

responded to a period of rest in bed and sanatorium regime now failed to show such response, collapse therapy being required on an ever-increasing scale. The records for the years 1940 to 1946 were inspected and the amount of collapse therapy carried out during those years calculated, with the results shown in the Table.

The figures suggest that the impression of less satisfactory pulmonary healing is correct, and it would appear reasonable to regard the stringent dietetic restrictions to which the patient has been subjected as an important causal factor in the absence of clear-cut evidence pointing to any other cause operating on a general basis throughout the sanatorium. It is much more difficult to assess the degree to which the curtailment of a specific element in the diet has been responsible; for experimental evidence of the part played by protein, carbohydrate, or fat in influencing resistance to tuberculosis is scanty and inconclusive. It is worth mentioning, however, that one of the most interesting and best-documented studies of nutrition and tuberculosis (Faber, 1938) adduces evidence to show that the rise in tuberculosis mortality in Denmark during the First World War was associated particularly with a deficiency of protein in the diet. In Britain it has been possible to maintain the total calorie intake by the use of carbohydrates, but the protein and fat content of the rationed diet has suffered severely, and the weight graphs suggest that the fluctuations in the meat and cheese rations are of significance. The importance of adequate protein for the tuberculous patient was recognized in America, where Ration Boards were empowered to grant extra meat allocations to patients suffering from the disease (Pottenger and Pottenger, 1946).

### Summary

Observations on the weight records of sanatorium patients during the years of rationing show that from 1943 onwards the average patient failed to show a gain in weight comparable with the gains recorded in pre-rationing years.

This failure to gain weight satisfactorily was accompanied by a diminution in the powers of natural healing of the disease.

It is impossible on the evidence to indicate definitely the specific elements lacking in the rationed diet, but there is a suggestion that the curtailment of protein and fat (meat and cheese) may be of significance.

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Sir Andrew Davidson, Chief Medical Officer of the Department of Health for Scotland, gave an address to the Royal Philosophical Society of Glasgow on Jan. 14. "Health," said Sir Andrew, "is something more than not being ill. A man cannot enjoy life to its fullest capacity if his diet is inadequate. Medical research will establish dietetic needs. He will be emotionally unhealthy if his work is too exacting or insufficiently varied—industrial psychology can play a part here—and he cannot enjoy optimum mental health if he is worried by economic insecurity and the constant dread of unemployment." He said that sickness cost the nation some 7% of its total annual income; that even before the war the work lost through illness reduced our national income by some £100 millions a year, and the cost of treatment amounted to a figure of a dimension of £185 millions. At present the expenditure on prevention of disease was only 4½% of the total cost of sickness. Therefore, while sickness was a misery to the individual it was also a considerable loss to the State, both in production and in finance. As a nation we were becoming at once more health-minded and broader in our outlook on social health, Sir Andrew concluded. Instead of crying, "Can we afford some new service?" we were now tending to realize that we could not afford ill-health and the resulting loss of productive work. We were beginning to realize that expenditure on preventive services and on health research paid an enormous dividend.

## GENERALIZED INFECTION WITH THE VIRUS OF HERPES SIMPLEX

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Our knowledge of infection with the virus of herpes simplex has been greatly increased by observations made within recent years. Dodd, Johnson, and Buddingh (1938) showed that stomatitis in children was often a herpetic infection, and this work was confirmed and extended by Burnet and Williams (1939), by Scott, Steigman, and Convey (1941), and by Black (1942). Herpetic stomatitis is usually a primary infection occurring during the first six years of life, and antibodies to the virus of herpes simplex appear during convalescence (Burnet and Williams, 1939; Scott *et al.*, 1941). These primary infections are often associated with fever and some general constitutional disturbance, and groups of cases may occur in families (Scott *et al.*, 1941). After the primary infection in childhood persons seem to carry the virus for years and may suffer from recurrent attacks of labial herpes, although these subsequent manifestations are milder and are associated with relatively trivial symptoms. Primary infection in adults appears to be relatively uncommon, and while those who are liable to recurrent attacks of labial herpes invariably have a high titre of antibodies to the virus in their serum, those who have no history of herpetic infection possess no such antibody (Burnet, 1946).

Although the virus of herpes simplex has become so adapted to parasitism in the human host that it causes a relatively mild illness in the primary infection and for the most part remains latent in the host thereafter, primary infection is occasionally more severe. Fatal encephalitis due to the virus of herpes simplex has been recorded in an infant 1 month old (Smith, Lennette and Reames, 1941) and in three adults (Zarafonitis *et al.*, 1944; Whitman, Wall, and Warren, 1946). In these instances the virus was recovered from the brain at necropsy. Armstrong (1943) isolated the virus of herpes simplex from the cerebrospinal fluid of a 14-year-old negro boy who was suffering from meningo-encephalitis; an increase of herpetic antibody was demonstrated in the boy's serum during convalescence. Symptoms of meningo-encephalitis were also noted by Warren, Carpenter, and Boak (1940) in a group of patients who suffered from herpetic infection following fever therapy induced by physical methods.

Primary generalized herpetic infection in adults associated with severe constitutional symptoms would, however, seem to be very rare, and the following case is reported because it presented an unusual problem in clinical diagnosis.

### Case Record

N., a motor engineer aged 37, a subject of plethoric build but of the type that never ails anything, made a business trip to Denmark and Sweden in August and September, 1946, and returned to this country on Oct. 3. On Oct. 15 he felt unwell, an event so unusual that he stayed at home from his work. On the 18th he sought medical advice because of backache, which distressed him more than his dirty foul tongue and throat and repeated vomiting. He was sweating profusely, with a temperature of 102.6° F. (39.2° C.) and pulse 120. There were no physical signs in the chest and nothing in the abdomen to warrant surgical intervention. The urine was not examined. Tentatively a diagnosis of virus influenza was made and he was given garg. pot. chlor. cum phenol for the mouth and throat

and mist. bism. sal. for the gastric irritability. The next day (Oct. 19) his vomiting was less troublesome, but the temperature remained at 102° F. (38.9° C.), the stools were frequent and loose, and he complained bitterly of the backache. On Oct. 21 he said he was better except for the backache, vomiting had ceased, the temperature was 99° F. (37.2° C.), but the bowels were still loose. As an afterthought he showed five "spots" on his hands and feet. Four of these were deep in thick skin, with amber heads surrounded by deep crimson areoles about 1 cm. across.

Examination of the rest of his skin showed a number of small septic papules such as are commonly seen on seborrhoeic skins under intense sweating, but the five vesicles mentioned were distinct and without any obvious explanation. Clinically the picture now appeared to be alastrim or variola minor. This diagnosis was supported by the prodromal discomfort lasting three days, the high initial temperature falling on the fourth day, severe backache for four days, and the distribution and character of the vesicles. The history of overseas travel suggested a possible source of infection and an incubation period of 12 days or longer. The case was therefore notified to the local medical officer of health as variola. This action produced three further clinical opinions—one for and two against the diagnosis of smallpox. Those against had no alternative diagnosis to offer other than "a septic state," and at no time was the true nature of the illness suspected. It should be recorded that the Ministry of Health's expert was definitely against the notified diagnosis. Because of the divergence of opinion a specimen of the patient's blood and fluid taken by swab from one of the vesicles was sent to the laboratory for examination; crusts and smears from the lesions were also sent four days later.

Inquiry into the patient's past history showed that he had been successfully vaccinated at the age of 10, and it was later ascertained that there was no history of previous herpetic infection.

#### Laboratory Investigations

A sample of clotted venous blood and a swab which had been moistened with the contents of one of the vesicles was received in the laboratory on Oct. 23. The blood serum failed to show variola antibody, a result which was considered of no diagnostic significance at this stage of illness. The material on the swab was insufficient for serological examination for variola antigen, and as fertile hens' eggs at a suitable stage of development were not available at this time the swab was placed in the refrigerator for examination at a later date.

Two small crusts and smears on glass slides were received on Oct. 28. No elementary bodies were seen in stained smears, and extracts of the crusts gave a negative result by complement-fixation test for variola antigen. It was considered, however, that the crust material was insufficient in amount for this result to be regarded as conclusive, and the extract was inoculated on the chorio-allantois of two 12-day chick embryos. At the same time the swab of vesicle fluid received on Oct. 23 was extracted with broth and the extract inoculated on two further membranes of developing chick embryos. After three days' further incubation all four eggs showed on the chorio-allantois numerous small raised opaque lesions about 1 mm. in diameter. That these lesions were due to a filtrable virus was shown by the finding that a suspension of these membranes was bacteriologically sterile, and subsequent tests showed that filtrates through a Chamberland L2 candle and a gradocol membrane of A.P.D. 0.725 $\mu$  were infective for the chorio-allantois of chick embryos. Although the lesions were smaller than those usually produced by variola virus in this tissue (Downie and Dumbell, 1947) this was considered to be due to the large number of lesions present, and, as the virus of chicken-pox and zoster produce no change on the chorio-allantois of the chick embryo, the result of the test was provisionally (and wrongly) reported as positive for variola virus.\*

Subsequent histological examination of the lesions on the egg membrane failed to show the cytoplasmic inclusions typical of variola infection, but degenerative nuclear changes suggestive of intranuclear inclusions were present. A neutralization test

made by chorio-allantoic inoculation of mixtures of egg membrane suspension with antivaccinal and with normal rabbit serum showed that the virus ("N" virus) was not neutralized by the antivaccinal serum—a result which, taken with the histological appearance of the lesions, indicated that the virus isolated from the patient was not variola.

#### Identification of the Virus

The "N" virus was transferred repeatedly on the chorio-allantois, and after six or seven transfers had become well adapted to this tissue. The lesions did not increase in size, but 0.1 ml. of a 1 in 1,000 dilution of the supernatant fluid from an infected membrane ground up in 5 ml. of broth regularly produced several hundred discrete lesions. Histological examination of the membranes after fixation in formol-Zenker showed intranuclear inclusions which ranged in appearance from a finely granular acidophilic variety surrounded by a clear unstained zone to a type of inclusion which was homogeneous and faintly basophilic and filled the entire nucleus. In all affected cells the chromatin was displaced to the periphery of the nucleus. The appearances conformed closely to the description by Slavin and Berry (1943) of nuclear inclusions in the lesions produced by herpes simplex virus in mice.

Early attempts to produce lesions by intradermal inoculation on the pads of guinea-pigs were unsuccessful, but virus from the tenth egg passage produced a vigorous "take" by this route and also on intradermal injection of the shaved hairy skin. Virus from the first and tenth egg membranes produced fatal encephalitis when injected intracerebrally in mice, and in two of four rabbits inoculated on the scarified cornea tiny vesicles appeared along the lines of scarification within 24 hours. Material from the seventh egg passage produced an acute orchitis after intratesticular inoculation in a rabbit.

In view of these considerations it seemed possible that the agent isolated was the virus of herpes simplex. A strain of herpes simplex virus, kindly supplied by Dr. Andrewes, of the National Institute for Medical Research, produced lesions on the chorio-allantois similar in appearance both macroscopically and microscopically to those produced by the "N" virus; the possibility that the "N" virus was a strain of herpes simplex was further strengthened by neutralization tests made with human sera, using the chorio-allantoic technique (Burnet and Lush, 1939). Sera from three persons with past histories of recurrent herpetic infection suppressed infection of the chorio-allantois by both viruses, while sera from three persons with no such histories failed to reduce the number of lesions produced by either virus.

Antisera to the two viruses were prepared by the immunization of rabbits. Both viruses produced orchitis when injected intratesticularly, and a week later virus was injected intradermally and subcutaneously. After a further interval of a week virus was injected intraperitoneally, and the animals were bled six days after this last injection. The sera were inactivated by heating at 56° C. for 20 minutes before being used in neutralization tests. Serum obtained from the rabbits before immunization contained no neutralizing antibody to either virus, and was used to control tests with the immune sera. Table I

TABLE I.—Lesions Produced on the Chorio-allantois by Mixtures of Rabbit Sera and Viruses

Rabbit Sera	"N" Virus	Herpes Simplex Virus
Normal	550, 740, 1,000, 1,000	1,000, 700, 360, 1,000
Immune "N"	0, 0, 0, 0	0, 2, 0, 0, 1
Immune herpes	0, 0, 0, 0	1, 0, 0, 0, 0

The figures indicate the number of lesions on individual membranes.

shows the results of the cross-neutralization tests with the two viruses and their antisera. It seems quite clear from these results and from its behaviour on the chorio-allantois and its pathogenicity for animals that the virus isolated from the vesicle fluid and from the crusts of the patient was a strain of herpes simplex virus.

\* See *British Medical Journal*, 1947, 1, 807; and 2, 395.

**Development of Antibody Following Illness**

The occurrence of herpetic infection in the course of a febrile illness is not uncommon when the fever itself is due to infection with some other agent. The patient, however, had no history of previous herpetic infection; the stomatitis and the subsequent appearance of the lesions on hands and feet

nized. More general application of the techniques of virus investigation in the diagnosis of obscure febrile illnesses associated with vesicular eruptions may be expected to extend our knowledge in this field. The virus of herpes simplex can be isolated from human material by inoculation on the cornea or nictitating membrane of the rabbit's

TABLE II.—Results of Four Separate Tests of Neutralizing Power of Sera from Patient N. against "N" and Herpes Simplex Viruses

Virus mixed with:	"N" Virus				Herpes Simplex Virus			
	1	2	3	4	1	2	3	4
Broth .. ..	250	>1,000, >1,000, >1,000	N.T.	N.T.	>1,000, >1,000	N.T.	34, 36	730
Serum A .. .	190, 160, 275	230, >1,000, >1,000	>1,000, >1,000, >1,000	509, 620	>1,000, >1,000	>1,000, >1,000	>1,000, >1,000	32, 33, 37
Serum D .. .	0, 0, 0	0, 0, 0	0, 0	0, 0	3, 7	0, 0, 0	0, 0, 0	0, 0, 0
Serum N1 .. .	36, 42, 40	200, 45, 60	770, 855	116, 136	390, 500	>1,000, >1,000, >1,000	10, 13, 18	51, 67, 45
Serum N2 .. .	0, 1, 0	0, 0, 0	67, 73, 210	0, 1, 0	6, 19	106, 26, 19	2, 4, 0	17, 5, 7

Figures indicate number of lesions produced on the chorio-allantois by mixtures of sera and viruses. N.T. = Not tested. Serum A = Control serum containing no antibody. Serum D = Control serum containing high-titre antibody. Serum N1 = Serum from patient 7 days after onset of illness. Serum N2 = Serum from patient 42 days after onset of illness.

suggested a generalized infection with herpes simplex virus rather than a localized herpetic infection complicating another acute infective condition. Evidence in support of the primary nature of his herpetic infection was obtained by examination of serum taken on the seventh day of illness and again after his recovery 35 days later. These two specimens of sera were examined for neutralizing antibodies against the patient's own virus and against the strain received from Dr. Andrewes. With each test there were included two human sera—one from a person liable to recurrent attacks of herpes and known to contain antibody, and the other from a person with no history of herpetic infection and devoid of neutralizing antibody. The results of four neutralization tests made by chorio-allantoic inoculation are shown in Table II.

It will be seen from Table II that, while some antibody had appeared in the patient's serum by the seventh day of his illness, after recovery the antibody titre of his serum was very much increased—a finding which supports the view that his illness was a primary herpetic infection.

**Discussion**

The outstanding feature of the case was the failure to recognize the nature of the patient's infection on clinical grounds. The general picture was suggestive of a mild variola in a previously vaccinated individual; the diagnosis of systemic infection with herpes simplex virus was not considered, as such cases have not often been recorded in the literature and are probably not of frequent occurrence. No mention is made of generalized herpetic infection in the differential diagnosis of smallpox in the textbooks of Price (1941) and Conybeare (1946). Once the diagnosis had been established it seemed that the significance of the severe stomatitis from which the patient suffered had not been duly appreciated.

Widespread herpetic eruptions superimposed on eczema and chronic dermatitis have been reported both in children and in adults (Thomas, 1941; Wenner, 1944; Barker and Hallinger, 1947), and virus studies have shown that at least some instances of the clinical condition referred to as Kaposi's varicelliform eruption are due to the same agent (Barton and Brunsting, 1944; Lane and Herold, 1944; Lynch *et al.*, 1945). In most of these patients, however, the herpetic rash was confined to areas of skin affected by the dermatitis. In the case reported above there was no such previous skin affection, and the distribution of the lesions suggests a dissemination of the virus by the blood stream.

The variety of clinical manifestations due to infection with herpes simplex virus has been increasingly appreciated in recent years, and it appears that this virus has greater pathogenic potentialities than is generally recog-

eye (Steigman and Scott, 1942), but the susceptibility of the chorio-allantois of developing hens' eggs makes this tissue a convenient alternative medium for the isolation of the virus.

**Summary**

A case of generalized infection with herpes simplex virus is described. The symptomatology and course of the illness simulated mild smallpox, but this diagnosis was not supported by the evidence of laboratory tests. Herpes simplex virus was isolated from the patient's skin lesions, and examination of the blood for antibodies supported the diagnosis finally reached.

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On Jan. 14 Lord Horder, Chairman of the Empire Rheumatism Council, gave a lecture demonstration at the Department of Rheumatism of the Royal Free Hospital. The cases were presented to Lord Horder by the Registrars to the Unit, Drs. Chalmers and Lush, and were cases picked from the Unit's wards for their general medical interest. A case of myelomatosis was presented first, and Lord Horder stressed the relation of this condition to other neoplastic blood conditions such as leukaemia. Another interesting case was one of proteinuria associated with rheumatoid arthritis, and the importance of an interpolated myxoedema was fully discussed. Further meetings of this type will be held periodically.