

CUTANEOUS NERVES IN HERPES ZOSTER

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The object of this investigation is to ascertain whether any changes can be found in the nerve fibres of the cutis and subcutis in cases of herpes zoster. Von Baerensprung¹ was the first to draw attention to the fact that herpes zoster is essentially a nerve disease. No attempt was made to prove this by means of pathological investigation until the classical researches of Head and Campbell,² published in 1900. They dissected the posterior root ganglia in cases suffering from herpes zoster who died of a concurrent or subsequent disease, and found haemorrhage and destruction of the ganglion cells. By means of the Marchi method they also demonstrated degeneration of the posterior root fibres. They traced the degeneration of the peripheral nerves as far as the skin but then had to admit that they had 'not succeeded in demonstrating degenerate fibres in the actual portion of the skin examined'.

Many papers on the pathology of herpes zoster have been published since this report first appeared. All have stressed the destruction of ganglion cells in the posterior root ganglia. Ramsay Hunt³ demonstrated the same degeneration in the cells of the geniculate ganglion in cases of otic zoster. He used the findings to map out the cutaneous distribution of the sensory branch of the facial nerve. In 1949 Ebert⁴ published an article in which he claimed to have shown degeneration in the intracutaneous nerve fibres by using the Gay Prieto modification of Cajal's silver method.⁵ He found definite signs of degeneration in the nerves 13 days after the commencement of the disease. The criteria used by Ebert to decide whether actual nerve degeneration was present can in some instances be criticized. He maintains that 'some nerve bundles in the middle and deeper parts of the corium were found to have *much less than the normal* number of fibres' (my italics). The number of fibres in various nerve bundles in the skin varies widely, and even in normal skin I have found that counting the fibres in different parts of one bundle, as it runs through the corium without apparent branching, will give very different figures. One must therefore question Ebert's statement about the 'normal number of fibres'.

Material

Biopsies were performed on 10 cases of herpes zoster, at times varying from 5 to 68 days from the onset of the disease. In one case, a 60-year-old European, with herpes zoster of

Th10, a biopsy was taken 15 days after the onset and another 68 days after the onset. In a few instances the biopsies were done by means of an electric punch without local anaesthetic, because it was feared that the procaine might interfere with the impregnation of the nerves. The majority, however, were done with a scalpel under local procaine anaesthetic. The full thickness of the cutis and subcutis down to the subcutaneous fat was removed.

Controls

Biopsies were performed on two cases of varicella 3 days after the onset of the disease, and on 1 case of herpes simplex. A considerable amount of normal material was accumulated, mainly from wide biopsies done for the removal of warts and naevi.

Technique

A modified Gros-Schultze⁶ method was used, as follows: Fix for a minimum of 14 days in 10% formol containing 8 minims of added pyridine puris in every 100 c.c. Cut frozen sections at 45μ and wash sections for $1\frac{1}{2}$ minutes in 2 changes of distilled water. Impregnate for 2 hours in 20% silver nitrate solution and transfer directly to 5 or 6 consecutive Petri dishes containing 1:4 formol at pH 6.8 for a total of about 20 minutes or until no more white sediment is discernible. Differentiate in a solution of silver nitrate and ammonia and wash in several changes of distilled water. Gild, dehydrate, and mount in Canada balsam.

With this technique the nerve fibres are stained black or purple and the co-staining of all mesodermal tissue can be kept to a minimum. The epi- and perineurium stains very faintly and no differentiation can be made between medullated and non-medullated fibres. Owing to the necessity of using frozen sections, serial following of any particular nerve is impossible.

The Marchi⁷ method was found to be impractical for skin material as it was impossible to prevent excessive co-staining of collagen fibres.

With the Gros-Schultze method normal skin shows 2 different types of nerve fibre, usually found together in small nerve bundles:

(a) Coarse fibres, often showing distinct beading, and resembling a rosary. (Fig. 1). In the past this beading has often been mistaken for a sign of degeneration. The number

of these fibres varies considerably in nerves of apparently the same size.

(b) Fine fibres, usually of about half the diameter of the above, seldom showing beading. These fibres are definitely in the majority in normal cutaneous tissue, the ratio of fine to coarse fibres never being less than 6 : 1.

In addition to bundles of nerve fibres running together enclosed in a sheath, there are also numerous loose, single fibres running criss-cross through the corium. (An incidental finding during this investigation was the fact that in the vaginal wall almost all these fibres run at right angles to the long axis of the vagina.)

In one biopsy taken from a recently bruised area of otherwise normal skin, no sign of degeneration of nerve fibres could be found in spite of considerable extravasation of blood etc., which was demonstrable with haematoxylin-and-eosin staining. This is of interest in the light of Klauder's views⁸ on the traumatic aetiology of herpes zoster.

The sections of the two cases of varicella showed no deviation from the normal as set out above, though admittedly the biopsies were taken before the end of the 7-day period which was found to be the minimum time in which nerve degeneration appears. Repeat biopsies were unfortunately not possible in these cases. Sections of the biopsy of a herpes-simplex lesion also showed no sign of nerve degeneration. Here again the biopsy was taken before the 7th day, for obvious reasons. With the Gros-Schultze technique it was found in apparently normal skin that in some instances only one or two fibres became impregnated in quite large bundles. The reason for this is unknown. Such nerves create the impression of degeneration on superficial examination. It was therefore decided that only a ratio difference or total disappearance (see below) could be accepted as evidence of pathological change.

FINDINGS IN HERPES ZOSTER

In no sections of herpes zoster biopsies made before the 7th day of the disease was any sign of nerve pathology seen. This differs from Ebert's findings, where degeneration was only demonstrated after the 13th day. In all the remaining sections, including those of the biopsy taken 68 days after commencement of the symptoms, the following was found on examination of the nerve bundles:

Most bundles, especially those immediately underneath the bullae or scars, showed complete absence of all fine fibres, but no difference was discernible in the coarse fibres (Fig. 2). The nerves immediately adjacent to the lesion often had no fine fibres but sometimes only one or two were found in a large bundle containing 15 or more coarse fibres (Fig. 3). Up to 2 mm. from the actual lesion 30% of the nerves showed either total absence of fine fibres or a great reduction in their numbers so that the ratio of coarse to fine fibres was never less than 3 : 1. All nerves more than 2 mm. removed from the lesion were apparently normal.

Underneath the lesion no loose, single fibres were found in any section examined, with the exception, of course, of the biopsies taken before the 7th day of the disease (see above). These loose fibres were again present almost immediately adjacent to the actual site of the lesion.

CONCLUSIONS

The only difference demonstrable with this technique between nerves in normal skin and those in cases of herpes zoster

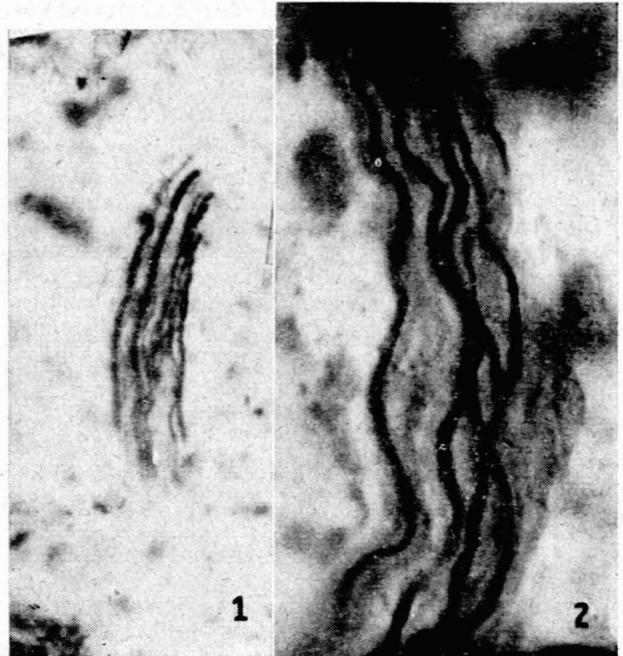


Fig. 1. Normal skin from Th9, European male. Four coarse fibres can be seen showing beading. The fine fibres are less clear because they are on a slightly different optic plane.

Fig. 2. Nerve directly under a scar in a case of herpes zoster. The biopsy was made 17 days from the onset of the disease. Five coarse fibres can be seen. Only one fine fibre is visible giving a ratio coarse to fine fibres 5 : 1.



Fig. 3. Skin from patient with herpes zoster of C.6. Biopsy done 13 days after onset of the disease. The nerve is just beyond the 2 mm. radius from the scab. Numerous fine fibres can be seen though not distinctly. High magnification to show marked beading.)

was the absence or reduction of the fine fibres in the bundles and the absence of loose running fibres. In no case was an actual degenerating fibre seen. The coarse fibres showed no apparent deviation from the normal. Counting the fine fibres is regarded as being more reliable than counting all the fibres as done by Ebert; it is the relative absence of fine fibres which is considered to be of significance.

SUMMARY

The cutaneous nerves in 10 cases of herpes zoster were examined by means of the Gros-Schultze method of silver impregnation. It was found that after the 7th day from the onset of the disease the fine fibres, which are normally more numerous than the coarse fibres, are either totally absent or greatly reduced in number. The nerves more than 2 mm. removed from the actual vesicle or its scar were completely normal. Control biopsies made on varicella and herpes-simplex cases showed normal nerves throughout.

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