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THE CLINICAL VAGARIES OF THE HERPES VIRUS*

BY

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The virus of herpes simplex is so widely spread that in all probability but few members of the human race avoid some passing acquaintance with it. Many are quite unaware that they have acquired the virus, which adapts itself so harmoniously to its host that the only clue to its presence is the steady level of specific antibodies in the blood. These are present, according to Buddingh *et al.* (1953), in over 90% of the population beyond the age of 15 years. Brain (1932) showed that the persistence of these antibodies was the rule in recurrent herpes and that this could be most readily explained by a carrier state. Since then the virus has often been recovered from the nasal and buccal mucosae and also from the stools, and it would appear that the latent virus merely needs some stimulus for its activation. A febrile illness is the most profound stimulus, but among others we find many toxæmias, anxiety states, menstruation, and a strange variety of local conditions which irritate or damage areas of skin or mucous membranes or the sensory nerves or ganglia related to them. Evidently the presence of herpetic antibody is insufficient to prevent frequent recurrent herpes, but this seems less remarkable since Scott, in 1953 (quoted by Blank and Rake, 1955), showed that no significant changes in the level of neutralizing antibodies could be observed before, during, or after each attack.

Common Recurrent Forms of Herpes Simplex

Let us consider the common recurrent form of herpes simplex first. The classical eruption consists of grouped small vesicles arising from inflamed bases, and it might be noted that "delling" is rarely a conspicuous feature. In severe cases large bullae may be present, or an area of herpes may become confluent, but, apart from slight tenderness and enlargement of the regional lymph nodes, the eruption is usually little more than a temporary blemish. It may appear on any part of the body (Fig. 1) and occasionally simulate the sensory root distribution of zoster. Herpes may occur on any of the mucous membranes, but according to Blank and Rake (1955) there is no evidence that recurrent aphthous ulcers of the mouth are due to herpes virus.

Berg (1955) noted that Pearce and Degrade had described four cases of oesophageal ulcers with intranuclear inclusion bodies in the epithelium at the margins, and that Fingerland *et al.* had isolated herpes virus from five other cases. Berg re-examined material from

455 necropsies and found 11 cases of oesophageal herpes. All had suffered from cancer and had been treated by irradiation or surgery, with consequent damage to the thorax and especially to the posterior mediastinum. He described the herpetic oesophageal lesions as multiple small brown plaques of friable fibrinoid material rising above the level of the adjacent white normal epithelium. The changes associated with the formation of the intranuclear inclusion bodies of herpes were observed. Second-

FIG. 1.—Dr. Lightwood's case of recurrent herpes.

dary infection was common; it usually increased the ulceration and obscured the features regarded as specific to herpes. No symptoms relating to this involvement were recorded. The preference of the virus for damaged or irritated tissues is shared by other organisms.

Recurrent herpes may affect the eye, and the ocular lesions of the virus most commonly affect the conjunctiva and cornea. They often arise in association with herpetic vesicles of the skin in adjacent or remote areas during the course of a febrile or chronic debilitating illness and are seen as the commonest ocular complication of malaria.

The conjunctiva is not often affected alone, and distinct conjunctival vesicles are rare. In the cornea the irregularly distributed superficial lesions are seen as small circular opacities and transient vesicles which are seldom apparent to the naked eye. These may remain discrete, so that the cornea is spattered with fine white opacities, producing the clinical picture of superficial

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punctate keratitis, or they may rapidly coalesce to form the typical sinuous dendritic ulcer. Involvement of the deeper layers of the cornea also often occurs, with the development of disciform keratitis as a central oedematous lesion. A relapsing iritis, sometimes of a haemorrhagic type, is an occasional complication.

A few instances have been reported in which the root ganglia of peripheral nerves, both sensory and motor, have been involved.

Wyllie (1936) presented the case of a boy aged 7½ years with recurrent cranial nerve and spinal paralyses associated with herpes. The patient had herpetic outbreaks on the right side of the chin when he had a cold or chill, but between the ages of 4 and 7½ years he had three attacks of paresis of the right third nerve, two attacks of left facial paralysis which persisted, and more recently paresis of the right side of the face and of the muscles of the left arm, which were innervated from the sixth and seventh cervical segments. With the exception of the first attack (right third and left seventh cranial nerves) herpes always appeared on the right side of the chin, usually a few days after the cranial nerve palsies had developed, but preceding the paralysis on one occasion. The episodes were always afebrile, and therefore it was less likely that the herpetic eruption was merely concomitant.

This association of recurrent palsies with recurrent herpes is surely significant, and it seems probable that the following instances were related to the presence and the activity of the virus in the sensory ganglia.

Trigeminal Neuralgia Associated with Herpes Simplex

Behrman and Knight (1954) reported three such associated cases, one of which is very instructive. A woman of 32 had recurrent attacks of pain in the left maxillary division for 20 years. Attacks occurred at intervals of three to four weeks, and the sequence of events was constant. Momentary paroxysms of pain appeared in the left upper jaw over a period of several days, and after a day or two typical herpetic vesicles erupted on the upper lip and cheek. The pain then became continuous but subsided gradually, leaving her free from symptoms four to five days after the first vesicles appeared. Here the herpes virus imitated the syndrome of zoster, but the latter virus usually does more damage to the sensory ganglion, occasionally leaving a lifelong neuralgia; but it rarely strikes twice.

The manifestations described as recurrent herpes occur in subjects possessing immune bodies, the presence of which, if we exclude the newly born who passively acquire them, implies a previous primary infection. Blank and Rake (1955) state that this probably produces recognizable clinical disease in less than 1% of the population, but this estimate is much too high if one relates the rare incidence of the primary herpetic diseases to the vast numbers of those who have acquired herpes antibodies without clinical signs of the infection. They believe that the commonest form of clinical primary infection is an acute ulcerative infectious stomatitis, but in our experience the condition is rarely seen. Maybe it is less severe in this country, and as a transient soreness of the mouth it would be likely to escape recognition and the virological studies necessary to establish its herpetic origin. The presence of Vincent's fusospirilla in the necrotic epithelium of more severe cases may also divert the search for the causative virus.

Primary Herpetic Gingivo-stomatitis

This condition usually occurs after the seventh month and up to the sixth year, with most of the cases occurring before the second year, presumably because this early age group contains the greatest percentage of children having no demonstrable specific antibodies (Fig. 2).

Buddingh *et al.* (1953) found that the serum of 79% of white and 93% of negro infants up to the age of 6 months contained herpes-neutralizing antibodies. The explanation of this fact is probably the passive transfer of the antibodies from the mother during pregnancy, for these workers found approximately the same level of antibodies in the maternal

FIG. 2.—Professor Moncrieff's case of primary herpetic gingivostomatitis with perioral herpes.

and placental circulations, and a similar finding of placental transmission of antibodies to vaccinia virus was reported by Kempe *et al.* in 1952. (Quoted by Buddingh *et al.*, 1953.)

This high incidence of passive immunity in infants falls sharply after 6 months, and between 7 months and 2 years only 43% of white children and 71% of negro children were found to have neutralizing antibodies in their sera, so that in this period of life there lies the largest pool of susceptibility. At the same time the carrier rate of 12% in white children and 26% in negro children is at its highest figure, and adult carriers are common and add to the risk of infection.

Scott *et al.* (1953) give lower figures for the incidence of herpes-neutralizing antibodies in the blood of 131 children, but the incidence in the various age groups follows a similar pattern, as is shown in Fig. 3.

Scott *et al.* (1941) have made a special study of herpetic gingivostomatitis, and they find that in about half of the cases the onset is insidious, the child being ill for two to three days before a sore mouth developed; in the remainder there is an early refusal to eat, or a complaint of a sore mouth. The constitutional reaction is variable, with irrit-

FIG. 3.—Incidence of herpes antibodies based on 311 children up to the age of 14 years. From Scott *et al.* (1953) and Buddingh *et al.* (1953) (pooled). Dots indicate age incidence of 36 cases of eczema herpeticum (28 males, 8 females).

ability and fever rising to 104–105° F. (40–40.6° C.). A greyish-yellow plaque representing a modified vesicle with a thickened roof is the typical buccal lesion, and the number and size of the plaques vary considerably. Later the roof is shed, leaving a shallow ulcer. The tongue and cheeks are commonly involved, but no part of the mouth or pharynx is immune. The gums are usually involved early and resolve more slowly than the ulcers. The gums may show a red line along the dental margins or general extreme redness and swelling, but are spared in the rare event of infection before the teeth have erupted. Submaxillary lymphadenopathy is common. The disease is self-limiting, running its course in about two weeks, and this may be reduced by controlling secondary infection with antibiotics. Scarring is slight or absent. Rarely the nasal mucosa is the site of primary infection.

Scott *et al.* found that during the active phase herpes virus was readily isolated from the mouth and stools, and, while it is reasonable to assume that the virus in the stools came from the oropharynx, it is probable that herpetic lesions develop in the mucosa of the other parts of the alimentary tract, also in the trachea and bronchi, for symptoms suggesting this involvement appear in some children with gingivo-stomatitis. Herpes virus may be found in the saliva and stools for at least one to two weeks after the clinical signs of infection have disappeared. Neutralizing antibodies were first detected from the fourth to the seventh day after the onset and increased rapidly up to the third week. After a variable period, which in one case was 16 weeks, the maximum level falls. Subsequent significant rises in neutralizing antibody levels were often but not always related to finding the virus in the saliva.

According to Blank *et al.* (1950) recurrent herpetic stomatitis is extremely rare, and the more common recurrent aphthous ulcers are probably not herpetic.

Primary Infections of Genitals, Eye, and Skin

The primary herpetic infection may occur as an acute vulvovaginitis, as was first established by Slavin and Gavett (1946). On the inflamed oedematous vulva, and sometimes beyond it, are larger isolated vesicles or small groups which may become confluent. The labia are often stuck together by a viscid serous discharge, and vesicles are usually present on the labia minora, and herpetic plaques on the lower part of the vaginal mucosa (Fig. 4). Primary infection in the male is rare, but Slavin (1951) described it in a boy with stomatitis who had a cluster of herpetic vesicles surrounding an inflamed meatal orifice, accompanied by a watery discharge and dysuria.

There are the usual constitutional reactions, as in the case of herpetic stomatitis, and the regional lymph nodes are enlarged.

FIG. 4.—Primary herpetic vulvovaginitis.

In susceptible children herpes virus may enter the skin through a wound, a burn, a napkin rash, or an abrasion (Fig. 5). Three or four days later the lesion becomes erythematous and vesicles appear with the usual constitutional disturbance of a primary infection. Within a few days a further vesicular eruption may extend up the limb, simulating zoster with regional lymphadenopathy. Stomatitis may occur during the course of the illness, which may last 10 to 20 days. Recurrent herpetic eruptions may occur subsequently on the site of the primary infection, but the vesicles are usually smaller and there is no constitutional disturbance.

FIG. 5.—Professor Moncrieff's case of primary herpetic infection on a napkin eruption. The lesions resemble those of Kaposi's varicelliform eruption, but there was no constitutional reaction.

The eye may be the site of a primary herpetic infection, and an acute keratoconjunctivitis develops. The conjunctiva becomes very inflamed and oedematous, and the lid margins are gummed up with a sticky discharge and vesicles often appear adjacent to the lids. The cornea becomes hazy with superficial erosions but may suffer no permanent damage. The pre-auricular gland is enlarged and tender. The course of the disease is about 20 days and it may be febrile. I have mentioned the less severe manifestations of recurrent herpes affecting the eye.

In these primary infections of the mouth, genitals, eye, or skin it is not difficult to recognize the herpetic nature of the lesions, and the general symptoms, even when severe, are rarely alarming, although indicative of a systemic infection. The revelation of the virulent propensities of the herpes virus may be first observed when an infant is infected during its passage through the birth canal. Then the clinical picture of herpetic infection in the newborn is suggested by the occurrence of lesions of the conjunctiva, oral mucosa, or skin. The systemic reaction begins about the fifth to the seventh day, with fever or hypothermia, increasing icterus, lethargy, respiratory distress, vomiting, dyspnoea and cyanosis, haemorrhagic tendencies, and the rapid development of circulatory collapse. Enlargement of the liver and sometimes of the spleen complete the picture of an acute septicaemia, and occasionally there is nothing but the failure of antibiotic treatment to arouse suspicion of a herpetic viraemia.

Primary Herpetic Infections in Infants

As might be expected, these infections are most likely to occur in infants and children who have little or no immunity. The newly born usually share their mother's antibodies, but when they have none a primary infection may be serious and is often fatal, especially in a premature infant. In such cases the herpes virus displays its powers of attacking many organs and tissues, but the most serious consequences occur when the liver, the suprarenal glands, and the central nervous system are involved. The benign course of the common eruption of herpes febrilis provided an alibi overlong for this virus, and it was not until 1935 that Hass laid suspicion upon it.

In a premature female infant who developed hepatitis and died in two weeks, numerous necrotic areas were present throughout the liver, and in many liver cells he found intranuclear inclusion bodies of herpetic type. Microscopic areas of necrosis were also present in the adrenal glands.

Quilligan and Wilson (1951) were able to incriminate the virus by isolating it from the skin on the second day of the illness and from the skin and liver at necropsy on the twelfth day. The mother of this patient had labial herpes nine days before delivery. The infant had herpetic lesions on the skin and developed a severe hepatitis, and intranuclear inclusion bodies were found in the liver cells.

Zuelzer and Stulberg (1952) reported observations based upon eight necropsies which showed that the herpes virus could produce a fatal septicaemia or haematogenous hepatitis in infants in the absence of major cutaneous involvement. Five of the cases were newborn and four of these were premature.

Case 1.—A premature male infant developed a conjunctivitis with vesicles on the lower eyelids on the sixth day, and later a few vesicles on the temple and right arm. He became feverish and his jaundice increased. He had much respiratory distress with blood-stained mucus, and died on the thirteenth day after birth. His mother stated that for years she had suffered from a recurrent vesicular eruption on the vulva, and had two attacks during the early part of pregnancy. The post-mortem examination revealed that the liver, suprarenals, and lungs were riddled with pale-yellow firm necrotic nodules 1–6 mm. in size, and the microscope revealed similar changes in the spleen, kidneys, bone marrow, lymph nodes, tongue, oesophagus, and brain. Numerous inclusion bodies of herpetic type were present in all these organs, and the results of animal inoculations and neutralization tests established the herpetic origin of the disease beyond reasonable doubt.

Case 2.—A negro infant became feverish and jaundiced after the fifth day and died on the tenth day.

Case 3.—This infant developed a severe kerato-conjunctivitis on the eighth day and died a day later.

Case 4.—This patient became ill on the sixth day with kerato-conjunctivitis and died the same day from what may be described as a fulminating herpes virus septicaemia.

Case 5.—The only full-term infant of the five collapsed on the fifth day with dyspnoea and cyanosis. The skin and eyes were icteric and there was bleeding from the rectum and vagina. Death occurred within three days of the onset. The post-mortem findings in all these cases showed maximal involvement of the liver, adrenals, lungs, spleen, and focal lesions in the bone marrow.

The other three infants were aged 22 months, 18 months, and 3 weeks, and two began with typical herpetic stomatitis. In these older children the course was not so swift, and death followed at intervals of two and half weeks, one week (this case being associated with whooping-cough), and six weeks. The same type of hepatitis was observed in these three cases. The fulminating course of the disease in premature infants suggests that the near embryonic tissues are especially susceptible, and this has been demonstrated with chick embryos and newborn mice.

Without any history of herpetic eruptions in the parents, infection may occur shortly after birth and run a mild course for some weeks before becoming widely disseminated and lethal. Such a case was described by Pugh *et al.* (1954). A one-week premature female infant developed stomatitis at the age of 7 days which progressed to such an extent that breastfeeding was impossible after the 21st day, and choking attacks later followed each feed. The family doctor noted white patches in the mouth and diagnosed thrush. The patient was seen in the casualty department on the 27th day; she then had a red tongue but no evidence of thrush or ulceration of the tongue or buccal mucosa. Her feeding improved, but she lost weight and looked dehydrated, so she was admitted to hospital on the 32nd day of life. The tongue and buccal mucosa were uniformly reddened and a few small white patches were present on the palate. Her temperature was 99° F. (37.2° C.); pulse 129 a minute; and weight 7 lb. 13 oz. (3.5 kg.). The oral lesions improved with local treatment, but feeding became difficult and her weight was stationary, but there appeared to be no cause for anxiety. On the ninth day after admission her temperature rose to 100.4° F. (38° C.), and her condition suddenly worsened, she became cyanosed, and numerous haemorrhagic lesions, some becoming abscesses containing *Ps. pyocyanea*, appeared on the limbs. Systemic treatment

with penicillin, streptomycin, and chloramphenicol was unavailing and she died at the age of 42 days. The liver was studded with yellowish nodules mostly 1–3 mm. in diameter, but a few larger ones were up to 1 cm. (Fig. 6). There were sharply demarcated areas of coagulation necrosis, and in the margins some liver cells showed the formation of the early basophilic, and later the eosinophilic, inclusion bodies. Herpes virus was isolated from the liver, and it seems probable that a transient viraemia accounted for the sudden change in the patient's condition and the diffuse herpetic hepatitis.

Epstein and Crouch (1954) reported the case of a negress who developed herpetic vesicles on the labia seven days before childbirth. On the second day of life her infant had a transient rash on the face and trunk; on the sixth day slight fever and a serous nasal discharge; on the seventh day clustered sterile pustules on the neck; and with a further rise in temperature on the tenth day groups of vesicles appeared on the chest and back. On the twelfth day there were signs of pneumonia and herpetic lesions were present on the lips; vesicular lesions were noted on the epiglottis and larynx, with considerable oedema, and a tracheotomy was performed. Apart from signs of a mild encephalitis affecting the left hemisphere this severe infection mainly involved the skin and mucous membranes, and these were clear by the 32nd day. Although herpes virus was not isolated in this case, a significant rise in neutralizing antibodies, and the clinical features, indicated a herpetic infection.

FIG. 6.—Necrotic nodules of primary herpetic hepatitis.

Relationship of the Virus to Encephalitis

France and Wilmers (1953) reported the occurrence of hepatitis and encephalitis in newborn twin boys, and the livers of both were studded with numerous round white nodules up to 2 mm. in diameter, in the borders of which they found intranuclear eosinophilic inclusion bodies. Similar nodules, but no inclusion bodies, were observed in the cerebral hemispheres of the second twin. Wildi (1951) also reported the recovery of herpes virus from the cerebral lesions of a full-term infant aged 13 days, and it is of interest to note that the mother had suffered from genital herpes in the fifth month of pregnancy. Further reported cases leave no doubt of the existence of this type of meningo-encephalitis.

In the first report of the Matheson Commission (1929) a summary of the literature concerning the relationship of the herpes virus to encephalitis mentioned only nine instances of the isolation of herpes virus from cases of encephalitis—five from the brain, three from the spinal fluid, and one from the nasopharynx.

Gay and Holden (1933) isolated a virus identical with the herpes virus from the brain of a man who died from an acute exacerbation of chronic encephalitis.

These early observations were regarded with some scepticism because the herpes virus is so ubiquitous and because it has been isolated from apparently healthy tissues, but further reports dispelled the doubts of its pathogenicity for the nervous system and for many organs and tissues.

For example, Smith *et al.* (1941) reported the case of a male infant, one month premature, who in the third week

became irritable, with bouts of sudden screaming, and resented being moved. Twitching of the left arm and leg was noted, and fever was slight and transient. The infant died when 4 weeks old, and the necropsy revealed an extensive inflammatory process involving the brain and meninges to some extent. Nuclear inclusion bodies typical of herpes were present in degenerative nerve cells in or about foci of infiltration or necrosis. The virus was identified as that of herpes by neutralization tests and by the inoculation of mice, guinea-pigs, rabbits, rats, and the chick embryo.

In contrast with the swiftly running courses of primary herpetic infection in premature infants is the case described by Florman and Mindlin (1952). This infant was the third of triplets, prematurely born, weighing 3 lb. 2 oz. (1.4 kg.), who developed two small vesicles on the upper lip when 11 days old. The following day many more vesicles, in clusters, were present on both lips, the left side of the face, and on the back, and continued to appear for 16 days, mainly on the extremities, but some on the tongue and palate. On the 21st day of life she had a general convulsion, and the spinal fluid was hazy, with 150 white blood cells per c.mm. Convulsions persisted for 24 hours, and the infant remained irritable, with rigid musculature and occasional tremors. She had a phase of raised intracranial pressure, and at 3½ months was found to have acute chorioretinitis, which left extensive scarring and total blindness. At about 8 months she had an attack of laryngo-tracheitis and pneumonia, and five days later a herpetic eruption on the right side of the chest and over the left scapula and upper arm. She was severely retarded, mentally and physically, and maintained her spasticity. Herpes virus was isolated from the vesicles, but not from the cerebrospinal fluid, on the 11th day of the illness, and neutralizing antibodies were later found in the serum.

Similarity to Generalized Vaccinia

So far, in the conditions described, whether mild or lethal, the herpetic eruptions of the skin or mucosae have been vesicular and typical of their origin. However widely spread the herpes lesions are, the diagnosis of generalized or disseminated herpes is adequately descriptive. Occasionally a similar generalization occurs with vaccinia. Undoubtedly the strangest cutaneous manifestation of the herpes virus is seen when it is sited in an area of damaged or infected skin, especially if eczematous (Figs. 7-9; these illustrations show the evolution of Kaposi's varicelliform eruption (eczema herpeticum) from the herpetic to the varioliform pattern). Then in a severe case, the eruption on the face and limbs, the hyperpyrexia, and the severity of the illness are most suggestive of smallpox, and, although Kaposi (1887) originally described the eruption less aptly as varicelliform,

FIG. 7.—Mild case of Kaposi's varicelliform eruption showing herpetic grouping of papulo-vesicles (cf. Fig. 5).

it was so unlike the recognized picture of herpes febrilis that 50 years were to elapse before suspicion began to fall on the latter virus. Not until 1941 was the herpes virus recovered and identified by Seidenberg in two of four children involved in a small epidemic of pustulosa varioliformis acuta reported by Esser (1941).

This tardy discovery of the herpes virus in a new role is all the more ironic because Kaposi originally suggested the title of eczema herpetiforme for the disease that has since been called his varicelliform eruption.

The aetiological problem was undoubtedly complicated by the vaccinia virus, which occasionally produces an almost identical condition (Fig. 10; cf. Fig. 11). In fact, the severe forms of Kaposi's varicelliform eruption cannot be differentiated clinically according to the particular virus, although in the milder cases the vaccinal lesions are usually more raised and more varioliform than the herpetic, and this may be the only clinical hint of its vaccinal origin. Kaposi's original and concise description based upon his observations of 10 children is as follows: "A very alarming complication of eczema infantum is an acute outbreak of numerous vesicles, partly scattered, partly arranged in groups.

The vesicles are as large as a lentil, filled with clear serum, and the majority are umbilicated. They look like varicella vesicles, but undoubtedly do not belong to this class. The integument which has been attacked in this manner now appears still more swollen, even tense. The little patients have high fever (40° C. or more) and are very restless. The vesicles develop very acutely, sometimes overnight, in large numbers, and often continue to appear in successive crops for three or four days, or even a week. Those which appeared first undergo desiccation or rupture and expose the corium, or they become encrusted and fall off. The largest number of these varicella-like vesicles are found on already eczematous skin, but smaller groups appear upon the previously intact skin of the neighbourhood, upon the forehead, ear, neck, and even the shoulders and arms."

Our first case (Brain and Lewis, 1937), seen on November 3, 1936, was easily recognized from this classical description. The patient, a schoolboy aged 15 with xeroderma, had developed eczema a week after being vaccinated at the age of 3 months. From that time he had run the usual course of Besnier's prurigo, with occasional attacks of asthma between the age of 18 months

FIG. 8.—Case of Kaposi's varicelliform eruption showing varioliform type of lesions.

FIG. 9.—Eczema herpeticum. Severe case showing confluence of lesions and oedema.

FIG. 10.—Dr. Sheldon's case of Kaposi's varicelliform eruption due to vaccinia virus.

and 4 years. He was an only child, with a family history of asthma, migraine, and eczema. When he was worried by his school examinations his eczema became worse and his cervical glands became swollen and painful, and he went early to bed on October 31 with slight fever. The next morning his temperature was 103° F. (39.4° C.) and the skin on his forehead, neck, and arms became inflamed and spotty. His temperature rose to 104–105° F. (40–40.6° C.), and on November 2 the characteristic eruption appeared and within 24 hours was almost confluent on

FIG. 11.—Professor Moncrieff's case of generalized vaccinia. Severe primary "take" with confluent lesions. Scattered discrete pock lesions.

the forehead and neck. The individual lesions were so vacciniiform that the subsequent virological investigations were biased in favour of vaccinia. He was admitted to the Royal Free Hospital on November 4; the pustulation and toxæmia were progressive, and he developed a purulent conjunctivitis, many vesicles on the tongue and buccal mucosa, purpuric lesions on the knees and ankles, a haemorrhagic diarrhoea, and a terminal bronchopneumonia. He died on November 15.

It seems more significant now than it did then, to observe that material from his skin lesions produced a pustular reaction in guinea-pig pads, and a sterile suspension

from these produced an acute kerato-conjunctivitis in rabbits which was transmitted through five passages.

Unfortunately, inclusion bodies were not observed, and the virological studies ended on a negative note with respect to the vaccinia virus.

The only adult we have seen with Kaposi's varicelliform eruption is a man aged 53 who was admitted to the Royal Free Hospital on December 15, 1955, with a seborrhoeic dermatitis extending over the previous nine years with the usual variations. He had never had a true eczematous eruption nor was there any family history of allergy. He made good progress in hospital, but developed a boil on the right arm on December 20; this was treated with antibiotics, but the scaly erythematous eruption on his body, arms, face, and neck relapsed. He had a sudden rise of temperature on the 23rd and this reached 103° F. (39.4° C.) on the 25th, when he had the typical vesico-papular eruption on his forehead and

cheeks, and larger lesions in the moist and slightly affected axillae. The picture was quite characteristic of the herpetic type of Kaposi's varicelliform eruption, and Dr. J. A. Dudgeon isolated the herpes virus from his lesions, which became confluent in the axillae and showed the typical pocking. The temperature persisted for five days; it then subsided and his skin eruption faded.

Since 1949, 36 instances of Kaposi's varicelliform eruption attributed to the herpes virus have been seen at the Hospital for Sick Children. In 30 the virus was isolated, or the typical intranuclear inclusion-bodies were observed in smear preparations from the lesions. The other six had no contact with vaccinia, and were of the herpetic pattern. During this period only two cases of the vaccinal type were seen. Both were fully confirmed, and the mothers developed accidental vaccinia infections from their infants. Our series of cases therefore shows a remarkable preponderance of herpetic infection, but this is partly accounted for by several minor epidemics in the hospital, and one involving six patients was reported (Brain, 1954).

As all these cases occurred in infants or children suffering from eczema we would prefer to adopt the suggestion of Lynch and Steves (1947) and describe them as cases of "eczema herpeticum," as distinct from the vaccinal type, which has been called "eczema vaccinatum." The distribution between the sexes has rarely called for comment, so presumably it is fortuitous that 28 of our patients were males and only 8 were females; Dr. Dudgeon kindly gave us a list of nine further cases from other sources in which he had confirmed the diagnosis of eczema herpeticum, and eight of these were in males.

As regards the age of incidence of this series, 24 were in the pool of greatest susceptibility in the age group of 5–15 months and the others below the age of 3 years with one exception, a girl aged 9 years.

Clinical Features

Approximately half our series of patients were seriously ill, and their clinical features conformed so closely with the description given by Kaposi that the diagnosis was obvious. The face was by far the most affected, because the weeping eczematous areas are more persistent there in infancy and are often more infected. Pyogenic cocci were almost invariably recovered from the lesions, and at first it was thought that they shared a dual role with the herpes virus in producing the severely toxic syndrome. This view is supported by the beneficial effects of treatment with the antibiotic drugs which have no lethal action upon the herpes virus; but we have shown how virulent the virus can be, and virological studies have demonstrated that some of the most severe pustular lesions of eczema herpeticum may be bacteriologically sterile. A further point to consider is whether the rapid confluence of the eruption over areas of infected eczema is related to the spreading effect of hyaluronidase produced by the pyogenic cocci. Against this concept is the fact that the appearance of many discrete lesions symmetrically on the limbs indicates a viraemia. It is known that the virus has a preference for damaged tissues, so that would explain the concentration of lesions on the weeping infected skin.

In mild cases the eruption may be mistaken for a type of impetigo, and the help of a virologist is necessary to establish the diagnosis. The sudden appearance of a crop of uniform small lesions should arouse suspicion, especially if preceded by a slight rise of temperature and pulse rate.

In cases of any severity the regional lymph nodes are usually enlarged and tender but do not suppurate. Another feature to be stressed is the marked oedema of the skin and subcutaneous tissues in the areas mainly involved, especially of the face.

In our series the temperature ranged from 99 to 105° F. (37.2 to 40.6° C.) and persisted for periods of 2 to 14 days.

Three infants died; two at the age of 10 months, the other at 11½ months. One had no post-mortem signs of systemic

herpes; another had herpetic lesions in the brain and suprarenals. The third showed focal necroses typical of herpes but with some unusual features that were described by Pugh *et al.* (1955). They found typical herpetic lesions in the skin and suprarenals, and the virus was recovered from the skin before and after death. In the skin and in the pharynx and lungs were areas of intense focal necrosis, the amorphous material being strongly basophilic and probably consisting mainly of deoxyribonucleic acid. It was thought that these atypical necroses were almost certainly due to spread of herpes virus along the bronchial tree, and the absence of the characteristic histology in such lesions reminds us of the necrotic tubercles and bacterides, and perhaps we must eventually accept the concept of necrotic "virides."

Usually in infants the herpetic type of Kaposi's varicelliform eruption is a primary infection, because in the early stages of the disease specific antibodies are not found in the serum, these appearing during convalescence. However, cases have been reported, such as that by Lynch (1945), in which serum collected on the third day, when the virus was recovered from vesicle fluid, contained a normal level of antibodies which had not significantly altered 75 days later. Thus the presence of herpetic antibodies does not necessarily protect the individual from either recurrent herpes or from a recurrence of Kaposi's varicelliform eruption, for Ruchman *et al.* (1947) reported a case in a patient aged 25 who was infected in spite of the presence of neutralizing bodies in the serum in the acute stage of the disease, and who developed a second attack six weeks after the onset of the first.

Boake *et al.* (1951) reported the case of a man aged 36 who had been known to be diabetic for 25 years, and about twice a year had attacks of herpes either on the lips or on the cheeks, ears, and eyebrows. These eruptions only accompanied a febrile illness and varied in step with its severity. After one attack 19 years previously he developed what was described as atopic eczema. In 1946 and 1948, and in the attack reported, a severe herpetic eruption followed pneumonia and diabetic imbalance, and was largely localized to the eczematous areas. The eyelids were oedematous and ulcerated, and there was a shallow corneal ulcer in the last attack. Herpes virus was isolated from lesions on the face and neck, and neutralizing bodies were present in the same titre in the patient's serum examined on the 3rd and 21st days of his illness.

Feldman and Newman (1955) reported three cases of recurrent Kaposi's varicelliform eruption. The first case had three attacks and the others two; these cases illustrate the previously observed fact that a recurrence had the usual dramatic onset of the primary infection, but its course was milder and of shorter duration.

Four of our series of 36 cases had a recurrence of Kaposi's varicelliform eruption, and the rarity of recurrent cases contrasts sharply with the frequency of banal recurrent herpes. Why attacks of either should recur in the presence of existing antibodies remains to be explained, and so does the insignificant change in antibody titre to successive attacks.

Conclusion

The final clinical vagary of the herpes virus to be mentioned is its unusual degree of infectivity, which has accounted for small epidemics of Kaposi's varicelliform eruption, and also for contact lesions on the hands or forearms of nurses and other attendants (Fig. 12). These are in marked contrast with the rarity of contact infections from cases of herpes simplex, especially as its lesions are usually on the lips or cheeks.

Juliusberg (1898) reported the occurrence of vesicular lesions on the eyelids of a mother whose child died of Kaposi's varicelliform eruption.

McLachlan and Gillespie (1936) reported an epidemic of 16 cases in a children's ward, with five deaths, but the causative virus was not identified. One nurse developed three large purulent bullae on the forearms.

Barton and Brunsting (1944) also reported that three nurses attending one of their cases developed vesicopustules on the hands without any constitutional symptoms.

Simpson (1953) described a nodular lesion on the thumb of a ward sister who had nursed an infant of

FIG. 12.—Localized herpes contracted by a nurse from a patient with eczema herpeticum.

11 months with Kaposi's varicelliform eruption. The incubation period was apparently five days when the first papule appeared, and she had fever, malaise, and regional lymphangitis. Two days later a second papule appeared on the base of the thumb, and developed into a slightly tender, round, firm red nodule 1.2 cm. in diameter, projecting 4 mm. above the mildly eczematous skin. The papule was surmounted by a vesicle 5 mm. in diameter which oozed blood and serum when the roof was removed. Herpes virus was isolated from the skin lesions of the child and the ward sister.

It is clear that contact lesions from patients with Kaposi's varicelliform eruption may be typical herpetic vesicles, bullae, or indurated papules, becoming bullous and pustular at their apices before necrosis of the central part forms a deep pock.

In our series of cases five nurses and a pathologist developed large vesicles or bullae, or small granulomatous nodules, somewhat similar to orf, which finally became bullous and then pocked.

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THE PROBLEM OF OTITIS EXTERNA

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Otitis externa is a form of dermatitis, either confined to the external auditory meatus or extending on to the concha or even over the whole pinna.

The external auditory meatus and pinna usually remain free from disease throughout life, the skin being able to keep itself healthy provided it is not damaged. The skin of the concha contains many sebaceous glands but no sweat glands, whereas the skin of the outer third of the meatus is well supplied with hairs, sebaceous glands, and modified apocrine sweat glands. The opening is only 7–8 mm. in its greatest diameter, and will not admit even the little finger. The hairs at the orifice are protective, like those in the vestibule of the nose.

Cerumen (wax) is a mixed accumulation of the products of sebaceous glands and modified apocrine sweat glands. It acts as a lubricant, as a bactericidal agent, and as an adhesive to prevent the entry of foreign bodies. The glomeruli and ducts of the apocrine glands have an inner layer of secretory cells and an outer layer of contractile myoepithelial cells.

Sebaceous glands are not under direct nervous control, but apocrine glands respond to sympathomimetic agents and to strong emotional stimuli of pain or fear (Shelley and Hurley, 1952, 1953). The action is believed to be a mixed one of contraction of the muscular elements and reduced reabsorption from the ducts (Ackermann, 1939). Lobitz and Campbell (1952) state that hypersecretion of the apocrine glands occurs in some patients with otitis externa. The ceruminous glands secrete and also sweat. The secretion is a slow, continuous, and

barely noticeable process. The sweat consists of drops of white fluid which are discharged on the surface by contraction of the myoepithelial sheath. Mechanical stimuli, adrenaline, severe pain, or fear, all cause emptying of the glands (Shelley and Perry, 1956). Qualitative and quantitative changes in the production of apocrine sweat can result in obstruction of the ducts by horny material, which may produce itching (Weddell, 1948). Trauma, with or without itching, is clearly the precursor of otitis externa.

The skin of the inner two-thirds is thin, with only a narrow band of collagen fibres between the epidermis and the periosteum. Hairs and glands are inconspicuous or absent. In healthy ears it is most unusual to see dust particles on the skin of this portion of the canal. Scratching the meatus, syringing the ear, blast injuries, swimming, or even washing the hair can carry dust, organic matter, or chemicals beyond the hairy barrier, but the barrier of hair and cerumen is a most efficient filter under all ordinary circumstances. Healthy wax travels slowly out of the meatus, like a glacier, carrying foreign bodies with it. The movements of the mandible probably help this mechanism. It is uncertain how dust particles and desquamated cells are removed from the skin of the inner part of the canal. They probably become embedded in the wax by gravity—for example, in the lower ear when sleeping.

Bacteriology of the External Ear in Health and Disease

Stewart (1951) made a bacteriological study of 104 apparently healthy external auditory meatuses. There were 34 sterile cultures, 62 cultures of saprophytic organisms, 6 of *Staph. pyogenes*, and 2 of *Bact. coli*.

We have each made clinical and bacteriological examinations of 50 patients attending our departments with otitis externa. In 43 of the otologist's patients the inflammation was confined to the meatus and in the remainder there was some dermatitis of the adjacent concha. In the dermatologist's patients there was usually both meatitis and dermatitis of the concha or even of the whole auricle. It so happened that each examined 24 males and 26 females, but the two series were independent of one another. The ages of the patients are shown in Table I.

TABLE I

	Otologist's Patients	Dermatologist's Patients	Total
Up to 9 years	1	1	2
10–19	7	1	8
20–29	15	6	21
30–39	5	8	13
40–49	14	11	25
50–59	5	15	20
60–69	3	6	9
70–79	0	2	2

TABLE II

	Otologist's Patients	Dermatologist's Patients	Total
<i>Staph. pyogenes</i>	10	13	23
<i>saprophyticus</i>	—	2	2
<i>Ps. pyocyanea</i>	—	2	2
<i>Pr. vulgaris</i>	—	2	2
<i>B. aerogenes</i>	1	—	1
<i>C. albicans</i>	1	—	1

Pure cultures were obtained from 31 patients (Table II). In the 69 mixed infections sometimes two and sometimes three different pathogenic organisms were recovered.

The total bacteriological findings from the 100 patients are shown in Table III. These organisms can be classified, so far as the skin is concerned, in three main groups—namely, pathogenic cocci, intestinal pathogens and sapro-