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Experiment in Cross Immunity Between Infectious Hepatitis and Homologous Serum Jaundice.*

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Planned experiments with human volunteers have demonstrated similarities in the properties[1-5] of the etiologic agent (or agents) of *infectious hepatitis* and *homologous serum jaundice* in that the agent (or agents) of both conditions is filtrable, resistant to heating to 56°C for 30 minutes, and can be transmitted in serial passage to human volunteers. Comparative studies of both clinical and experimental cases, however, reveal apparent differences between the two conditions. Primarily there is a more or less consistent difference in incubation period with a prolonged period (60-120 days) in homologous jaundice[6-9] in contrast to the shorter period (20-40 days)[10-13] of infectious hepatitis; there may, however, be some overlapping. Secondly, in contrast to the infective character of infectious hepatitis there is usually failure of contact cases to develop in homologous serum jaundice, although exceptions to the latter are recorded.[14-15] Because of these apparent differences and similarities, there is confusion concerning the nature of the two conditions. Homologous serum jaundice may represent the artificial production of infectious hepatitis but this does not seem to be always true. As yet there is no means of clarifying this situation. Findlay together with Martin and Mitchell[15] have suggested that *size of dose, individual susceptibility* and *route of inoculation* may be the factors conditioning the differences.

There is little available information concerning immunity in infectious hepatitis or immunological relationships between these two conditions. Recently Oliphant[16] reported failure to infect 10 human subjects, convalescent 6-19 months from homologous serum jaundice, when inoculated with a strain of

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infectious hepatitis which produced jaundice in 4 of 10 normal control subjects, with incubation periods ranging from 85-106 days.

The present report describes the lack of demonstrable immunity in human volunteers, convalescent from homologous serum jaundice when re-infected with a strain of infectious hepatitis.

Strains Employed. Serum jaundice. The strain of homologous serum jaundice was derived from a pool of serum obtained from 11 men in the first 24 hours of sandfly fever in the Middle East. This pool was prepared by Lt. Col. A. B. Sabin, M.C.[17] This icterogenic agent conforms in behavior to other strains of serum jaundice in that out of 23 trial inoculations, 11 cases have been produced, with incubation periods ranging from 60-132 days in both 1st and 2nd passages.[4]

The patients who furnished the pool of serum described above had all been living (during June, 1943) within an area endemic for infectious hepatitis, although at the time the samples were obtained the prevalence of the disease was low. The donors had been questioned specifically at the time the blood was drawn and had stated that they had not had jaundice recently. Subsequent information from 10 of these men, 4 months after bleeding, revealed that none of them had developed jaundice. The 11th man had left the country and could not be traced.

The first transmission experiments, carried out in the Middle East, were originally concerned with sandfly fever.[17] The pool of serum described above produced sandfly fever in 9 out of 10 inoculated human volunteers after the usual incubation period of from 3-5 days. Subsequently, 4 of these 10 volunteers developed jaundice at intervals of 72 to 94 days after inoculation, indicating that the original pool of serum also contained an icterogenic agent.

Several months later this experiment was repeated in the United States inoculating the original pool of serum alone (and mixed with first passage serum).[13] The serum was heated to 56°C for 30 minutes before inoculation to destroy the virus of sandfly fever known to be present. Jaundice was produced in 3 out of 5 human volunteers with incubation periods of 56 to 70 days.

Subsequent test of these 3 men for cross immunity to the naturally occurring disease infectious hepatitis is reported here.

Infectious hepatitis. The virus employed was obtained from a pool of stools and urine of patients with infectious hepatitis hospitalized in the Middle East. It was originally transmitted to 2 human volunteers by feeding with incubation periods of 20 and 22 days.[13] This virus is filtrable, resistant to a temperature of 56°C for 30 minutes[1] and has been through 3 passages in human subjects, producing hepatitis after ingestion or parenteral inoculation of the infectious agent with incubation periods ranging from 16 to 34 days.

The inoculum employed in this experiment was serum obtained during the first 5 days of infectious hepatitis (pre-icteric phase) which had been experimentally induced in 2 human volunteers by feeding feces (and urine) obtained from *naturally occurring* cases. As such it constitutes *first human passage* material. The serum was stored at dry ice box temperature for a period of 2-5 months. Before using, it was thawed at room temperature, pooled, filtered through a Chamberland No. 2 filter and immediately afterward heated to 56°C for 30 minutes.

The heated filtrate of serum was administered in amounts of 1 cc (parenterally or orally) to each of 16 human subjects and the results are described in Table I. These men were residents in a penal institution and a hospital for mental disease, and volunteered for the experiment. There had been no infectious hepatitis in either institution for the preceding year and no other cases have occurred during the period of the experiment.

It is of interest that the 3 men who had previously contracted ***homologous serum jaundice*** with a long incubation period of 56, 66, and 70 days respectively after parenteral inoculation, when re-inoculated sub-intracutaneously after 6 months of convalescence with a strain of naturally occurring ***infectious hepatitis,*** all contracted infectious hepatitis with

[17] Sabin, A. B., Philip, C. B., and Paul, J. R., *J. A. M. A.*, 1944, **125**, 603, 693.

TABLE I.
Results of Administration of Icterogenic Serum (Infectious Hepatitis) to Human Volunteers.

Group	Subjects	Route	Number of volunteers		Incubation period, days
			Inoculated	Jaundiced	
A	Normal subjects	Par.*	7	2	24, 31
B	Inoculated unsuccessfully 6 months before with agent of homologous serum jaundice	"	1	1	21
C	Convalescent 6 months from homologous serum jaundice	"	3	3	20, 20, 25
D	Normal subjects	Oral	4	3	23, 24, 34
E	Fed unsuccessfully 6 months before with agent of homologous serum jaundice	"	1	1	29

* Par. = Parenteral inoculation.

jaundice after 20, 20, and 25 days respectively. It is also of note that the incubation periods in these experimental cases have ranged from 20-34 (average 24) days, with no appreciable difference between those inoculated parenterally and those fed equal amounts of the same infectious agent.

Summary. Previous experimental infection (or inoculation without infection) with a strain of *homologous serum jaundice* obtained in the Middle East failed to protect 5 human volunteers against subsequent experimental infection induced 6 months later with a strain of *infectious hepatitis* also obtained in the Middle East.

These results are in contrast to those found by Oliphant, who has described immunity in human subjects convalescent 6-19 months from homologous serum jaundice, when inoculated with serum from acute cases of infectious hepatitis.

Using a strain of the *naturally occurring disease,* infectious hepatitis, no appreciable difference in incubation period was observed in experimental cases when equal amounts of the same infectious agent were inoculated parenterally or fed. Incubation periods ranged from 20-34 (average 24) days.

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Immunologic Relationships of MM, Lansing Poliomyelitis and Mouse Encephalomyelitis Viruses.

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A number of viruses have the physical properties of poliomyelitis virus and induce poliomyelitic lesions in rodents. Those discovered by Theiler are known as mouse encephalomyelitis virus.[1] The others are thought to be strains of human poliomyelitis which have been adapted to rodents.[2-6] Both groups include strains which differ clinically and in infectivity from human poliomyelitis and spontaneous mouse encephalomyelitis.† Largely because of this Jungeblut's suggestion[7] that

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