FURTHER OBSERVATIONS ON THE RELATION OF THE EYE TO IMMUNITY IN EXPERIMENTAL SYPHILIS

II. The Development of Immunity after Primary Intracorneal Inoculation

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(Received for publication, July 26, 1944)

In a previous paper (1) experiments were reported which dealt with the question of the extent to which the corneas of rabbits that have acquired a general immunity to syphilis after intratesticular inoculation share in the immune process. In brief, it was found that the corneas of syphilitic rabbits treated late in the course of the disease (163 or more days after a first intratesticular inoculation) are frequently susceptible to a second inoculation with the homologous strain of treponemes, although the skin of the same animal may be refractory to an inoculation made with the same treponemes at the same time. The frequency of corneal susceptibility under these conditions amounted to as much as 66⅔ per cent in one series of our animals.

The purpose of this paper is to record some observations designed to determine if a primary inoculation of syphilitic virus into the corneas of normal rabbits is followed by (1) the development of a general immunity toward the infection as manifested by a negative response to a subsequent inoculation of homologous syphilitic virus made into the skin, and (2) by the development of local immunity in the cornea itself. Both of these questions have been investigated in the past by others but the earlier experiments dealing with them are few in number and for the most part were carried out at a period when the importance of the factor of time in the development of immunity to syphilis was not fully understood, nor the importance of using homologous syphilitic virus for reinoculation if one wishes to study in rabbits the phenomenon of acquired immunity to syphilis. If rabbits are treated with antisyphilitic reagents before being subjected to reinoculation it is most important to know the time at which such treatment was instituted, for, as pointed out in the previous paper (1), reinoculations carried out before the 90th day in untreated syphilitic rabbits, or in rabbits treated prior to the 90th day of the disease, cannot be taken into consideration in determining whether or not particular tissues such as the cornea, are refractory to a second inoculation of syphilitic virus. One must limit consideration to those experiments in which reinoculation is carried out after the 90th day of the disease in untreated animals or, in the case of treated animals,

to those in which treatment was given on or after the 90th day. When the foregoing criteria were applied to the earlier experiments cited in the literature, in which the first inoculation was made in the cornea and subsequent inoculations were made in other tissues, most of the experiments had to be excluded from consideration, leaving very little really convincing data.

Uhlenhuth and Mulzer (2) inoculated the anterior chambers of both eyes of 4 rabbits with syphilitic virus and in all a bilateral keratitis developed. About 1 month after the keratitis had healed spontaneously the animals were inoculated intratesticularly with syphilitic virus and in 3 of the 4 orchitis developed in about one month and a half. There is no statement as to whether homologous or heterologous virus was used for the second inoculation, nor is there any indication of the duration of the first infection at the time the second inoculation was performed.

Tomasczweski (3) concluded that rabbits with syphilitic keratitis are just as susceptible to scrotal reinoculation months after infection as are normal animals. This statement is based upon 6 rabbits inoculated "intraocularly." In all 6 keratitis developed 48, 20, 53, 51, 33, and 32 days after inoculation. Reinoculations were made subsequently on the scrotum 128, 93, 66, 16, 2, and 1 day after the occurrence of the keratitis. The reinoculations were therefore carried out 176, 113, 119, 67, 35, and 33 days after the first inoculation. Presumably the reinoculations were made with homologous virus although there is no statement to that effect. In all but the last animal typical syphilitic lesions developed after the second inoculation. If the development of immunity to syphilis after intraocular inoculation follows the same pattern that it exhibits after intratesticular inoculation one would have expected negative results from the reinoculations carried out 176, 113, and 119 days after the first inoculation, and positive results from the other three.

Adachi (4) inoculated a series of rabbits "in the eye" with syphilitic virus. In 17 of these animals, in all of which keratitis developed, reinoculations were carried out by scrotal scarification 46 to 120 days after the first infection. No antisyphilitic treatment was given. In 8 of the 17 a typical chancre developed at the site of the second inoculation. Unfortunately in the English abstract which accompanies the article the duration of the first infection at the time of the second inoculation is not given for each animal, but Matsumoto (5) in his monograph states as follows: "The (8) animals were among those which were subjected to superinfection 46–109 days after (first) infection." Nor is there any statement as to whether homologous or heterologous virus was used for the reinoculation. Information on both these points is necessary if one is to evaluate the experiments correctly. The author concludes that "the syphilitic lesion in the eye may (although inconstant) produce immunity in the whole organism, because the reinoculation experiments in the scrotum of such animals was (sic) sometimes negative."

About all that one can conclude from the foregoing experiments is that syphilitic keratitis in rabbits is sometimes followed by the development of general immunity to the infection but the precise conditions which determine whether or not the immune state will develop are not clearly understood.

Experiments in which rabbits were first inoculated in the cornea and then subsequently inoculated in the same tissue are very few in number, and for the most

part do not contain the necessary data for evaluation. Adachi (4) inoculated 5 rabbits in the eye and in all keratitis developed. They were treated with salvarsan (0.03 to 0.04 gm. per kilo of body weight) intravenously, 6 injections being given at weekly intervals. Reinoculations were carried out in the same eye and no lesions developed.

Technique

Inoculum. The Nichols strain of *T. pallidum* was used in all experiments, both for primary inoculations and for reinoculations. Emulsions of treponemes in physiological salt solution, prepared by grinding syphilitic testicular lesions in a mortar and centrifuging the emulsion to throw down the larger tissue particles constituted the inoculum in each instance.

Treatment.—All treated animals received 6 intravenous injections of arsphenamine at weekly intervals. Each dose was 20 mg. per kilo of body weight.

Intracorneal Inoculation.—Under ether anesthesia, an eye speculum was placed beneath the lids and nictitating membrane, and the episclera was grasped above with fixation forcaps. Using a No. 26 gauge needle and a tuberculin syringe, the needle was thrust between the lamellae of the cornea until the bevel was fully in the corneal parenchyma, and an intracorneal injection of 0.1 cc. of the virus was made, care being taken not to enter the anterior chamber. The injected material spread out as an opaque film between the layers of the cornea and covered as a rule about two-thirds of that structure. Occasionally, there was either some tearing of the conjunctiva with deposition of the virus on the torn surface, or accidental puncture of the anterior chamber, with deposition of the virus in the anterior chamber.

The eyes of the animals were examined at weekly intervals and the degree of ciliary inflammation, corneal reaction, and inflammatory reaction in the iris was noted. For purposes of recording, the total reaction in the eye was given a number based upon the picture as a whole, the schedule 0 to 8 being employed uniformly. In none of the animals were reactions in the vitreous, orbit, or fundus noted.

Cutaneous Inoculation.—All injections to test the susceptibility of the skin were made by intracutaneous inoculations, in shaved areas on the back, of 0.1 cc. of the virus emulsion.

Animals.—The rabbits used belonged to all the commoner breeds, and were not limited to any particular variety. Females only were used, however, for if males were used in such an experiment there would always be the possibility that a metastatic lesion might develop in the testis and conceivably vitiate the experiment by itself giving rise to a general immunity.

EXPERIMENTS

Experiment 1.—A series of 33 female rabbits were inoculated intracorneally (left cornea) with syphilitic virus and the disease allowed to run its course for a period of 160 days. At the end of that time treatment with arsphenamine was begun. Eighty-six days after the last injection of the drug the surviving animals were inoculated simultaneously in the same cornea and also the skin of the back with homologous syphilitic virus. At the same time a series of control animals were inoculated with the same emulsion and in the same manner. In the test series 19 animals survived for the duration of the experiment and in the control series 16 survived. The results of the experiment are shown in Table I.

Examination of Table I shows that in all 16 of the normal animals intracutaneous inoculation was positive, whereas in 14 of them the intracorneal inoculation was positive and was negative in the other two. The character of the lesions developing in the corneas of the 14 normal animals was the same as that

TABLE I

Reinoculation of Cornea and Skin in "Immune" Syphilitic Rabbits after Primary Inoculation in the Cornea

	Rabbit No.	Corneal reinoculation				Skin reinoculation		
		Result	Incubation period	Maximum intensity of lesion	Duration of lesion	Result	Incubation period	Duration of lesion
			days		*days*		*days*	*days*
"Immune group"	56-41	Neg.	—	—	—	Doubtful*	—	—
	56-42	Pos.	136	4	21	Neg.	—	—
	56-44	Neg.	—	—	—	Pos.	10	43
	56-50	Neg.	—	—	—	Neg.	—	—
	56-52	Pos.	136	2	14	Pos.	32	91
	56-54	Pos.	67	6	43	Neg.	—	—
	56-55	Neg.	—	—	—	Neg.	—	—
	56-56	Pos.	46	6	153	Pos.	25	196
	56-57	Neg.	—	—	—	Pos.	10	85
	56-58	Neg.	—	—	—	Neg.	—	—
	56-59	Neg.	—	—	—	Neg.	—	—
	56-64	Pos.	172	4	49	Pos.	10	22 (relapse)
	56-66	Pos.	150	2	71	Doubtful*	—	—
	56-67	Neg.	—	—	—	Pos.	38	153
	56-79	Neg.	—	—	—	Neg.	—	—
	56-80	Neg.	—	—	—	Doubtful*	—	—
	56-81	Neg.	—	—	—	Neg.	—	—
	56-83	Neg.	—	—	—	Neg.	—	—
"Control group"	58-82	Pos.	38	8	147	Pos.	10	105
	58-84	Pos.	38	4	78 (relapse)	Pos.	32	70
	58-85	Pos.	46	4	90	Pos.	25	103
	58-87	Pos.	32	6	104	Pos.	25	63
	58-90	Pos.	46	4	133	Pos.	25	49
	58-91	Neg.	—	—	—	Pos.	25	85
	58-93	Neg.	—	—	—	Pos.	38	85
	58-94	Pos.	32	2	35	Pos.	32	14
	58-95	Pos.	46	4	97	Pos.	19	153
	58-96	Pos.	46	4	139	Pos.	53	126
	58-97	Pos.	32	2	35	Pos.	19	48
	58-98	Pos.	32	8	118 (relapse)	Pos.	19	55
	58-99	Pos.	46	4	64	Pos.	38	64
	59-03	Pos.	32	2	147	Pos.	19	153
	59-05	Pos.	53	1	12	Pos.	19	27
	59-06	Pos.	46	6	97 (relapse)	Pos.	19	104
Summary of Results								
Immune group	18 animals	6 pos. 12 neg.	118 (av.)	4 (av.)	58 (av.)	6 pos. 9 neg. 3 doubtful	20 (av.)	98 (av.)
Control group	16	14 pos. 2 neg.	40 (av.)	4.2 (av.)	85 (av.)	16 pos. 0 neg.	25 (av.)	81.5 (av.)

* This lesion was transitory (duration 14 days) and never attained a size greater than 2 mm. It never showed any necrosis.

observed in our former experiments. For a detailed description of the appearance and development of these lesions the reader is referred to our previous paper (1). The average incubation period of the corneal lesions in the normal animals was 40 days, the average maximum intensity of the lesions was 4.2 (on a 0 to 8 basis), and the average duration exclusive of relapses was 85 days.

In the so called "immune" or test group, 6 of the 18 animals gave a positive result on reinoculation of the same cornea. In these animals the lesions were greatly delayed (incubation period 118 days on an average, against an average of 40 days in the controls), the average maximum intensity was 4 (about the same as the controls), and the average duration was shorter. In this same group of animals the intracutaneous reinoculation gave 6 positive, 3 doubtful, and 9 negative results.

It is of interest that the result in the cornea did not always parallel that in the skin. Thus in 2 rabbits (Nos. 56-42 and 56-54) the corneal reinoculation was positive and the skin reinoculation negative, in 2 (Nos. 56-41 and 56-80) the corneal reinoculation was negative and the skin reinoculation doubtful, while in 3 others (Nos. 56-44, 56-57, and 56-67) the corneal reinoculation was negative and the skin reinoculation positive. In 1 animal (No. 56-66) the corneal reinoculation was positive and the skin reinoculation doubtful. In 7 rabbits both types of reinoculation were negative in the same animal and in 3 both were positive.

The fact that as many as 6 of the 16 test animals gave a positive result after intracutaneous reinoculation with homologous syphilitic virus, indicating that no general immunity had developed in these animals after a primary intracorneal inoculation, raised the question whether the virus had made its way into the blood stream in these instances. Unfortunately lymph node transfers had not been carried out prior to treatment and, although metastatic lesions had not been observed, it was not possible to say if the virus had or had not made its way from the cornea into the circulating blood. If it had not, one might explain the failure of the animal to acquire an immunity against syphilis on that basis.

The fact that 3 of the test animals gave a negative response to the corneal reinoculation but showed a characteristic syphilitic lesion at the site of the intracutaneous reinoculation raised the question whether in these animals the negative corneal reactions represented instances of local immunity developing at the site of syphilitic inoculation. It would be important to multiply such instances, if possible, for little is known of the existence of local immunity in syphilitic infection. For that reason, and in order to determine if the lack of development of general immunity in some animals after intracorneal inoculation was due to failure of the syphilitic virus to gain entrance to the blood stream it was decided to undertake a second experiment along the same general lines as the first but with some modifications added.

Experiment 2.—A series of 30 normal female rabbits were inoculated intracorneally (left cornea) with syphilitic virus and the disease allowed to run its course for 275 days. Both popliteal lymph nodes were transferred from all the surviving animals to normal rabbits 236 to 256 days after inoculation. Treatment was begun 275 days after the original inoculation. Eighty-five days after the last injection of arsphenamine all of the surviving (15) animals were inoculated intracorneally and intracutaneously on the back with homologous syphilitic virus. Both corneas of the test animals were also inoculated in order to determine if there was any difference in their resistance to reinoculation. At the same time a series of 20 control animals were inoculated in one cornea only and in the skin with the same batch of syphilitic virus. The results of the experiment are shown in Table II.

Table II shows first of all that of the 14 animals which were inoculated in the cornea and in which lymph node transfers were completed, treponemes were recovered from the popliteal nodes in 12, thus establishing the fact that the syphilitic virus does not remain localized in the cornea after intracorneal inoculation but makes its way into the circulating blood as a rule. This is, of course, what one would expect.

The number of positive results in the control group after inoculation of the cornea was smaller than in any previous experiments. We have no explanation for this fact. The fact that in the same animals characteristic syphilitic lesions developed in every instance after intracutaneous inoculation shows that the strain of treponemes had not lost its virulence. In the test or "immune" group there were only 2 positive results in the corneas which had been inoculated originally whereas in the opposite corneas there were 4 positive results. It is questionable how much significance should be attached to this difference. The average incubation period of the lesions developing in the corneas of the test animals was longer and their average duration shorter than in the controls. In none of the test animals did characteristic syphilitic lesions develop after intracutaneous reinoculation. In 5 of them a small papule appeared at the site of reinoculation which lasted about 15 days on the average, never attained a size greater than 2 mm. in diameter, and never showed any tendency to ulcerate. These lesions did not at all resemble those observed in the control group and have been classed as doubtful.

It will be observed that in the first experiment the incidence of positive results occurring in the cornea of the "immune" group after reinoculation (33.3 per cent) was greater than in the corresponding animals in the second experiment (13.5 per cent). The only explanation which we can offer for this observation is the fact that the animals of the first experiment did not have their syphilis as long (160 days) before treatment was instituted as did the animals of the second experiment (275 days). Whether or not this is the correct explanation of what was observed it is impossible to say.

If the results of the two experiments are combined, excluding the reactions obtained after reinoculation of the right cornea, since this was the cornea not

TABLE II

Result of Lymph Node Transfer and of Reinoculation of both Corneas and Skin in "Immune" Syphilitic Rabbits after Primary Inoculation in the Cornea

	Rabbit No.	Result of lymph node transfer	Corneal reinoculation								Skin reinoculation		
			Right Cornea				Left Cornea						
			Result	Incubation period	Maximum intensity of lesion	Duration of lesion	Result	Incubation period	Maximum intensity of lesion	Duration of lesion	Result	Incubation period	Duration of lesion
				days		*days*		*days*		*days*		*days*	*days*
"Immune group"	62-55	Pos.	Pos.	34	1	14	Neg.	—	—	—	Neg.	—	—
	62-57	Pos.	Neg.	—	—	—	Neg.	—	—	—	Neg.	—	—
	62-58	Pos.	Pos.	63	4	14 (two relapses)	Pos.	90	6	28	Doubtful	8	21
	62-60	Pos.	Neg.	—	—	—	Neg.	—	—	—	Doubtful	8	14
	62-64	Pos.	Neg.	—	—	—	Neg.	—	—	—	Neg.	—	—
	62-66	Pos.	Neg.	—	—	—	Neg.	—	—	—	Neg.	—	—
	62-67	Pos.	Neg.	—	—	—	Neg.	—	—	—	Neg.	—	—
	62-68	Neg.	Neg.	—	—	—	Neg.	—	—	—	Neg.	—	—
	62-71	Pos.	Neg.	—	—	—	Neg.	—	—	—	Neg.	—	—
	62-72	Incomplete*	Pos.	90	4	91	Neg.	—	—	—	Neg.	—	—
	62-73	Pos.	Neg.	—	—	—	Pos.	76	6	56	Doubtful	8	14
	62-78	Pos.	Neg.	—	—	—	Neg.	—	—	—	Neg.	—	—
	62-80	Neg.	Neg.	—	—	—	Neg.	—	—	—	Doubtful	8	14
	62-82	Pos.	Neg.	—	—	—	Neg.	—	—	—	Doubtful	8	14
	62-14	Pos.	Pos.	118	1	28	Neg.	—	—	—	Neg.	—	—
Control group	65-55						Neg.	—	—	—	Pos.	8	112
	65-56						Pos.	34	2	91	Pos.	8	105
	65-57						Pos.	20	6	105	Pos.	15	105
	65-58						Pos.	41	6	84	Pos.	8	105
	65-59						Pos.	48	2	77	Pos.	8	119
	65-60						Pos.	55	3	63	Pos.	8	112
	65-61						Neg.	—	—	—	Pos.	8	105
	65-62						Pos.	13	6	154	Pos.	8	41
	65-63						Pos.	48	4	70	Pos.	8	112
	65-64						Neg.	—	—	—	Pos.	8	56
	65-65						Pos.	34	4	84	Pos.	8	112
	65-66						Neg.	—	—	—	Pos.	8	127
	65-67						Pos.	34	6	134	Pos.	8	161
	65-68						Neg.	—	—	—	Pos.	8	175
	65-69						Neg.	—	—	—	Pos.	8	105
	65-70						Pos.	13	8	112	Pos.	8	98
	65-71						Pos.	48	4	70	Pos.	8	63
	65-72						Pos.	13	6	133	Pos.	8	105
	65-73						Pos.	48	8	77	Pos.	8	127
	65-75						Pos.	41	4	105	Pos.	22	119
Summary of Results													
Immune group	15 animals	13 pos. 1 neg. 1 incomplete	4 pos. 11 neg.	76 (av.)	2.5 (av.)	37 (av.)	2 pos. 12 neg.	83 (av.)	6 (av.)	42 (av.)	5 doubtful 10 negative	8 (av.)	15 (av.)
Control group	20 animals						14 pos. 6 neg.	35 (av.)	5 (av.)	68 (av.)	20 pos.	8.2 (av.)	108 (av.)

* Both animals to which lymph nodes were transferred died prematurely.

TABLE III

Combined Results Shown in Tables I and II

	Corneal reinoculation				Skin reinoculation		
	Result	Incubation period	Maximum intensity of lesion	Duration of lesion	Result	Incubation period	Duration of lesion
		days		*days*		*days*	*days*
Immune group 33 animals	8 pos. 25 neg.	109 (av.)	4.5	54.3 (av.)	6 pos. 8 doubtful 19 neg.	20 (av.) — —	98 (av.) — —
Control group 36 animals	28 pos. 8 neg.	37.7 (av.) —	4.6 —	95 (av.) —	36 pos. 0 neg.	16.6 (av.) —	88 (av.) —

TABLE IV

Incidence of Various Types of Response to Reinoculation in Both the Cornea and the Skin

Theoretically possible types of response		No. of instances response was observed	Interpretation
Corneal reinoculation*	Skin reinoculation		
+	+	3	No immunity of cornea or skin
+	?	3	No immunity of cornea, partial immunity of skin
+	0	5	No immunity of cornea, immunity of skin
?	+	0	Partial immunity of cornea, no immunity of skin
?	?	0	Partial immunity of both cornea and skin
?	0	0	Partial immunity of cornea, immunity of skin
0	+	3	Immunity of cornea, no immunity of skin
0	?	5	Immunity of cornea, partial immunity of skin
0	0	17	Both cornea and skin immune

* All instances of positive corneal reinoculation are included, irrespective of which cornea was involved.

originally inoculated and was also not tested for immunity in the first experiment, one obtains the data which are set forth in Table III.

Since the test animals in these experiments were reinoculated in both the

cornea and the skin, it is obvious that any of these animals might have given one of several different responses to reinoculation. All of the theoretically possible responses are shown in Table IV together with the number of observed instances of each type of response and the interpretation placed upon it.

It is apparent from Table IV that in one-half of all the test animals both cornea and skin were immune to a second inoculation of homologous syphilitic virus. In addition to these there were 5 animals in which the cornea was immune and the skin nearly so for the lesions which developed in the skin of these animals were minimal in extent and duration and were in no way comparable to those which were observed in the controls. Thus in two-thirds of our animals there developed in both the skin and the cornea, after a primary intracorneal inoculation, a high degree of resistance toward a second inoculation with homologous syphilitic virus. In the remaining third the resistance was less marked or altogether absent.

DISCUSSION

The experiments show conclusively that if rabbits are inoculated intracorneally with a virulent strain of *T. pallidum* and a lesion develops at the site of inoculation the organisms do not remain localized in the corneal tissue but quite regularly make their way into the circulation and may be recovered from distant lymph nodes in every instance. A large proportion of such animals acquire a high degree of resistance against the same strain of treponemes when injected into the skin, as judged by whether or not a syphilitic lesion develops at the site of reinoculation but not every animal becomes immune. In our hands 6 of 33 animals showed no evidence of immunity of the skin, in 8 there was evidence of partial immunity while in 19 the immunity appeared to be complete, using the term in the sense that no lesion appeared at the site of reinoculation.

In the majority of instances the cornea which was originally inoculated becomes immune also, as does the opposite cornea, but the percentage of successful reinoculations in each cornea is higher than that in the skin, indicating that the cornea does not always share in the immune process to the same extent as does the skin, not even the cornea which was originally inoculated and in which a syphilitic lesion had developed. This finding is similar to that which we encountered in our original experiments after intratesticular inoculation. It should be pointed out, however, that the lesions which did develop in the corneas of the "immune" animals had a longer incubation period and were of shorter duration on the average than was the case in the controls. These findings suggest that these animals were partially resistant to reinoculation.

Sometimes the cornea originally inoculated proved to be immune but not the opposite cornea. There was one instance in which the reverse appeared to hold true. There were only two instances in which the cornea originally inoculated gave a negative response to reinoculation while the skin gave a positive response.

These may be examples of the development of a local immunity, as stated previously.

In general, intracorneal inoculation of rabbits may be said to be followed by a general immunity in a high percentage of the animals tested, but this percentage is probably below that observed after intratesticular inoculation.

SUMMARY AND CONCLUSIONS

Two experiments are reported in which an attempt was made to determine the extent to which a primary syphilitic infection of the cornea in rabbits is followed by the development of a local corneal immunity, by the generalization of the virus, and by the development of a general immunity to the infection. Female rabbits were inoculated intracorneally with a virulent strain of *T. pallidum* and the disease was allowed to run its course until the lesions which had developed at the site of inoculation had healed spontaneously. Popliteal lymph nodes were transferred from about one-half of these animals (in the second experiment only) to normal male rabbits and in almost every instance the nodes were proved by this method to contain virulent treponemes, showing that generalization of the syphilitic infection is the rule after intracorneal inoculation. All animals were treated with arsphenamine after the local lesion had subsided (160 and 275 days after the original inoculation). The rabbits were then reinoculated with the homologous strain of treponemes, injections being made into the cornea originally inoculated and also into the skin of the back. In one experiment both corneas were reinoculated.

The incidence of lesions developing in either cornea after reinoculation was higher than the incidence of lesions developing in the skin. The lesions developing in the corneas of the "immune" animals had a longer incubation period and were of shorter duration on the average than the lesions in the control group. As far as intensity of reaction was concerned no difference was observed.

Inoculation of the cornea of rabbits with syphilitic virus is often followed by the development of immunity to the homologous strain of organisms. This immunity is imparted to the skin to a greater extent than to either the cornea inoculated originally or to the opposite uninoculated cornea. It persists after treatment with arsphenamine. It appears to be more marked the longer treatment is postponed.

It is apparent from Table IV that in one-half of all the test animals both cornea and skin were immune to a second inoculation of homologous syphilitic virus. In addition to these there were 5 animals in which the cornea was immune and the skin nearly so, for the lesions which developed in the skin of these animals were minimal in extent and duration and were in no way comparable to those which were observed in the controls. Thus in two-thirds of our animals there developed in both the skin and the cornea, after a primary in-

tracorneal inoculation, a high degree of resistance toward a second inoculation with homologous syphilitic virus, but syphilitic disease of the cornea does not always impart to the cornea itself an absolute immunity to reinoculated homologous virus.

The authors desire to acknowledge the technical assistance of Dr. Ira L. Shamberg, Dr. Frank W. Reynolds, and Dr. Virgil C. Scott in carrying out this study.

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