MALIGNANT CHANGE FOLLOWING HERPES SIMPLEX

BY

R. WYBURN-MASON, M.D.

Late Gordon Jacob Research Fellow, Royal Marsden Hospital, London

In 1955 I described a series of cases in which herpes zoster of the skin or breast was followed after a variable period by malignant change in the affected tissues (Wyburn-Mason, 1955). During the investigations at the Royal Marsden Hospital there were also observed a number of cases of malignant change in the skin of the lip which were preceded by herpes simplex. No mention of herpes simplex as a premalignant condition has been found in an exhaustive search of the literature. A brief account of six of these cases follows.

Case Reports

Case 1.—Man aged 65. For five years he had been subject to recurrent herpes at the right angle of the mouth. After the last attack three months prior to hospital attendance a lesion had persisted, gradually increased in size, and bled from time to time. On examination a circular raised ulcer with everted edge was present, measuring 1.5 cm. in diameter (Fig. 1). Biopsy showed the lesion to be a squamous carcinoma.

Case 2.—Man aged 72. Three years previous to hospital attendance he developed herpes of the left upper lip. This was followed by the formation of a wart and by recurrent herpetic attacks in the same area. After the last attack, four months previous to examination, a growth had appeared (Fig. 2) and biopsy showed the presence of a squamous carcinoma.

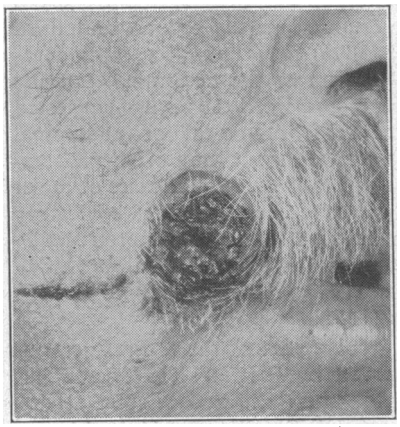

FIG. 1.—Case 1. Squamous carcinoma arising in lesions of herpes simplex.

Case 3. — Man aged 62. Eight weeks prior to attendance he developed herpes of the right upper lip, which almost healed within a fortnight, but then broke down again and ulcerated, gradually increasing in size and bleeding at intervals. The appearance is shown in Fig. 3. Biopsy showed the lesion to be a squamous carcinoma.

Case 4.—Woman aged 67. Seven weeks prior to attendance she developed a severe coryza, during which there appeared extensive herpes of the lower lip and the right angle of the mouth spreading on to the cheek. The lesion healed within a fortnight, except for a small area near the angle of the mouth, and during the next four weeks this rapidly increased in size and began to bleed. Biopsy showed the presence of a squamous carcinoma.

Case 5.—Woman aged 65. Eighteen months prior to hospital attendance she developed herpes of the left lower lip, which continually healed and broke down, particularly after exposure to sunlight. After such an exposure some three months prior to hospital attendance the lesion appeared, failed to heal, and then rapidly increased in size and began to bleed. It was found on biopsy to be a squamous carcinoma. She was treated with *x* rays with complete healing. Eighteen months later, after a further exposure to sunlight, she developed a fresh herpes in the same area.

Case 6.—Man aged 65. A year previous to attendance he pulled a piece off the lower lip with a cigarette. Next day herpes appeared in the denuded area and spread to involve the entire mucocutaneous margin of the lower lip. This was followed by crusting and bleeding after mild trauma, but never by complete healing (Fig. 4). Biopsy a year after the onset showed the presence of a squamous carcinoma. He was treated by *x* rays with complete healing. A year later, after exposure to sunlight, he developed a further herpetic lesion in the original area.

Discussion

The six patients were aged between 60 and 70 years at the time of onset of the herpetic lesion. One (Case 2) developed a wart, and two (Cases 5 and 6) showed recurrence of the herpes when exposed to sunlight. Such an abnormal sensitivity to sunlight is also observed in the skin of tar-workers, those exposed to *x* rays and arsenic, and in cases of xeroderma pigmentosa, in all of which malignant change may also occur in the affected skin. The cases described are of more than academic interest, as they might serve as evidence of the virus theory of cancer causation. It is important to consider certain observations about herpes simplex (see Van Rooyen and Rhodes, 1948 ; Stoker, 1957).

The pathological changes of herpes simplex or zoster and herpetiform lesions are those of an inflammation with oedema between the epidermal cells, and there is nothing specific about the changes. Herpes simplex and herpetiform lesions may be produced by many different factors, which include general infections or intoxications ; respiratory infections ; the administration of drugs, such as arsenic, antigenic substances, or antisera ; the local application of irritant (blistering) agents ; or chronic exposure to tar, *x* rays, etc. They may also occur on skin which is the site of causalgic

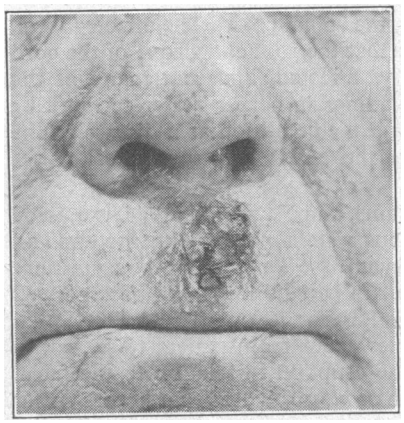

FIG. 2.—Case 2.

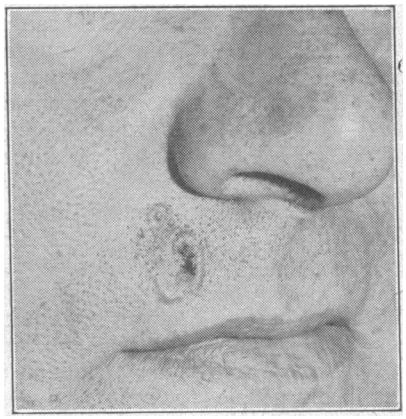

FIG. 3.—Case 3.

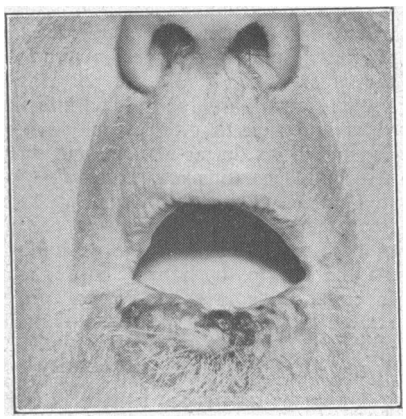

FIG. 4.—Case 6.

pain. In cases of herpes zoster the same type of lesion is produced as a result of disturbance of the innervation of the affected part. The virus of herpes simplex is the causative agent not only of herpes on the lips or nostrils, but also of herpes genitalis and cornealis, herpetic (aphthous, Vincent's, or ulcerative) stomatitis, eczema herpeticum (a type of Kaposi's varicelliform eruption), and meningo-encephalitis. The last three conditions do not recur, but many individuals are subject throughout life to recurrent attacks of herpes around the lips and nose, of the genitalia, or of the cornea, and these develop in response to non-specific stimuli, such as sunburn, fever, or trauma and not through exposure to another source of herpes virus. In women, recurrence is often associated with the menstrual periods.

The vesicle fluid from herpes simplex lesions affecting the face, genitalia, or cornea may produce herpetic vesicles when inoculated into the skin or keratitis when applied to the conjunctiva of the rabbit, and it is therefore usually considered that all simple herpetic lesions are due to the same virus. There is, however, some doubt whether a virus can be demonstrated in all herpetic simplex lesions. According to Stoker, " there is no doubt that the virus is present during each of these recurrent attacks, because it can invariably be isolated in the early stages." It has been suggested (Burnet and Williams, 1939) that in recurrent cases herpetic infection occurs in childhood and persists throughout life. This is based on serological and skin tests, the sera of most adults containing antibodies against the virus. It is supposed that the virus remains within the epidermal cells, dividing with them, and normally causing no damage. A number of non-specific stimuli which lead to cell breakdown may release the virus particles.

Stalder and Zurukzoglu (1936) showed, however, that areas of facial skin subject to recurrent herpes no longer developed the disease if transplanted to another part of the body. Yet a recurrent attack usually occurs in roughly the same site. Because of this some favour the central nervous system, dorsal root ganglia, or cutaneous nerve endings as the permanent home of the virus. In this respect it will be recalled that the lesions of herpes zoster, which are due to infection with the herpetic zoster virus, are identical pathologically with those of herpes simplex, but the causative lesion for the skin change is found in the posterior nerve root ganglia (Lewis, 1927). It is thus by no means certain that the lesions of herpes simplex are always due to, or contain, a virus affecting the skin. It seems possible that this type of tissue reaction in the skin may result from various forms of irritation, of which the herpes simplex virus is one example ; that even in recurrent cases of herpes simplex local irritation plays a part in causing the recurrence, and that, as in cases of herpes zoster, disturbance of local nerve fibres may be a factor in causing this.

Whatever the explanation of recurrent herpes simplex, it seems that the appearance of the original lesion may predispose to malignant change in elderly subjects. Malignant change following herpes simplex may simply be an example of what may occur, especially in elderly subjects, at the site of any chronic irritation or inflammation, such as eczema or psoriasis, and not the specific result of virus infection. On the other hand, if all, and particularly recurrent, cases of herpes simplex are due to local infection with herpes simplex virus, and since the subjects may exhibit abnormal sensitivity to sunlight as do tar-workers and those subject to *x* rays or arsenical dermatitis and xeroderma pigmentosa, it may be that infection by the virus, which is widespread, is an important cause of malignant change. Since the buccal mucosa and the skin of the genitalia and other tissues may also be infected by herpes simplex there is a possibility that in some cases in these tissues, too, the infection may be related to the later appearance of malignancy.

Summary

Six cases of herpes simplex of the lips in old people followed by the development of squamous carcinoma six weeks to five years afterwards are described. The significance of the observation in relation to the virus theory of cancer causation is briefly considered.

The above observations were made while holding a Gordon Jacob Research Fellowship at the Royal Marsden Hospital. I should like to express my thanks to the Medical Committee of the hospital for permission to publish the brief case histories.

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MOTOR COMPLICATIONS OF HERPES ZOSTER

BY

DAVID KENDALL, D.M., M.R.C.P.

Neurologist, South-west Metropolitan Regional Hospital Board

The occasional appearance of muscular weakness in association with herpes zoster has been recorded in numerous papers since Broadbent (1866) described a patient with extensive weakness of an arm preceded by a herpetic eruption. Head (1899) quotes as examples an eruption in the territory of the first dorsal root with severe hand weakness, ophthalmic herpes with oculomotor palsy, and facial palsy with an eruption in the second and third cervical area. Taylor (1896) drew attention to the occasional presence of weakness of the abdominal muscles with herpes of the trunk, and Ford (1944) has suggested that localized weakness of intercostal or abdominal muscles may be quite common, but may often pass unnoticed in the absence of disability. Other cases of lower motor neurone paralysis have been described by Joffroy (1882), Waller (1885), Buzzard (1902), and more recently by Cornil (1930), Barham-Carter and Dunlop (1941), Taterka and O'Sullivan (1943), Parkinson (1948), Scobey (1949), and McIntyre (1951).

Evidence of direct involvement of the central nervous system was first observed by Brissaud (1896) and has since been described by Lhermitte and Nicolas (1924), Lhermitte and Vermes (1930), Worster-Drought and McMenemey (1933–4), and Whitty and Cooke (1949). Following the observations of Lhermitte and Nicolas of segmental changes in the spinal cord at the affected level, it has been suggested that the root entry zone of the cord is often if not always affected, and that many of the anomalous clinical findings in herpes zoster can best be explained by regarding the condition as a disease of the central nervous system in addition to the posterior root ganglion.

Denny-Brown, Adams, and Fitzgerald (1944) examined at necropsy the nervous system of a patient who had had the " Ramsey Hunt syndrome " and found no significant change in the geniculate ganglion. It has become well known since Ramsey Hunt's (1907) original description that wide discrepancies occur from patient to patient in the distribution of the eruption in relation to the facial palsy. Denny-Brown *et al.* postulated that herpes zoster may therefore be primarily a unilateral segmental polio-