above the spine of the scapula and the lower border leave a considerable part of the subspinous portion of the scapula uncovered. The lateral flap would extend further down the axillary border of the arm and nearly reach the elbow. The upper border of the anterior flap would run along the upper border of the 2nd rib, and the lower border would end some considerable distance above the nipple.

This was exactly he area occupied by the eruption in one case out of the twenty cases.

If, on the other hand, this area were post-fixed, *i.e.*, pushed nearer the tail end of the nervous system, it would more closely resemble the 4th dorsal than normal. The upper border of the posterior patch would scarcely touch the spine of the scapula and the lower border would come closer to the angle of this bone, covering a larger portion of the subspinous area. The lateral flap would be shortened so as only to occupy a few inches of the axillary border of the arm. The upper border of the anterior patch would lie over the 3rd rib and the lower border would send a downward tag to envelop the nipple from above.

This condition occurred in seven out of the twenty cases.

Thus out of twenty cases where a well developed eruption occupied the area of the 3rd dorsal, twelve were what we have called normal, one was prefixed, and seven were post-fixed. We do not look upon these figures as more than an indication of how this area may vary ; for twenty cases are too few to form the basis of any statistical conclusions.

We believe, however, that the areas on the trunk are less liable to true variation than those on the limbs. Those which affect the terminations of the limbs are the most variable of all, but the infrequency with which they appear renders a more definite statement impossible.

It might be object that the instances given above are not cases of variation but of false enumeration. This is rendered improbable by comparing the two cases in our series (Case 3 and Case 13) in which the *post-mortem* examination showed the 6th dorsal to have been affected. In Case 3, that of a child, the eruption (fig. 3) ran almost straight round the body, passing just below the angle of the scapula and below the nipple. In Case 13 on the other hand, the upper border of the eruption (fig. 13) touched the lower angle of the scapula and passed forward beneath the nipple, sending an upward tag to just implicate the lowest part of the areola. Yet in both these cases the *post-mortem* examination showed that the 6th dorsal was affected. Now the eruption in Case 3 followed what we should call the normal course ; in Case 13 it was pre-fixed. Moreover, this eruption showed exactly the characteristics we laid down as necessary for a pre-fixed area, when discussing the variations in the 3rd dorsal ; for it resembled the area above it, the 5th dorsal, in sending a branch to the nipple, and yet its upper border was distinctly lower than that of a normal 5th dorsal.

So far we have met with no case where an eruption that lay entirely over an area to which we had habitually given one number, turned out on *post-mortem* examination to have been due to an affection of the ganglion above or the ganglion below. That is to say, in each case where from examination of a previous case we had been led to suppose that the 3rd cervical, the 4th dorsal, the 7th dorsal, or the 12th dorsal would be affected, the enumeration again turned out to be correct.

Thus, in conclusion, we believe that when a certain ganglion is affected the eruption most frequently lies over a definite tract of skin, which may be called the normal area from which fibres enter that ganglion. This tract of skin may, however, in some cases be situated further headwards, and occupy about one-half or less of the area usually supplied by the segment in front (pre-fixed). It may also be situated further towards the tail end of the body, and occupy about one-half or less of the area usually supplied by the segment behind it (post-fixed). But its displacement never exceeds half an area in either direction, and in no case did we find that an eruption, which lay over what we supposed to be the complete normal area of a certain segment, was produced by a lesion of either the ganglion above or the ganglion below.

§4. *Overlap and Interdigitation.*—After what we have said in the preceding sections concerning the possibility of change in the shape of these segmental areas owing to individual differences in the shape of the patient's body or to actual variation of nerve-supply, it will at once be seen how difficult it is to determine to what extent these areas overlap. Thus in every case it becomes necessary to consider whether the area occupied by the eruption belongs to the normal type. If this be so we can then only determine the extent of the overlap by comparing it with the normal distribution of the area in front of it and the area behind it in a case where the body of the patient was of approximately the same shape. For it is useless to attempt to compare the 10th dorsal, however normal it may be, when spread out round the body of a baby, with the 9th dorsal around the small waist of a woman in the hope of determining to what extent these two segments overlap.

A third difficulty with which we have to deal is the extraordinary interdigitation of the serrated margins of these areas. They can rarely be defined by straight lines, for the eruption is made up of a series of outbursts, each of which follows the course of a tiny nerve-twig. Now it is quite impossible to say how far the downward tags of one area fit into the notches of the area below, but all we can say is that of the downward tag is a large one and forms an integral and distinctive feature of the area in its normal form, a notch of greater or less depth will be found in the area below corresponding, though not to the full extent, with this downward projection of the area above. (Compare the downward course of the posterior patch in fig. 5 with the notch in the upper border of the posterior patch of fig. 8 and fig. 4.).

Let us then first compare the extent of the eruption in Case 2 or Case 9, which occupied the 7th dorsal area, with that of Case 16, that lay over the 8th dorsal. All these cases were men, and the rash in Case 2 was almost identical with that in Case 9. It will be seen that the lower border of the area in figs. 2 and 9 scarcely encroaches at all on the upper border of that in fig. 16. Moreover, the apex of the anterior half of the eruption in fig. 16 fits into the notch made by the junction of the anterior with the posterior half of the area in figs. 2 and 9. In fact, the overlap does not consist of one-third of the extent of either of these areas. This slight overlap we believe to be typical of the areas of the trunk.

Turning next to the cervical region, fig. 6 shows a typical third cervical, and fig. 10 a fourth cervical with a rather extended anterior border, but a normal posterior border. In both cases the patients were men. It will be seen that the anterior or cephalic border of the fourth cervical (fig. 10), lies over the area occupied by the third cervical (fig. 6). But although these two areas habitually overlap, the extent of the overlap is not so great as might at first sight appear, for the third cervical runs in two main streams across the outer part of the supraclavicular fossa, and between these two streams the skin is affected either lightly or not at all. In the same way the anterior or cephalic portion of the fourth cervical (fig. 10), which also covers the outer part of the supraclavicular fossa, is always lightly marked both by erythema and vesicles in obvious contrast to that part which lies over the shoulder.

We believe that the overlap is more marked on the limbs, especially at their termination, but owing to the comparatively small number of cases on the fore-arm and leg (p. 394) it is impossible to be certain of the amount of this overlap.

Thus, in conclusion, the areas marked out by the eruption of herpes zoster overlap one another to a very variable extent. On the trunk this overlap is slight when individual differences and variation in nerve-supply are taken into account. In the neck this overlap consists more of a sharing of a certain territory than of true overlap, but on the limbs, especially at their termination, the overlapping is distinct.

Yet in no case does the zone of overlap equal in extent more than one-half of the area above and below, whilst in many cases it is considerably less.

DISCUSSION

Three main aspects of this paper can be considered separately.

Neuropathological descriptions of the affected ganglia and other tissues

A great deal of the paper is concerned with detailed descriptions of the pathological changes detected in the nervous systems of the various cases, which is in keeping with the actual title. They provided accurate details, for example, of the acute ganglionitis typical of HZ. In 1863 Von Barensprung had already described similar changes in posterior ganglia in HZ cases post-mortem,[4] but Head and Campbell pointed out that 'he thought this structure stood in no connection with the fibres of the posterior root or peripheral nerve, but had special nerve fibres of its own'. Head and Campbell clearly identified the main lesion in HZ as being located peripherally rather than centrally, and in the dorsal root ganglion or the trigeminal ganglion. From the records of no less than 392 cases they were able to determine the distribution of affected ganglia, with some ganglia being 'more prone to attack than others'. Thus the third and fourth cervical, all the thoracic and the first two lumbar dorsal ganglia were most frequently affected. They stated that 'the ganglia most frequently affected are those which receive afferent impulses from the viscera through the white ramus of the sympathetic'. They reported marked cellular (including neuronal) necrosis in the posterior root ganglia as well as an acute inflammatory reaction and haemorrhagic changes. They also described pathological changes in structures outside the ganglia in uncomplicated cases of HZ. They detected secondary degeneration of the posterior nerve roots, the peripheral nerves distal to the ganglia, and degeneration of the spinal cord. Such findings have been clearly confirmed and extended in subsequent studies.[5,6] Pathological changes which are now recognised as occurring frequently in HZ include a mild localised leptomeningitis, inflammatory changes in the adjacent cord or brainstem segments, myelitis mainly affecting the posterior horns and roots, and Wallerian degeneration of cutaneous nerves.[7] The extent of these abnormalities is consistent with both the severity of HZ and the diversity of the neurological complications of this condition. It is unfortunate that we still do not understand the pathogenesis of that most distressing complication of HZ-namely post-herpetic neuralgia which affects so many patients, especially the elderly although a recent review in this Journal summarises current knowledge.[8] The severity of the pathological changes, especially neuronal necrosis, in the ganglia may provide the basis for at least part of the explanation, but the pathophysiological mechanisms are not known. It is possible that central changes may contribute to the pain in such individuals, and careful pathological analyses in this disorder have revealed damage to both small and large fibres.[9]

Mapping of sensory dermatomes based on pathological-clinical relationships

Head and Campbell performed a meticulous and masterly analysis in which the ganglionic location of the HZ in a particular patient was correlated with the distribution of the HZ rash. They were able to construct a series of

diagrams, now referred to by clinicians as 'dermatomes', which showed the root equivalent of segmental areas of the surface of the body. Thus, 'the segmental areas to which we refer in this paper are those marked out on the skin of the body by the eruption of herpes zoster, and when we speak of an area as, e.g. ''the 4th dorsal'', we mean that that area corresponds with disturbance of the 4th dorsal ganglion'. They pointed out, however, that the supply of afferent ganglionic fibres was subject to variation which results in a degree of overlap in particular cutaneous regions. Although they produced a combined figure of the segmental nerve supply (reprinted here), they stressed that no such diagram can be absolutely accurate, and clearly this needs to be borne in mind at all times. In effect the changes induced by the virus actually defined the anatomical distribution of the rash, an excellent example of the contribution of virology to neuroanatomy.[1] As a contemporary clinical neurologist I can testify to the importance and utility of dermatomal charts in neurological diagnosis, particularly in localising spinal root lesions—indeed it would be unthinkable to practise neurology without such knowledge.

The possible cause of herpes zoster

While Head and Campbell would undoubtedly have recognised the importance of their observations to neurology, they were not in a position to assess its intrinsic virological significance. With refreshing candour they stated that 'of the nature of the agent which is responsible for this process we are completely ignorant'. They were not able to detect any signs of a bacterial infection although cultivation studies of ganglion material were not attempted. However, they clearly regarded an acute infective process of some kind as the most likely cause. They thought that HZ was 'an acute specific disease of the nervous system', and noted that 'it starts with a prodromal period of varying length, during which the temperature is raised'. They likened some of the temporal features of HZ to acute lobar pneumonia, and also compared it with measles. They stated that HZ had a tendency to occur in epidemics, this indicating 'some atmospheric influence or conjunction of which we are as yet ignorant'. Head and Campbell considered HZ as analogous to acute anterior poliomyelitis in the sense that in both conditions there is an affinity of the disease process for a specific region of the nervous system: the dorsal root ganglion in the case of HZ and the anterior horn cell in the case of poliomyelitis, and with similar histopathological features. They went so far as to state that 'zoster might justly be spoken of as acute posterior poliomyelitis'. At this time, of course, the viral aetiology of polio had not been established. They also pointed out that HZ may occur in patients with 'general disease processes' e.g. malignant disease such as lymphosarcoma. Inflammatory processes secondary to 'malignant disease, tubercle or injury' affecting the posterior root ganglion could also produce HZ indistinguishable from that occurring spontaneously. This phenomenon is now well-recognised, and such reactivation of latent VZV is presumably secondary to local stimulation following inflammatory responses and/or to the immunosuppression characteristic of some of these conditions. They also noted that HZ could arise during the course of neurological diseases such as neurosyphilis.

Identification of the causal agent of HZ was eventually achieved in 1952 when VZV was isolated in cell culture by Weller and Stoddard.[10] Subsequently, serological data obtained by Weller and Whitton in 1958 showed that the viruses causing varicella and HZ were identical.[11] Despite the clarity and widespread acceptance of Hope-Simpsons 1965 hypothesis of VZV reactivation following latency in sensory ganglia, compelling experimental data helping to confirm this was not obtained until several years later. For example, Straus and colleagues showed that viruses isolated from varicella and subsequent HZ in the same individual were identical,[12] and Oakes and colleagues used molecular techniques to show that different viral isolates from a number of cases of varicella and HZ were indistinguishable.[13]

The pathological studies of Head and Campbell clearly implicated primary damage to neurons in the dorsal root ganglion in HZ, and Hope-Simpson suggested that the neuron was the cell type in which latent VZV resides. However, the precise cellular location of latent VZV in human sensory ganglia is currently a question of considerable controversy. While some studies have identified latent VZV in neurons (e.g. refs. 14, 15 and 16), others have found latent virus in non-neuronal cells such as satellite cells,[17] and a recent study has identified VZV in both neurons and satellite cells.[18] It is likely that this question will be answered definitively quite soon with the use of sophisticated molecular techniques.

The fact that many neurologists, neuroanatomists, pathologists and virologists all regard Head and Campbells paper as a classic in their respective fields is an impressive indication of its quality and enduring significance, one that has clearly been evident in several different disciplines. Finally, perhaps one of the most important lessons of this paper is that careful and precise clinical observation can still provide key clues to disease pathogenesis, even before a causative agent has been identified.

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