Homologous Serum Hepatitis

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In 1937 MacNalty reported the first obvious cases of homologous serum hepatitis in Great Britain. The disease occurred in individuals who had been injected with pooled serum from measles convalescents or pooled serum from supposedly normal adults. At the same time Findlay and MacCallum described cases of hepatitis, probably of similar origin, in individuals who had been injected with yellow fever vaccine containing human serum. Further incidents of a similar nature occurred in Brazil, Great Britain and U.S.A. As a result of the use of blood products on a massive scale during the period 1939-1945, a sufficient number of different "outbreaks" of homologous serum hepatitis occurred to make the condition recognized as a definite entity. Because the disease could not be transmitted to laboratory animals experimental studies have been carried out in man. The information obtained by inoculation of known icterogenic sera of this type was summarized by MacCallum in 1944. Since then numerous reports of experimental work on this disease have appeared. The relevant data, old and new, which bears on the possible nature of the disease is summarized in Tables I, II and III.

TABLE I.—EXPERIMENTAL TRANSMISSION OF SERUM HEPATITIS TO MAN.

Author	Source of inoculum	Route	Dose	Recipients	Jaundice	Incubation period—days
Beesen, Chesney, McFarlan	Mumps convalescent plasma (22 donors)	I.V.	4–14·0 ml.	266	101	44–123
Bradley, Loutit, Maunsell	Dried transfusion serum—pool B	I.D.	0·10 ml.	47	26	46–104
		Tr.(X)	1700·0 ml.	17	10	45–96
Findlay and Martin	(1) Nasopharyngeal washings of Y.F. vaccine jaundice	I.N.	10·0 ml.	4	3	28,30,50
	(2) Serum on 3rd day jaundice	I.N.	Not given	5	0	—
	(3) Whole blood on 3rd day jaundice	S.C.	2·0 ml.	5	0	—
	(4) Whole blood	S.C.	0·5 ml.	2	?	
	(5) Fæces on 3rd day jaundice	Oral	1·0 ml.	2	0	—
MacCallum and Bauer	Dried transfusion serum—pool A	S.C.	0·5–2·0 ml.	11	4 (2)	59–129
		I.N.	2·0 ml.	5	0	
MacCallum, Stewart, Bradley	Dried transfusion serum—pool B	S.C.	1·0 ml.	18	9	60–114
		I.N.	5·0 ml.	10	0	—
		Oral	5·0 ml.	10	0	—
Neefe, Stokes, Rheinhold	(1) Serum	I.V.	1–100 ml.	7	4	73–100
	(2) Fæces from serum induced cases above. 3 pools from 7 days before to 18 days after jaundice	Oral	4–15 ml.	19	0	—
Oliphant, Gilliam, Larson	(1) Y.F. vaccine	S.C.	0·5 ml.	50	12	
	(2) Pool of sera from cases in (1)	S.C.	0·5 ml.	10	2	
	(3) Pooled weekly specimens in pre-icteric stage of 1 case in (1)	S.C.	0·5 ml.	14	4	35–140
	(4) Plasma pool	S.C.	1·0 ml.	15	0	
	1 donor became jaundiced 4 days after bleeding	I.V.	10·0 ml.	10	0	
Paul, Havens, Sabin, Philip	(1) Pool of sandfly fever convalescent serum (11 donors)	S.C.	1·0 ml.	10	4	72–94
		Oral	1·0 ml.	3	0	
	(2) Blood from case in (1) 60 days before jaundice, 34 days after inoculation	S.C.	1·0 ml.	8	3	74–132

S.C. = Subcutaneous
I.N. = Intranasal
I.V. = Intravenous
I.D. = Intradermal
Tr. = Transfusion
(2) = 2 Subicteric hepatitis
(X) = I.D. as well

TABLE II.—IMMUNITY.

Author	First attack	Reinoculation: Serum hepatitis No.	Serum hepatitis Jaundice	Infective hepatitis No.	Infective hepatitis Jaundice
Beeson, McFarlan, Chesney	Infective hepatitis in childhood	11	8		
Havens	Experimental serum hepatitis			3	3
MacCallum and Bauer	Serum hepatitis	10	0		
	Natural infective hepatitis	2	1		
Neefe, Stokes, Gellis	Experimental serum hepatitis	6	0	6	2 (3)
	Experimental infective hepatitis			8	0
Oliphant	Experimental serum hepatitis	10	0		
	Experimental serum hepatitis			10	0

(3) = 3 cases of subicteric hepatitis

TABLE III.—ATTEMPTS AT "INACTIVATION" OF ICTEROGENIC SERA.

I.	*Heat*: (1) Survived 56° C. for 1 hour—routine (2) Dried Y.F. vaccine-agent survived 1½ years at room temperature				
II.	*Triple ether extractions in the cold* MacCallum, Stewart, Bradley		Pool B	19 recipients,	10 jaundice
III.	*Ultraviolet light*				
	Oliphant	(1) (*a*) Icterogenic Y.F. vaccine—untreated		10 recipients,	2 jaundice
		(*b*) Vaccine exposed for 1 hour at 2,650 Å 1½ hours at 2,537 Å		10 recipients,	0 jaundice
		(2) (*a*) Pool of pre-icteric sera—untreated		13 recipients,	2 jaundice
		(*b*) Serum in (*a*) exposed for 45 minutes at 85%, 2,537 Å		11 recipients,	0 jaundice
		(3) (*a*) Pool of pre-icteric serum—untreated		9 recipients,	1 jaundice
		(*b*) Serum in (*a*) irradiated in thin quartz cell 2½ secs. by high energy, low-pressure water, cooled mercury lamp		20 recipients,	0 jaundice
	MacCallum Stewart, Bradley	(1) (*a*) Pool B—untreated		14 recipients,	6 jaundice
		(*b*) 30 minutes at 80%, 2,537 Å		10 recipients,	2 jaundice
		(2) (*a*) Pool B—untreated		4 recipients,	3 jaundice
		(*b*) 30 minutes at 95%, 2,536 Å		10 recipients,	1 jaundice
IV.	*Phenol*: Pool K 60 convalescent measles serum —still active after contact with 0·25% phenol for fourteen months				
V.	*Tricresol*: No evidence at present *Possible methods of control*: (1) *Gamma globulin*—Addition of known immune gamma globulin to pools (2) Very large pools 50,000 donors Small pools 10 donors Very small pools, or single specimens				

In 1943 Oliphant *et al.* showed that an icterogenic agent was present during the pre-icteric and early icteric stages in the blood of individuals who developed hepatitis with jaundice as a result of the injection of certain batches of yellow fever vaccine containing human serum made in the U.S.A. At the same time MacCallum and Bauer in England were able to confirm previous theories as to the origin of yellow fever vaccine jaundice by showing that an icterogenic agent was present in a pool of supposedly normal human serum collected at a blood bank and used to make certain icterogenic batches of yellow fever vaccine. Further studies of such pools have shown that they can produce hepatitis when injected intradermally, subcutaneously, intramuscularly or intravenously, but not intranasally or *per os*. Different pools of proven icterogenicity have different attack rates. The size of the inoculum has, within certain wide limits, no effect upon the attack rate, duration of the incubation period or severity of the illness. The agent has been detected circulating in the blood of one recipient thirty-four days after inoculation and 60 days before the appearance of jaundice and in another recipient seven days after the appearance of jaundice, but not two months later. A single specimen of serum collected on the seventh day of jaundice from a presumedly induced case produced hepatitis and jaundice when injected intranasally, though the original pool used as inoculum did not. Transmission of the disease to man by intranasal inoculation of nasopharyngeal washings collected in the pre-icteric and early icteric stages has been reported in West Africa by Findlay and Martin. This is a contradiction of the results obtained by intranasal injection of icterogenic serum pools, but the difference may be related to the state in which the agent is present in the pools. (No successful transmissions with nasopharyngeal washings from cases of naturally occurring infective hepatitis have been recorded.) It has not been possible to transmit the disease by oral administration of fæces from cases induced by the injection of icterogenic pools. All the results of the experimental inoculation by different routes of serum and other excreta serve to distinguish the usual form of homologous serum hepatitis from naturally occurring infective hepatitis.

The reinoculation, accidentally or experimentally, of individuals convalescent from either homologous serum hepatitis or infective hepatitis suggests that homologous but not heterologous immunity is usually produced by one attack of either disease. In fact, the suggestion has been made that a previous attack of the one disease makes the individual more susceptible to the other. No explanation is forthcoming for the results of Oliphant's experiments in cross-immunity unless he had by chance selected 10 individuals who were not susceptible to infective hepatitis.

There is at present no test which will detect the presence of the icterogenic agent in a suspected serum except observation of the result of injection of the serum into man. Therefore it is desirable to obtain some method of routine treatment of all sera which will inactivate the agent, if it is present in them, without destroying the essential properties of the serum. As can be seen in Table III, the agent is extremely resistant to heat at the temperature usually used for inactivation. The effect of higher temperatures has not been tested, but most sera will coagulate when heated above 60°C. Phenol in a concentration of 0·25% has also failed to inactivate the agent.

Several experiments carried out by Oliphant suggested that the agent could be inactivated by ultraviolet light, but experiments by MacCallum *et al.* indicated that difficulties might arise in determining the suitable energy to be used and the duration of exposure. In their first experiment the supposedly suitable exposure failed to inactivate. In the second experiment the irradiation may have been effective, but when the serum was examined electrophoretically by Dr. R. A. Kekwick it was found that gross changes had occurred in the proteins. A very small residue of probably unchanged gamma globulin was detectable. Since the immune bodies in convalescent serum appear to be associated with the gamma globulin fraction this serum had been rendered useless for such a purpose. Even so, of the 10 recipients of this serum, one became jaundiced twenty-seven days after inoculation.

It has been suggested that very large pools would be safe because there would be sufficient immune bodies to neutralize any agent present. That such an event may occur has been shown by Oliphant, who inoculated a commercial pool of serum which contained serum of an individual taken four days before he became jaundiced (the total number of contributors to the pool was not stated). The jaundiced donor in this case was presumably suffering from infective hepatitis. This pool failed to produce hepatitis when injected subcutaneously or intravenously. Since the probability of neutralization occurring is unpredictable, this method does not seem safe. Though impracticable in wartime, the safest procedure would seem to be to process sera individually or at most small pools of two or three sera, thus limiting the number of recipients at risk if an icterogenic agent is present. If some idea could be obtained of the number of units of the agent that are neutralized by a given quantity of immune gamma globulin, the latter might be added to all pools as a routine.

SUMMARY

The available evidence suggests that the agent responsible for most cases of homologous serum hepatitis is not the same as that causing naturally occurring infective hepatitis.

The agent will pass through the usual filters which retain bacteria, but its actual size has not been determined. It is extremely resistant to heat and disinfectants, and no satisfactory method for the routine treatment of serum is known a present.

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Dr. H. E. Magee: Two Cases of Homologous Serum Jaundice.

My remarks are concerned mainly with the history of two cases of homologous serum jaundice, treated with protein hydrolysates.

Intravenous alimentation with protein hydrolysates and glucose was used in the treatment of severe cases of starvation in Holland and in the German horror camps. The treatment was not a resounding success; it was also employed with a fair amount of success in the treatment of a few cases of advanced starvation in repatriated men from Germany in the spring and summer of 1945. I have already discussed the principles of treatment in a paper given to the Section of Medicine last year (*Proc. R. Soc. Med.*, 38, 388) and again in the Milroy Lectures given in February (*Brit. med. J.*, 1946 (i) 475). After the arrival of the first case of starvation in England in 1945, the Ministry of Health established emergency supplies of hydrolysates ready for administration at Headquarters in Whitehall and in the Regional Offices throughout the country.

On September 18, 1945, Dr. ap Simon of Park Prewett Hospital telephoned me saying that he had a case which he thought might benefit from intravenous alimentation and he gave me a history of the case. At first I doubted whether it was suitable because our experience, small as it was, had been confined to cases of plain starvation, and it was for such cases that the very limited supplies of hydrolysates were intended. However, when Dr. ap Simon informed me that the prognosis was hopeless, that the patient was comatose and had not retained any food for nearly a week, I asked my colleague, Dr. Adcock, to take a sufficient supply for the case straightaway to Park Prewett Hospital. The treatment was commenced the next day.