HERPES LABIALIS AFTER SULPHAPYRIDINE AND T.A.B. THERAPY

BY

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Although herpes labialis is clinically a harmless infection its causal agent has been the subject of much research. The condition is often seen in soldiers, and a Swiss regimental physician (Mayer, 1921) has described a spontaneous outbreak of 30 cases among 70 soldiers who slept in one barrack-room. Five of the 6 officers attached to the same unit were also involved. Last winter we observed 33 cases among hospital patients and investigated them from the laboratory point of view. Two classes of persons suffering from herpetic eruptions were studied—namely, normal healthy nursing orderlies, who developed it spontaneously, and a larger group comprising patients treated for gonorrhoea.

Before beginning our description of the clinical-pathological findings and animal inoculation results we should like to present a summary of modern conceptions regarding the aetiology and pathogenesis of herpes. The disease was first proved to be infective by Vidal (1873), and thereafter the classical researches of Levaditi, Doerr, and others showed that the causal agent was a filterable virus which was highly pathogenic to the rabbit, and which produced violent keratitis if implanted upon the scarified cornea of that animal, occasionally followed by meningitis and death. Individual strains of virus differed in their neurotropic affinities for the rabbit; consequently attention turned to herpes simplex virus as being a possible cause of encephalitis lethargica, and Levaditi and Harvier (1920) claimed to have isolated the virus from such cases. Unfortunately, independent confirmation of Levaditi's researches was lacking and the work fell into disfavour, but it may still prove that his investigations were made in advance of the times. The clinical nomenclature employed for the designation of the various manifestations of herpetic infection in man is unsatisfactory. Thus the usage of terms such as "herpes simplex," "febrilis," "labialis," "recurrent herpes," and "idiopathic and symptomatic herpes" indicates that the classification is inconsistent, and not based on anatomical, clinical, or aetiological grounds. For the convenience of readers over-seas the following account contains a summary of the facts respecting the clinical types of herpes and their aetiology. At the outset it should be understood that all forms of herpes affecting man, *other than herpes zoster*, are due to one and the same virus, which is pathogenic to the rabbit, whereas the virus of herpes zoster is a separate entity which is non-pathogenic to the rabbit and probably related to the virus of varicella. Both herpes and zoster viruses are particulate and visible organisms which occur in the form of minute virus elementary bodies, and Elford *et al.* (1933) have succeeded in measuring herpes simplex virus, estimating it to be 100 to 150 m μ in diameter. Herpes virus also produces specific histological changes, and acidophilic intranuclear inclusion bodies have been described in human corneal epithelium (Fuchs, 1933) and in the large epithelial cells present in human vesicle fluid (Da Fano, 1923).

Clinical Varieties of Herpes

Herpetic infection may appear in a variety of forms, as follows:

Herpes febrilis is the term applied to herpes arising during the course of a pyrexial disease, such as pneumonia, malaria, influenza, and other febrile disorders. The usual situation is on the lip, the term "herpes labialis" then being popularly used; but when other areas of the face are involved it is called "herpes facialis." Aphthous stomatitis is another disease which has been proved to be due to the herpes virus (Dodd, Johnston, and Buddingh, 1938; see also Gottron, 1938; Burnet and Lush, 1939). Herpetic vesicles are seldom bigger than a large pin-head and develop on a reddened base, being usually filled with clear fluid, although suppuration may occur. The commonest site for vesicles is on the lips, inside and around the mouth, the cheeks, and the auricles.

Herpes simplex is the designation applied to herpetic eruptions, unassociated with pyrexia, which may arise spontaneously, or secondarily to a variety of causes, such as after the injection of vaccines, milk, and colloidal metals (see Fischer, 1927); or the ingestion of certain foodstuffs followed by gastric disorder.

Herpes Genitalis.—Herpetic eruptions are not uncommon on the genitals, being found on the glans or body of the penis, and, in the female, on the labia. It is frequently associated with syphilis (Cranston Low, 1939).

Herpes Cornealis.—Herpetic infection of the cornea may assume a variety of forms, of which the dendritic ulcer is the best known (see Duke-Elder, 1938). The inflammatory reaction may be severe and result in serious scarring of the cornea.

Recurrent Herpes.—Certain persons are very susceptible to herpes, and why this should be is not clear. It is possible that they carry the virus in their saliva or elsewhere in the body, and Burnet and Lush (1939) have suggested that in such instances the infection is contracted in infancy, as an aphthous stomatitis, and persists throughout life. Some particular recurring susceptibility of the tissues may allow the virus to exert its pathogenic action from time to time, and, for instance, recurring genital herpes is apt to occur in cases of irritation due to chronic gleet and prostatitis (Avit-Scott, 1931). In women recurrent herpes is often associated with the menstrual period (Blum, 1926). Apart from the question of variations in the host as the predisposing factor in recurrent herpes, it is possible that the strain of virus itself may possess unusual tenacity. Thus Nicolau and Banciu (1924) inoculated a number of persons with strains of virus from cases of recurrent infection and found that two of these persons themselves developed recurrent herpes.

Nervous Manifestations.—Although herpes is usually regarded as a mild local lesion, more serious manifestations may arise from time to time. For example, French authors (e.g., Levaditi, 1922, 1926) describe *herpès névralgique de Mauriac*, with symptoms of severe pains, crises of hyperaesthesia in the perineum, tenesmus, sphincter spasm, and sciatica, all preceding the appearance of the eruption. In less severe cases herpes may be accompanied by pruritus, backache, and neuralgia. Doubtless these are due to the fact that the virus involves the corresponding ganglia, producing an inflammatory reaction (see Howard, 1905).

Herpetic meningitis is a distinct clinical entity, with sudden onset, rapid course, favourable outlook, and a lymphocytosis in the cerebrospinal fluid (see Abiteboul, 1936).

The Common Aetiology of Herpetic Eruptions

To-day all herpetic eruptions (always excepting, of course, those of zoster) are regarded as due to one and the same virus, based on the following evidence:

Vesicle fluid from all varieties of herpetic eruption can be inoculated into the human skin, with consequent production of a typical crop of "simplex" vesicles (Vidal, 1873; Lipschütz, 1921b; Teissier *et al.*, 1922b; Frei, 1931; Zurukzoglu and Hruszek, 1933).

Vesicle fluid from herpes febrilis produces a severe keratitis when applied to the rabbit's eye (Löwenstein, 1919, 1920; Grüter, 1920). Herpes cornealis yields a virus with the same characteristic effect (Doerr, 1920; Doerr and Vöchting, 1920; Luger and Lauda, 1921).

Herpes labialis yields the same virus, and will produce typical herpes cornealis when suitably applied to the human cornea (Doerr, 1920; Doerr and Vöchting, 1920; Fuchs, 1921, and see Fuchs, 1933).

Vesicle fluid from herpes genitalis also produces keratitis in the rabbit, and man can be reinfected with material taken therefrom (Fontana, 1921; Blanc and Caminopetros, 1921).

Herpes occurring in such diseases as cerebrospinal meningitis, pneumonia, diphtheria, influenza, catarrhal jaundice, erythematia, and secondary syphilis yields a virus showing the same characteristics as does that obtained from cases of primary herpes (Teissier *et al.*, 1922a).

Similar intranuclear inclusion bodies have been reported in human herpes febrilis, cornealis, and genitalis, and in experimental lesions in animals (Lipschütz, 1921a, 1921b, 1921c; see Fuchs, 1933).

Distribution of Virus in Infected and Healthy Persons

Herpetic Vesicle.—The virus is abundantly present in the vesicular stage, but disappears after the crust forms (Teissier, Gastinel, and Reilly, 1926a).

Blood.—The agent may be found in the blood of persons suffering from herpetic eruptions, although this is rare (Löwenstein, 1919; Bastai and Busacca, 1924b; Teissier, Gastinel, and Reilly, 1926a, 1926b).

Cerebrospinal Fluid.—Flexner and Amoss (1925a) examined the cerebrospinal fluid of 100 persons, including some suffering from epidemic encephalitis, but in only one case were they able to isolate herpes virus, and this from a syphilitic patient with no herpetic eruption. This is an important observation, and indicates that the virus may, although rarely, be found in the cerebrospinal fluid of patients who at the moment do not suffer from herpes. Zurukzoglu (1937) has also isolated two strains of herpes virus from the cerebrospinal fluid of healthy persons. With regard to the cerebrospinal fluid of herpetic patients, the consensus of opinion is that the virus may be found on occasions (Ravaut and Rabeau, 1921; Bastai and Busacca, 1924a; Zurukzoglu, 1937), but a number of competent investigators have been unable to detect it (for example, Doerr and Zdansky, 1924; Levaditi, 1925; Teissier, Gastinel, and Reilly, 1926a, 1926b).

Saliva.—Herpes virus has been found in the healthy saliva by a number of workers (for example, Levaditi, Harvier, and Nicolau, 1921; Doerr and Schnabel, 1921; Teissier, Gastinel, and Reilly, 1926b). The virus is attached to the salivary epithelial cells and is probably associated with the buccal mucus, because suspensions of salivary gland tissue are avirulent (Levaditi, Harvier, and Nicolau, 1921). The presence of the virus has usually been detected by its ability to produce keratitis in rabbits. Levaditi and his collaborators have stated that 80% of normal specimens of saliva produce experimental keratitis, but only in 15% is keratitis severe enough to be followed by cerebral involvement (see below). These high figures have not, however, been generally accepted by other workers, who

have failed to find any virus in normal saliva (for example, Flexner and Amoss, 1925b). Nevertheless there seems no doubt that the virus can on occasion be found in this site, as described below. Several workers have investigated the saliva of persons suffering from herpes and have, though rarely, been successful in demonstrating the presence of the virus (for example, Isaicu and Telia, 1922; Flexner and Amoss, 1925b; Nicolau and Poincloux, 1922, 1924). Thus it has been found in the saliva of patients suffering from labial and facial herpes and herpes of the finger. The saliva of persons predisposed to herpetic eruptions contains the virus more often than that of other persons, and it may be found in the intervals between attacks (Levaditi, 1926).

Conjunctival Sac.—The virus can apparently be carried in a latent form in the conjunctival sac, but if the cornea be injured it may produce keratitis (Grüter, 1924; Busacca, 1925). It may also cause severe unilateral conjunctivitis, developing without obvious reason (Gränström, 1937).

Other Skin Lesions.—The agent of herpes has been recovered on rare occasions from zoster vesicles and sycosis pustules (Naegeli and Zurukzoglu, 1935).

Our present article deals with the condition of herpes labialis which developed in healthy (often perfectly fit) male adults or, as in the majority of our cases, in patients under treatment for gonorrhoea. Below we describe our own work, which is subdivided into clinical data, laboratory findings, and animal inoculation experiments (performed by Dr. Rhodes), followed by a discussion on the aetiology of the condition.

The Present Research: Clinical Data

Altogether 33 cases of herpes labialis were studied by us; 6 occurred spontaneously in healthy nursing orderlies and 27 in patients suffering from gonorrhoea who had received a full course of sulphapyridine and subsequently developed herpes labialis after a provocative dose of T.A.B. The dosage of sulphapyridine administered was that employed before the latest Army instructions, and consisted of 9 grammes on the first day, 6 on the second and third, and 4 on the fourth, the total quantity given being 25 grammes in four days. The clinical results of such therapy were excellent, and in the majority of instances the urethral discharge had abated by the fifth day, so that on the sixth day patients underwent a test of cure consisting of a 0.2 c.cm. dose of T.A.B. vaccine injected intravenously. It was following this provocative dose of T.A.B. that herpes frequently manifested itself. In the first batch of subjects 22 patients received 0.2 c.cm. of T.A.B. vaccine intravenously, and forty-eight hours later it was noticed that all the men developed herpes labialis. Sixteen showed only a slight eruption, which cleared up spontaneously without any treatment; but in the remaining 6 the lesions were severe, and a 50% absolute alcohol dressing was applied with good effects.

Following these results Captain J. A. Scott, R.A.M.C., decided to reduce the dose of vaccine, and the next batch of 6 cases received 0.1 c.cm. of T.A.B. intravenously. Once again herpes was observed, and 3 persons were affected. Subsequently one of us (A. C. E.) decided to dispense with intravenous T.A.B. as a provocative measure, and thereafter hypertonic saline solution (instilled and retained in the urethra for a short time) was substituted as an alternative, following which no further cases of herpes appeared. The obvious conclusion to be drawn from such results is that if herpes labialis is to be avoided, intravenous T.A.B. vaccine should not be given to persons immediately after they have received a course of sulphapyridine. This is particularly so during the winter months, when, as we shall mention later, the herpes carrier rate is relatively high.

To provide a reason for this curious phenomenon is not easy, and at first sight it seemed that the T.A.B. was the primary exciting cause, since it is an acknowledged fact that the parenteral injection of bacterial protein (such as T.A.B. and gonococcus and other vaccines) may cause slight herpes labialis in a small proportion of individuals. But we had reason to suspect that the predisposition to herpetic infection was greatly enhanced by the intake of sulphapyridine, because no fewer than 24 out of 25 patients who received 0.2 c.cm. of T.A.B. intravenously and 3 out of 6 receiving 0.1 c.cm. of T.A.B. after sulphapyridine developed herpes. Thus we have inferred that while a course of sulphapyridine does not provoke herpes itself, the drug increases the susceptibility to herpes if a subsequent and large enough dose of T.A.B. is given intravenously. We need hardly add that for obvious reasons one cannot answer the question how many patients would have developed herpes if they had received T.A.B. intravenously without sulphapyridine, but it is most unlikely that such a high proportion would have done so.

The possibility of the batch of T.A.B. vaccine used having become accidentally contaminated with herpes virus was explored, but animal inoculation and sterility tests proved that the product was faultless. Finally one of us (C. E. v. R.) received 1 c.cm. of this same vaccine subcutaneously without developing herpes.

Laboratory Investigations

Animal Experiments.—Herpes virus was recovered from 6 out of 7 cases examined by employing the following technique:

Vesicle fluid was collected in sterile capillary glass tubes; a drop of the fluid was placed on the corneal surface of an anaesthetized rabbit and the surface of the organ lightly scarified with a needle. After forty-eight hours acute kerato-conjunctivitis had developed. A proportion of our animals contracted meningitis and died, and the condition could be transmitted to healthy rabbits by inoculating them intracerebrally or corneally with infected brain or corneal tissue suspensions. We also demonstrated the presence of elementary bodies of herpes in films prepared from the conjunctival exudate and from corneal scrapings of infected rabbits. Likewise, dark-background microscopical examination showed numerous highly refractile particles not unlike elementary bodies; but, for reasons already discussed by van Rooyen and Rhodes (1940), not much reliance was placed on this method of examination.

Examination of T.A.B. Vaccine.—The phial of material used for provocative injection was carefully examined for possible evidence of contamination with herpes virus, but although rabbits were inoculated by various routes none could be recovered. Simultaneously, general tests for absence of bacterial growth were conducted, and 1-c.cm. amounts of bacillary emulsion were inoculated in suitable solid and fluid media and incubated aerobically, and anaerobically in a Mackintosh and Fildes jar, at 37° C. for fourteen days, but, as previously, results were negative throughout. No blame could therefore be attributed to the T.A.B. vaccine.

Leucocyte Counts.—These were done for two reasons: first, to keep check on the white cell level during sulphapyridine treatment, and, secondly, to ascertain whether herpes occurred more often in patients possessing a low polymorph count. Results showed that no correlation existed between the degree of leucopenia and the onset of herpes, for in some cases after sulphapyridine the white cells fell to 6,000 per c.mm., whereas in others it remained as high as 9,000; but, nevertheless, both categories developed herpes labialis after a provocative dose of T.A.B. Likewise, 12 additional patients with white cell counts intermediate to the above also came under review, but again herpes developed indiscriminately. Finally, no

relation could be shown to exist between the state of the differential white cell picture and the predisposition to herpes.

Carriers of Herpes Virus

It is universally accepted that herpes virus may occur as a commensal in the saliva of a large proportion of normal healthy human beings. According to Andrewes and Carmichael (1930) specific virus-neutralizing serum antibodies were discovered in 75% of individuals at the time of their experiments. What percentage of normal persons carry herpes virus it is difficult to calculate, but it is certain that the figure would vary from time to time, and most probably would be highest among those living in camps and hospitals, especially during the winter months, under conditions favouring the spread of droplet infections. To obtain a rough estimate of the carrier rate in a single ward in a hospital during December, 1940, we collected early morning specimens of saliva from 10 cured patients awaiting discharge to duty and examined them for evidence of herpes virus. Nine of these specimens of saliva were negative, but from the tenth a typical strain of herpes was recovered and passaged serially through three rabbits. Owing to the high cost of animals a larger number of tests could not be performed. The presence of herpes virus in one of the ten persons examined illustrates how easily it can be demonstrated in the mouths of normal individuals, and therefore something like 10% of persons could be assumed to be carriers of virus at the place and time of our observations. It should be remembered that every carrier of the virus does not necessarily show herpetic lesions; but, on the other hand, the converse is true, for every patient who develops herpes is proof of the presence of the agent in that individual's saliva. Thus it is quite feasible for a high virus-carrier rate to exist among a community which may exhibit a relatively low case incidence of herpes labialis—unless methods of therapy which are known to exert a herpetogenic action are used. In support of this hypothesis we would point out that during the winter months we noticed 6 cases of herpes which occurred spontaneously among healthy nursing orderlies and others in a unit about 300 strong. But when patients were treated with sulphapyridine and 0.2 c.cm. of intravenous T.A.B. no fewer than 24 out of 25 developed it, thus proving the high carrier rate existent.

Observations Repeated Three Months Later

From December, 1940, to March, 1941, intra-urethral saline was substituted for T.A.B. vaccine as a provocative measure, and over a hundred cases of gonorrhoea were effectively treated with sulphapyridine without any sign of herpes. At the end of this interval 3 cases of chronic gonorrhoea which had responded unfavourably to sulphapyridine arrived for attention, and it was decided to try the effect of mild protein-shock therapy. Accordingly each patient received intravenously 0.2 c.cm. from a fresh phial of T.A.B., and five days later two of the men developed herpes labialis. These results are of particular significance, since they support the principal points we had established earlier—namely, that the 25 cases already observed were not due to a spontaneous outbreak—and although virus was still prevalent in the saliva of most patients the use of sulphapyridine alone did not provoke herpes, but no sooner was intravenous T.A.B. used than herpes reappeared.

Discussion

Clinically, herpes labialis is such a trivial affection that it seems scarcely to warrant much attention, but there is reason to suggest that the virus is responsible either in part or in whole for certain other pathological lesions in man (see Levaditi and Lépine, 1938), and we believe that continued study of herpes may yield valuable information.

Certain facts have long been recognized, such as that it is frequently present in human saliva and is apt to attack healthy persons without the slightest provocation. More often, however, it is customary to meet with it in those whose health is poor, who have suffered from an acute febrile illness such as influenza or pneumonia, or whose vitality has been temporarily lowered by treatment such as pyretotherapy or protein shock.

Warren *et al.* (1940) reported that symptomatic herpes developed in 190 (46%) of 411 persons treated with fever induced by radiotherapy (30 metres), infra-red radiations with carbon filament lamps, and hot-water baths. The temperature employed was 39.5° to 41.5° C. for periods ranging from 1 to 47 hours. Several important points were established during the conduct of their researches; for instance, it was not possible to link the frequency of herpes with the height of pyrexia attained, the duration of its application, or the method employed for its generation. The only relation which could be adduced was the fact that the incidence of herpes seemed to be maximal during seasons of the year when nasopharyngeal infections were prevalent. Thus during the month of November 57 fever treatments were administered and 50% developed herpes, while in the summer month of June 32 patients received treatment and only 12% contracted herpes. Cases seemed to occur in series, and at times for intervals of ten to thirty days none appeared, but at others every patient who was treated within a period of a week or longer developed it.

Warren and his associates have not offered any explanation of the latter phenomenon, but it is likely that variation in the normal herpes carrier rate was the reason why cases were more numerous at certain times than at others. Under normal circumstances herpes labialis tends to be a self-limiting process which heals readily without complications; but the careful observations of Warren *et al.* have disclosed that this is not invariably so, since some of their patients revealed signs and symptoms of meningo-encephalitis, resembling a condition named herpetic fever, described by Plessing in 1929 (Warren *et al.*, 1940). In the present article we have adduced further evidence in support of two well-established facts concerning the pathogenesis of herpes: first, that it is frequently to be found in apparently normal human saliva; and, secondly, that following protein-shock therapy herpes labialis may develop. Two new points are also mentioned—namely, that large doses of sulphapyridine sufficient to cure gonorrhoea fail to abolish herpes virus in the saliva of carriers, and that, after a course of sulphapyridine, pyretotherapy or protein shock is more likely to provoke herpes labialis.

At this stage it may well be asked, Why should a course of sulphapyridine render an individual liable to an attack of herpes? Unfortunately we are unaware why this should be so. It is conceivable that the phenomenon may resemble an effect opposite to that of non-specific stimulation of antibody formation by the injection of certain chemical salts—e.g., beryllium chloride, manganous chloride, colloidal manganese, salvarsan (Browning and Mackie, 1937). According to Nicolau (1938) benzol, arsenic, arsenobenzol, iodine, mercury, alcohol, and cocaine also have a tendency to be herpetogenic, and consequently sulphapyridine is unique, since it does not cause herpes itself but enhances the herpetogenic effect of T.A.B. It might be that sulphapyridine depresses the natural antibody level of human blood to herpes virus (see Brain, 1937), so that, in a carrier, a subsequent mild protein shock precipitates an attack; but this fails to explain everything.

In conclusion, we feel that there is something to be learnt in connexion with our experiences, and the obvious lesson

is that sulphapyridine ought not to be used for treating herpes labialis or any other disease caused by herpes virus. Unfortunately very little is known of the pathogenesis of herpes virus, and although certain workers have claimed that such diseases as encephalitis lethargica and dendritic ulcer of the cornea are manifestations of herpetic infection, the whole question of the pathogenicity of herpes virus needs reinvestigation in the light of modern knowledge of virus infections.

Conclusions

Twenty-seven patients developed herpes labialis after a course of sulphapyridine followed by an intravenous injection of 0.2 to 1 c.cm. of T.A.B. emulsion.

All these persons probably carried the herpes virus in their saliva.

Large doses of sulphapyridine (25 grammes in four days) do not destroy herpes virus in human saliva, neither do they cause herpes labialis in carriers.

Although sulphapyridine does not provoke herpes the drug appears greatly to enhance the herpetogenic effect of T.A.B. vaccine if administered intravenously.

The phenomenon we have described is not due to leucopenia.

We desire to thank Colonel J. M. Mackinnon for permission to publish the data recorded, and Dr. Mervyn H. Gordon of St. Bartholomew's Hospital, London, and Captain A. Scott, R.A.M.C., for their interest.

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