SYMPTOMATIC HERPES, A SEQUELA OF ARTIFICIALLY INDUCED FEVER*

Incidence and Clinical Aspects; Recovery of a Virus from Herpetic Vesicles, and Comparison with a Known Strain of Herpes Virus

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Plate 11

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Symptomatic herpes is frequently a sequela of fever that has been artificially induced by physical methods. The disease is similar to herpes simplex accompanying acute febrile diseases, particularly infections of the upper respiratory tract, typhoid fever, and pneumonia. Both produce the same type of lesion and involve the same areas of the face. The lesions are usually limited to the distribution of the sensory branches of the fifth cranial nerve. The prevalence of herpes in patients treated with fever in our clinic prompted us to record the incidence of the disease and to investigate its relationship to herpes simplex. The distribution and character of the lesions, the course of the disease, the sequelae, and the seasonal variation were likewise studied. An encephalitis-like syndrome which developed concurrently with herpes in some patients is also described herein. A virus which was recovered from the herpetic lesions was compared with a known strain of herpes virus.

Incidence and Clinical Manifestations

During the 5 year period, January 1, 1931, to January 1, 1936, 411 patients were given 545 treatments with artificially induced fever for afebrile diseases, notably acute or chronic gonococcal infection, chronic infectious arthritis, advanced syphilis of the central nervous system, multiple sclerosis, asthma, and malignant tumors, diseases which usually are unaccompanied by herpes. The age of the patients ranged from 6 to 75 years. Approximately half of the group were males and half females. 190, or 46.2

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per cent, developed herpes. Only 7 of this group had a second attack with a subsequent treatment.

Fever was produced by four different methods, *i.e.*, diathermy (300 meters), radiothermy (30 meters), infra-red irradiation with carbon filament lamps, and hot water baths. The temperature elevation varied from 39.5–41.5°C., and the duration of the fever from 1 to 27 hours. No correlation could be found between the occurrence of the infection and the method used to produce the temperature or the duration or height of the

TABLE I

Incidence and Seasonal Distribution of Symptomatic Herpes in Fever-Treated Patients

Month	1931		1932		1933		1934		1935		Incidence for 5 year period by month		
	Fever treatments	Cases of herpes	Fever treatments	Cases of herpes	Fever treatments	Cases of herpes	Fever treatments	Cases of herpes	Fever treatments	Cases of herpes	Fever treatments	Cases of herpes	Cases of herpes after fever
													per cent
Jan.	7	0	10	7	9	4	11	3	9	2	46	16	34.8
Feb.	11	0	5	3	14	12	8	5	8	1	46	21	45.6
Mar.	12	3	7	5	17	10	8	2	13	6	57	26	45.6
Apr.	19	5	13	3	17	5	12	5	8	2	69	20	29.0
May	13	2	13	2	12	2	9	4	6	1	53	11	20.7
June	8	2	6	1	10	0	4	1	4	0	32	4	12.5
July	2	0	8	3	0	0	3	2	0	0	13	5	38.4
Aug.	8	2	6	2	5	2	7	0	2	2	28	8	28.5
Sept.	10	3	12	6	8	4	8	1	6	4	44	18	40.9
Oct.	6	1	17	6	14	6	15	8	5	3	57	24	42.0
Nov.	14	6	20	7	15	10	6	4	2	2	57	29	50.8
Dec.	4	3	15	5	13	4	4	2	7	1	43	15	34.9
Total for year	114	27	132	50	134	59	95	37	70	24	545	197	

fever. Herpes appeared in 12 of 40 patients whose oral temperature was elevated to 38.5°C. by hot water baths and then immediately allowed to subside. It developed, likewise, in approximately one-third of the patients with a rectal temperature maintained at 41.5°C. from 10 to 24 hours by general irradiation from carbon filament lamps.

Although herpes occurred somewhat more frequently and was of greater severity during the time of the year that infections of the upper respiratory tract were prevalent, no definite seasonal incidence could be discovered (Table I). The cases, however, usually appeared in series. At times, no cases of herpes developed for periods of from 10 to 30 days, and at other

times, for periods of a week or longer, almost every patient given fever therapy acquired the disease. Since 1936 a complete record has not been kept of the occurrence of herpetic lesions, but it may be stated in general that the course and severity of the disease and the frequency of its appearance vary little from the period between 1931 and 1936 reported in detail.

The course of the disease was similar in almost every case. About 24 hours after fever treatment, the patient complained of sensations of warmth and itching about the lips and nose. An erythema developed at these sites and small vesicles appeared on the surface of the skin from 6 to 18 hours later. The vesicles slowly increased in size, gradually coalesced, ruptured from 3 to 4 days later, and then became pustular. Thick, dry scabs formed over the site of the pustules, then desquamated and disappeared in from 10 to 14 days, leaving no scars (Figs. 1 to 6). Mild cases ran a shorter course and healed more promptly.

The lesions were usually confined to the skin about the mouth and nose and appeared most frequently on the mucous membranes of the lips near the mucocutaneous borders, following in general the distribution of the fifth cranial nerve. In a few patients, the skin on the sides of the face, the eyelids, the tip and ventral surface of the tongue, and the gingival margins were involved. Occasionally lesions appeared on the borders of the nares, and rarely on the mucosa of the hard and soft palates, on the uvula, on the buccal mucosa, and in the external auditory canal. In some cases all of the vesicles appeared simultaneously, while in others they developed successively at intervals of from 12 to 72 hours. A definite symmetry was observed in a few instances.

2 of 4 cases treated at 39°C. (rectal temperature) for 48 hours developed itching, burning, and redness about the lips shortly before the termination of the treatment and the next day had well developed vesicles on the lips. One patient developed vesicles over the entire face from the temples to the lower borders of the mandibles. The eyelids, the pinnas of both ears, and the skin adjacent to each ear and over the mastoid regions were also involved. The nose and the tragus and external meatus of the ears were not affected. The sclerae were congested, but no corneal vesicles or ulcers developed. No general symptoms, such as headache, fever, or malaise, were associated with the local disease. The lesions disappeared in 2 weeks without scars. This was the first attack of herpes ever noted by this patient, and there was no recurrence during the 2 years that he was followed after the fever treatment.

During the first 2 weeks of November, 1934, 3 patients developed herpetic ulcers of the cornea, a type of lesion which had not been observed previously in this clinic. Under the care of ophthalmologists the lesions healed without scarring. In 2 instances, the ulcers were accompanied by inconspicuous vesicles on the lips and, in the third case, the patient exhibited extensive herpes of the skin of the face.

Because of the prevalence and severity at that time of herpes in fever-treated patients, a survey was made of the incidence of symptomatic herpes in 500 persons who had had no recent fever—either spontaneous or artificial. Members of the hospital staff and patients without febrile diseases were included. 72 cases of symptomatic herpes were noted, representing 14 per cent of the group, which was an unusually high incidence in this community. Several persons stated that this was their first attack of herpes in from 2 to 5 years, and a number who exhibited extensive lesions had previously had only inconspicuous fever blisters about the lips.

Cases Suggestive of Meningoencephalitis

Every one of the 15 patients subjected to fever therapy during the month of February 18 to March 20, 1933, developed extensive symptomatic herpes associated with mild symptoms of a meningoencephalitis. A spontaneous fever of from 38–38.5°C., headache, general malaise, and lethargy accompanied the development of the local lesions and persisted for from 24 to 72 hours (Chart 1). Examinations of spinal fluid, colloidal gold determinations, and Pandy tests were made on several of these patients before and after fever therapy. The spinal fluid from a patient who had been treated for arthritis exhibited a slight midzone colloidal gold reaction for several days following treatment and then returned to normal. The colloidal gold reaction of the spinal fluid from a patient with dementia paralytica shifted from a typical paretic curve to a midzone position after the appearance of extensive herpetic lesions and the development of an emotional instability. The encephalitis-like symptoms disappeared gradually within 2 weeks, and at the end of 5 weeks the spinal fluid again showed a colloidal gold reaction characteristic of paresis (Table II).

The records of 200 patients who had been treated with fever prior to February, 1933, were reviewed for information on the occurrence of encephalitis-like symptoms prior to that time. 8 patients had had a similar clinical entity, lasting from 1 to 2 weeks, and 53 other cases had had a febrile reaction accompanying the herpetic lesions without evidence of central nervous system involvement. No further sequelae have occurred in these patients, however, some of whom have since been under observation for 5 years.

Between 1936 and 1939 several cases of encephalitis-like symptoms were noted during February and March of each year. In March, 1938, 2 patients treated for gonococcal infection developed a delusional state, one being so severe as to require restraint for 2 days, after which time the symptoms disappeared rapidly with no sequelae.

Signs of Acquired Immunity

Of the 190 patients who had herpes after a treatment with artificially induced fever, 183 apparently developed some immunity to the disease. A subsequent fever treatment was seldom followed by herpes, even during the periods of the highest incidence of the disease. In the few recurrences, the lesions were usually less extensive than during the first attack. The shortest period between fever treatments that were followed by herpes was 9 weeks. This patient developed a few typical lesions on the face after the first treatment, a 3 hour fever at 40.5°C., and 9 weeks later presented

a more extensive herpetic infection after an 8 hour fever at 41.5°C. 4 patients subjected to fever while recovering from a spontaneous herpetic infection showed no extension or exacerbation of the lesions, which healed promptly. A fifth patient, on the other hand, who had a small labial

TABLE II

Observations on Patient with Encephalitis-Like Symptoms Following Artificially Induced Fever

Results of Tests on Spinal Fluid Showing Changes in Colloidal Gold Reaction

Date	Clinical notes	Colloidal gold reaction	Pandy test	Number of leucocytes	Wassermann test	
					Spinal fluid	Blood
1933						
Feb. 16		4555544220	2+	12	4+	4+
Mar. 1	First fever treatment: 5 hrs. at 41.5°C. (see Chart 1)					
" 3	Herpes developed, followed by encephalitis-like symptoms	4555555220	1+	15	4+	4+
" 13		0555430000	1+	20	4+	
" 18	Subsidence of symptoms	0013210000	1+	13	4+	
Apr. 25		0012332100	1+	7	4+	4+
" 26	Second fever treatment: 5 hrs. at 41.5°C.					
" 27		5554432000	1+		4+	

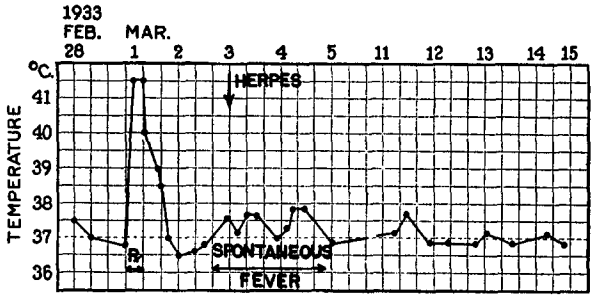

CHART 1. Characteristic spontaneous fever accompanying onset of herpes following artificially induced fever.

herpetic vesicle at the time fever was given, developed extensive herpes about the mouth and nose. Another, who frequently had herpes after windburn or sunburn or with a respiratory infection, suffered a severe attack of 2 weeks' duration following a 5 hour fever at 40.5°C. She has had

recurrences of the disease at frequent intervals during the 2 years she has been under observation since that time.

Examinations for Herpes Virus

A. Recovery of Virus from Herpetic Lesions

Because of the clinical similarity of the type of herpes occurring after artificially induced fever to symptomatic herpes associated with acute infectious diseases, the lesions from 8 patients were examined for the presence of a filter-passing virus. The procedure and findings were as follows:—

Several small 24 hour old typical herpetic vesicles, from 2 to 3 mm. in diameter, which appeared about the lips of the patient, were cleansed with soap and water. Approximately 0.1 cc. of fluid was withdrawn by means of a sterile tuberculin syringe with a 24 gauge needle and added to 5 cc. of sterile physiological salt solution. The syringe was rinsed with the mixture, the punctured vesicle flushed with a small amount of the fluid, and the material then added to the washings.

Diluted vesicle fluid from 6 of the patients was passed through Berkefeld N filters and from 2 others through Berkefeld W filters. 0.2 cc. of each filtrate was injected intracerebrally into ether-anesthetized rabbits.

The rabbits that had received the W filtrate had a slight elevation of temperature on the 2nd day, but showed no other symptoms. The animals injected with the N filtrate became febrile with temperatures of from 39.5–41.5°C., and exhibited symptoms of encephalitis, such as hyperkinesia, dorsiflexed head and neck, marked disturbance of equilibrium, grating of teeth, and paralysis of posterior extremities. All died within 15 days and were autopsied immediately (Table III).

The brain was removed aseptically and small areas of cortical substance retained for animal passage. Sections were taken for histological examination from several parts of the brain, and the remaining tissue was preserved in a 50 per cent neutral glycerine solution for subsequent work.

Serial animal passage was carried out with filtrates from the brains of 5 of the 6 rabbits. 1 gm. of cortical substance was triturated with 9 cc. of physiological salt solution and the suspension filtered through a Berkefeld N candle. Intracerebral injection of 0.2 cc. of the filtrate brought about a febrile response and typical symptoms of encephalitis which caused death in from 8 to 10 days.

The cortical substance from 3 of the 6 rabbits that had been injected with vesicle fluid from the patients was also used for corneal inoculation. Suspensions prepared by emulsifying 1 part of brain tissue with 3 parts of physiological salt solution were inoculated onto the scarified cornea of rabbits. A fatal encephalitis ensued in every case.

Throughout the study the absence of bacteria was established by the inoculation of material from the brains of all autopsied rabbits, as well as all filtrates and suspensions, into culture media with subsequent aerobic and anaerobic incubation.

Histological sections were prepared from the brain of each rabbit and were stained by Giemsa's method. All specimens showed intranuclear inclusion bodies in the motor ganglion cells, which were morphologically and tinctorially like those resulting from

invasion with the herpes virus. Typical inclusion bodies were also demonstrated in the epithelial cells of the cornea of the rabbits inoculated by corneal scarification.

B. Comparison of the Virus with a Known Strain of Herpes Virus

4 of the 6 strains of virus recovered from herpetic lesions were identified further by investigating their immunological relationship to a known strain of herpes virus (Frank strain[1]) by means of cross-immunization of rabbits. The plan, in brief, was to immunize rabbits to each of the unknown strains and test for immunity to the Frank strain; and likewise, to

TABLE III

Effects of Intracerebral Inoculation of Rabbits with Filtrates from Herpetic Vesicles

Rabbit No.	Patient	Type of filter	Date of inoculation	Results of intracerebral inoculation with 0.2 cc. filtrate		Serial passage in rabbits by intracerebral inoculation
					Histological examination of brain for herpes inclusion bodies	
			1931			
16-41	Mu	Berkefeld N	Oct. 20	Died 9 days	Positive	Successful
16-83	Bo	" "	Nov. 5	" 5 "	"	"
16-99	St	" "	" 13	" 4 "	"	"
			1932			
17-54	Ra	" "	Jan. 18	" 7 "	"	"
21-40	Ch	" "	Feb. 27	" 15 "	"	Not attempted
			1933			
23-65	Go	" "	Nov. 4	" 6 "	"	Successful
			1932			
17-59	We	" W	Jan. 23	Remained normal	Not done	Not attempted
18-05	Vi	" "	Mar. 26	" "	" "	" "

immunize a series of animals with the Frank strain and test for immunity to each of the recently recovered strains.

Procedure.—Brain suspensions were prepared from rabbits that had been injected intracerebrally with a strain of virus originally recovered from herpetic vesicles and maintained by animal passage. 1 gm. of brain tissue was emulsified with 2 cc. of sterile physiological salt solution and dilutions of 1:5, 1:30, and 1:100 made with saline. Rabbits were injected at 2 day intervals with the following amounts of inoculum: 1:100 dilution, 0.2, 0.3, 0.4, 0.6 cc.; 1:30 dilution, 0.2, 0.3, 0.4, 0.6 cc.; 1:5 dilution 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 cc.; undiluted brain suspension, 12 injections increasing in

[1] Obtained from The Rockefeller Institute for Medical Research through the courtesy of Dr. Peter K. Olitsky.

amount from 0.1 to 1.2 cc. 5 and 10 days later, 0.2 cc. of the undiluted material was inoculated onto the scarified cornea, and 5 days thereafter, 0.1 cc. of the undiluted suspension was injected intracerebrally. During the course of immunization, some of the animals developed symptoms of nervousness and irritability. When they occurred, injections were withheld until the subsidence of symptoms, and then resumed, using a smaller amount of inoculum. The total number of injections varied from 34 to 46.

TABLE IV

Effect of Frank Strain of Herpes Virus on Rabbits Immunized to Strains of Herpes Virus Recovered from Patients after Artificially Induced Fever

Rabbit No.	Production of immunity				Test strain (0.1 cc. of 10 per cent brain suspension)	Results
	Strain of virus used as antigen	Number of injections of brain suspension				
		Subcutaneous	Corneal	Intracerebral		
17-48	Mu	38	2	1	Frank	Remained normal
17-49	Bo	43	2	2	"	Died of encephalitis 10 days after injection of test strain
17-76	St	31	2	1	"	Remained normal for 21 days. Died as result of trauma incurred when rectal temperature was taken. No clinical evidence of encephalitis or histological evidence of inclusion bodies
17-77	Ra	37	2	1	"	Remained normal
17-03	St	Intracerebral injection of 0.2 cc. of brain suspension heated 6 hrs. at 41.5°C.			"	" "
18-35	Bo	Intracerebral injection of 0.2 cc. of Berkefeld N filtrate			"	" "
18-33	None	Control			"	Died within 3 days of typical encephalitis
18-54	"	"			"	Died within 5 days of typical encephalitis

10 days after the last inoculation, the rabbits were tested for immunity by the intracerebral injection of 0.1 cc. of a 10 per cent brain suspension of the Frank strain of virus, which had been carried by intracerebral series from rabbit to rabbit. 2 other rabbits, which had survived encephalitis resulting from intracerebral injection of strains of herpes virus, were likewise tested for immunity to the Frank strain. One, 17-03, had been given an intracerebral inoculation of 0.2 cc. of a brain suspension of strain St which had been heated 6 hours at 41.5°C. The other had received an injection of Berkefeld N filtrate of strain Bo after serial passage through rabbits. For controls, 2 normal, uninoculated rabbits were given the test dose of 0.1 cc. of the Frank strain.

Attempts were made to immunize 5 rabbits against the Frank strain of the virus in like manner, to be tested with the unknown strains of virus.

Results.—The results are presented in Table IV. 3 rabbits, 17-48, 17-76, and 17-77, immunized to the strains of herpes virus, Mu, St, and Ra, respectively, showed no signs or symptoms of encephalitis after intracerebral injection of 0.1 cc. of a 10 per cent brain suspension of the Frank strain. 2 of them, which were under observation for a period of 6 months, at no time showed any evidence of the disease. The third died after 21 days from trauma incurred while the rectal temperature was being taken. It was normal prior to the accident, and at autopsy revealed no evidence of herpes, either in the gross or in histological sections of the brain. Rabbit 17-49, injected with the Bo strain of herpes virus, died of typical encephalitis 10 days after the administration of the Frank strain. The 2 animals, 17-03 and 18-35, which had recovered from encephalitis during the course of animal passage of strains St and Bo, both survived inoculation of the Frank strain. The control rabbits, 18-33 and 18-54, which had been injected with only the Frank strain of herpes virus, died in 3 and 5 days, respectively, with characteristic symptoms of herpes encephalitis.

Of the 5 rabbits in which attempts were made to induce immunity to the Frank strain, only 1 survived the entire course of inoculation. This animal, when injected with strain Bo intracerebrally, died within 4 days. 2 others developed encephalitis during the course of immunization, which terminated in death, and the remaining 2 died of intercurrent infection during the experiment.

DISCUSSION

Symptomatic herpes is most frequently associated with the fever incidental to acute infections. Whether the disease develops as a result of some change in the resistance of the host, caused by the primary infectious agent, or of elevation in temperature has not been clearly demonstrated. In this clinic 46.2 per cent of patients with afebrile diseases who were treated with fever produced by physical methods developed a herpetic infection. This suggests that temperature elevation rather than the infectious agent provides the stimulus for the development of the disease. The method of producing fever in no way affected the incidence or extent of lesions. Neither did the degree of temperature elevation nor the duration of the fever bear a direct relation to the occurrence of herpes, because even very short fevers were followed by herpetic vesicles.

Although the pathogenesis of experimental herpes in rabbits has been reported in detail by Goodpasture and his associates (1), the series of events

that precedes the disease in man is unknown. It is probable that the virus of herpes is not introduced from without during the fever, but is carried by the patient, and that the temperature elevation disturbs the normal relationship of host and parasite, thus permitting the development of the disease. The specific rôle of fever in bringing about herpes is still undefined, and whether it causes a change in the virus or in the host, or in both, is yet to be demonstrated. It is our impression that herpes rarely occurs without an elevation of temperature in the skin of the face, and that in those cases described as "idiopathic herpes," in which the biological factors responsible for the onset of the disease are unknown, fever has not been excluded. Chemical intoxication with heavy metals or with foreign proteins may produce the disease, it is true, but in these instances fever is usually present.

Another explanation of the development of herpes considerably discussed at the present time is cell trauma. In the case of artificially induced fever, elevation of the skin temperature may in some manner alter the cell nucleus, thereby giving rise to a new agent which can be recovered from the resultant lesions as a filter-passing virus.

The presence of herpes virus on or in the skin of the face, on the mucous membrane of the mouth and pharynx, and in saliva, without clinical signs of the disease, has been reported by a few investigators. In a group of our patients, the susceptible areas of the skin were cleansed and treated with various local antiseptics before, during, and after fever therapy to determine whether herpes might be prevented. The use of antiseptic alcohol before fever did not check the development of the lesions, although the frequent topical application of 50 per cent alcohol as soon as the vesicles appeared seemed to inhibit their spread and shortened the course of the disease.

The possibility of the transfer of the virus to the patients by the personnel in the fever clinic was considered, but in view of the precautions taken and the absence of the disease in this group, this seems very unlikely. On only two occasions did the nurses who administer the treatments have symptoms suggesting herpes, *i.e.*, erythema and itching, but there were no vesicles, and furthermore, the appearance of the symptoms was not coincident with the periods of high incidence of herpetic infection among the patients.

One attack of herpes appeared to confer a temporary immunity. Very few patients who had the disease following the first fever treatment developed lesions after subsequent fevers.

The simultaneous appearance of spontaneous fever and encephalitis-like symptoms with extensive herpetic facial lesions after induced fever suggested that both the herpes and the "encephalitis" were due to the same

causative agent. The occurrence of such a syndrome has not been reported by other investigators, although Plessing (2) has described a clinical entity referred to as "herpetic fever." Attempts to recover the virus from the spinal fluid of 10 of these patients by inoculating 0.5 cc. intracerebrally into a series of 16 rabbits were unsuccessful. The negative results, however, do not preclude its presence in the tissues of the central nervous system in view of the inconsistent results of similar experiments by other investigators. Greenbaum and Harkins (3) were unable to produce keratitis in a rabbit by the injection of spinal fluid taken from a rabbit showing typical symptoms of herpes encephalitis. Levaditi and Harvier (4), on the other hand, recovered a virus from the brain tissue of human cases of epidemic encephalitis which they demonstrated to be immunologically identical with known strains of herpes virus. Other observers, especially Netter, Cesari, and Durand (5), Luger and Lauda (6), and Perdrau (7), were successful in similar experiments. Doerr and Zdansky (8) and Flexner (9) have reported the occasional recovery of herpes virus from the spinal fluid of patients with encephalitis or with other diseases of the central nervous system, but are of the opinion that it was an intercurrent infection or an incidental finding. Further observations are necessary before it can be stated that encephalitis in man may result from invasion with the herpes simplex virus. The absence of sequelae certainly indicates that the encephalitis-like syndrome is of mild character even though it is rather acute at the time.

The recovery of a filter-passing virus similar to known strains of herpes virus from herpetic vesicles on fever-treated patients indicated that the disease accompanying artificially induced fever is similar to herpes simplex resulting from acute infectious diseases.

The cross-immunization of rabbits with known and unknown strains of the virus was only partially completed because of our failure to immunize a group of rabbits to the Frank strain. Better results, however, were obtained with the strains of virus that had been recently recovered from herpetic vesicles on patients. By gradually increasing the amount of inoculum and withholding injection at the first sign of unfavorable reaction, most of the animals survived the entire course of immunization. The death of rabbit 17-76, immunized to strain St, from an injury 3 weeks after the injection of the Frank strain, limited the period of observation. An examination of the animal at autopsy and of histological sections of the brain for intranuclear herpes bodies, however, revealed no evidence of encephalitis at that time. Evidently the course of immunization to strain St protected it against the Frank strain. Further evidence of a relationship

between the St and Frank strains is demonstrated by the fact that rabbit 17-03, which had acquired immunity to St as a result of a single injection of heated brain suspension, showed no symptoms of encephalitis after inoculation of the Frank strain. The results obtained with strain Bo may appear inconsistent. The death of rabbit 17-49 was, we believe, an indication of incomplete immunization, rather than evidence that the strain Bo was unrelated to the Frank strain of the virus. Inasmuch as rabbit 18-35, which had recovered from an attack of encephalitis following injection of strain Bo during the course of animal passage, did not develop encephalitis when tested with the Frank strain, the two strains are related.

Although tests were not made for evidence of neutralizing antibodies in the sera of rabbits, successful cross-protection permits the inference that an immunological relationship exists between the Frank strain and the strains of virus isolated from the patients with herpes.

Perdrau (10) recently reported that a fatal herpetic encephalitis occurred spontaneously in rabbits 6 months after immunization to herpes virus by intratesticular inoculation. Our rabbits were sacrificed after observation for 6 months without determining whether living virus was present in the central nervous system.

SUMMARY

1. Symptomatic herpes occurred in 190 (46.2 per cent) of 411 patients treated with fever induced by physical methods.

2. Herpes recurred in only 7, or 5.3 per cent, of 131 patients given subsequent fever treatments, suggesting that some immunity develops with the first attack.

3. An acute encephalitis-like syndrome of short duration and without sequelae developed in a group of patients with severe herpes following fever therapy.

4. A filter-passing virus, recovered from herpetic vesicles on patients treated with artificially induced fever, produced a fatal encephalitis in rabbits when inoculated intracerebrally and by corneal scarification. Intranuclear inclusion bodies were observed in corneal epithelial cells and in motor ganglion cells of the brain similar to those observed in rabbits injected with known strains of herpes virus.

5. Four strains of virus that had been recovered from herpetic vesicles appearing on patients subsequent to artificially induced fever were shown by cross-protection tests on rabbits to be immunologically related to the Frank strain of herpes virus.

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EXPLANATION OF PLATE 11

Symptomatic herpes following artificially induced fever.

FIG. 1. 36 hours after 5 hour fever treatment at 41.5°C. The largest vesicles are 6 hours old, the minute ones of recent appearance.

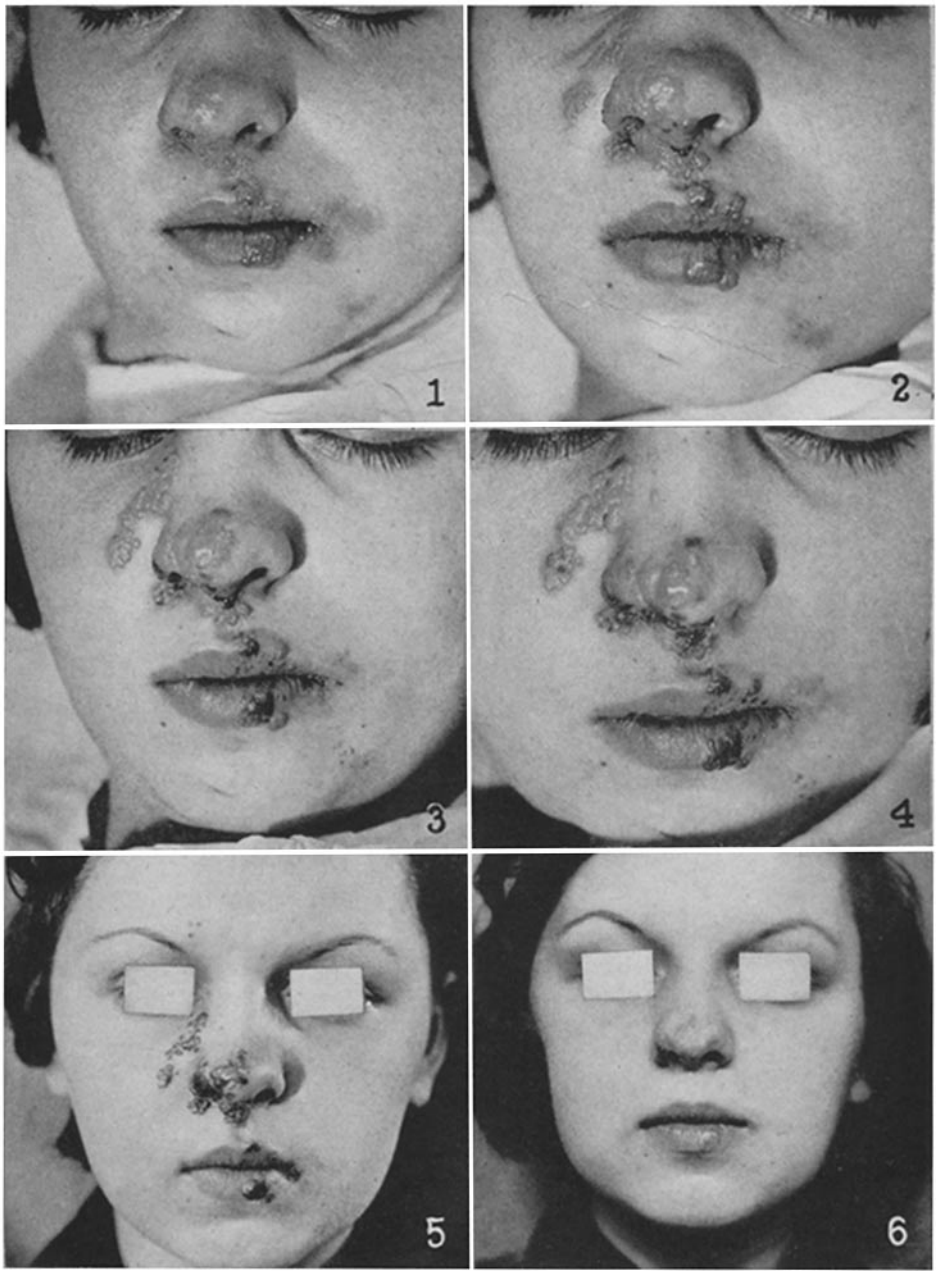
FIG. 2. 48 hours after fever. Vesicles have increased in size and number. Some have coalesced. Temperature 38.8°C. Patient shows extreme malaise.

FIG. 3. 3 days after fever. Temperature 37.2°C. Some vesicles have become pustular; others have ruptured and are encrusted.

FIG. 4. 4 days after fever. More of the lesions have become encrusted. General symptoms have subsided.

FIG. 5. 8 days after fever. Desquamation of crusts is occurring.

FIG. 6. 12 days after fever. There is slight residual pigmentation, but no scarring. No recurrence of herpes during one year's observation.



(Warren *et al.*: Symptomatic herpes, sequela of induced fever)