

Experimental Production of Hepatitis by Feeding Icterogenic Materials.*

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Although *infectious hepatitis* has become a military problem of great importance,¹⁻¹⁶ its natural mode of transmission is obscure.

Reports by MacCallum and Bradley¹⁷ and perhaps others^{18,19,20} already indicate that

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¹ Senevet, G., Moutrier, P., Gros, H., Alcay, L., and Bougarel, R., *Arch. Inst. Pasteur d'Algerie*, 1941, **19**, 47.

² Dietrich, S., *Deutsche med. Wchnschr.*, 1942, **68**, 5.

³ Gutzeit, K., *München med. Wchnschr.*, 1942, **89**, 161, 185.

⁴ Siegmund, H., *ibid.*, 1942, **89**, 463.

⁵ *Bull. War Med.*, 1942, **3**, 394.

⁶ van Rooyen, C. E., and Gordon, I., *J. Roy. Army M. Corps*, 1942, **79**, 213.

⁷ di Benedetto, J., *La Settimanne Medico*, 1942, **30**, No. 50.

⁸ Cameron, J. D. S., *Quart. J. Med. N. S.*, 1943, **12**, 139.

⁹ (Editorial), *J. A. M. A.*, 1943, **122**, 1186

¹⁰ (Editorial), *J. A. M. A.*, 1943, **123**, 636.

¹¹ Dixon, H. B. F., *J. Roy. Army M. Corps*, 1944, **82**, 44.

¹² Spooner, E. T. C., *Proc. Roy. Soc. Med.*, 1944, **37**, 171.

¹³ Gear, H. S., *Brit. M. J.*, 1944, **1**, 383.

¹⁴ *Bull. U. S. Army M. Dept.*, 1944, No. 76, 26.

¹⁵ Witts, L. J., *Brit. M. J.*, 1944, **1**, 739.

¹⁶ Havens, W. P., Jr., *J. A. M. A.*, 1944, **126**, 17.

¹⁷ MacCallum, F. O., and Bradley, W. H., *Lancet*, 1944, **2**, 228.

hepatitis can be acquired by man following ingestion or nasal instillation of the infectious agent in feces, serum, or possibly nasal washings and duodenal drainage. The present report describes 5 definite examples of clinical infectious hepatitis induced by feeding material containing an icterogenic agent in feces and serum.

"Infectious" materials, listed in Table I, employed here were obtained in 1943 from American and British soldiers in Africa and Sicily. Sera and fresh stools were kept at dry-ice box temperature for 8 months; dehydrated Seitz

TABLE I.
Source of Material.

Material	Material obtained from	
	Inoculated case	Natural case
Serum P	*	
" No. 1	—35	
" 2	—21	
" 3	—42	
" 4	—7	
" 5	+ 1	
" 6	+ 1	
" 7		—6
Stool B		+8
Dehydrated filtrates of stool and urine extracts V.R.†	?	?

* Serum P was pooled from 11 men in the first 24 hours of sandfly fever. It was later found to be icterogenic. This pool was prepared by Maj. A. B. Sabin, M.C., and was used in studies reported by Paul *et al.*²¹ Serum P was inactivated at 56°C for 30 minutes before intracutaneous inoculation.

Sera Nos. 1-6 were passages from Serum P.

† These filtrates were prepared and dried by Maj. C. E. van Rooyen, R.A.M.C., from patients in various stages of infectious hepatitis at the 15th Scottish Hospital, Middle East Forces.

(—) indicates days before onset of icterus.

(+) indicates days after the onset of jaundice.

¹⁸ Voegt, H., *Abstr., Bull. Hyg.*, 1942, **17**, 331.

¹⁹ Findlay, G. M., and Martin, N. H., *Lancet*, 1943, **1**, 678.

²⁰ MacCallum, F. O., and Bauer, D. J., *ibid.*, 1944, **1**, 622.

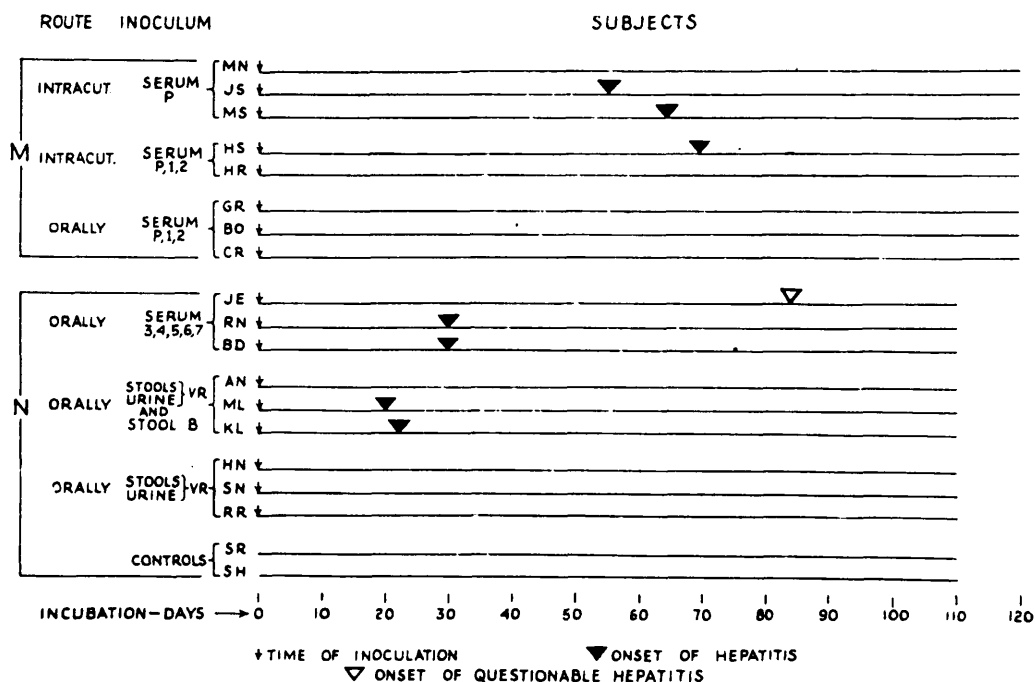


FIG. 1.

Illustration of results of administration of icterogenic material to 2 groups of volunteers at institutions M and N respectively, each subject being represented by a horizontal line. The inoculum which these patients received is indicated by numbers in the left hand column of Table I.

filtrates of urine and stool extracts at room temperature or ice box temperature for 4 months. Both sera and the dried filtrates of urine and stools were sterile on culture before use. Stool B contained no pathogenic bacteria.

The experiment consisted in administering these materials by different routes to 2 groups of human volunteers located in 2 different institutions. For purposes of clarity certain points are illustrated in Fig. 1.

At Institution M, 8 men have been observed for 125 days. Five of them were inoculated *intracutaneously* with serum known by previous tests²¹ to contain icterogenic agent. Of these, 3 contracted infectious hepatitis with moderately severe clinical jaundice in 2, and mild jaundice in the third after 56, 65, and 70 days respectively. The remaining 3 volunteers of this first group were *fed* (and given *intranasally*) icterogenic serum; to date they have remained well. No other cases of infec-

tious hepatitis have occurred in this institution (M) during the period of observation.

At Institution N, 11 men have been observed for 110 days. They were divided into 3 subgroups of 3 men each, with 2 men kept as controls. One subgroup of 3 was *fed* (and given *intranasally*) sera suspected to contain icterogenic agent. Of these, 2 contracted infectious hepatitis with severe clinical jaundice 30 days after feeding and a third developed mild subicteric hepatitis after 84 days. From the blood of one of these men an organism of the salmonella group (*sal. cholera suis*) was cultured during early stages of jaundice. His stool contained no pathogenic bacteria. See Fig. 2.

Another subgroup of 3 men was *fed* urine and stool extracts V.R. *plus* Stool B. Of these men, 2 contracted hepatitis 20 and 22 days respectively following feeding. From the blood of one man *Salmonella cholera suis* was recovered. His stool contained no pathogens.

The third subgroup of 3 men was *fed* urine and stool extracts V.R. All of these patients have remained well.

²¹ Paul, J. R., Havens, W. P., Jr., Philip, C. B., and Sabin, A. B., *J. A. M. A.*, to be published.

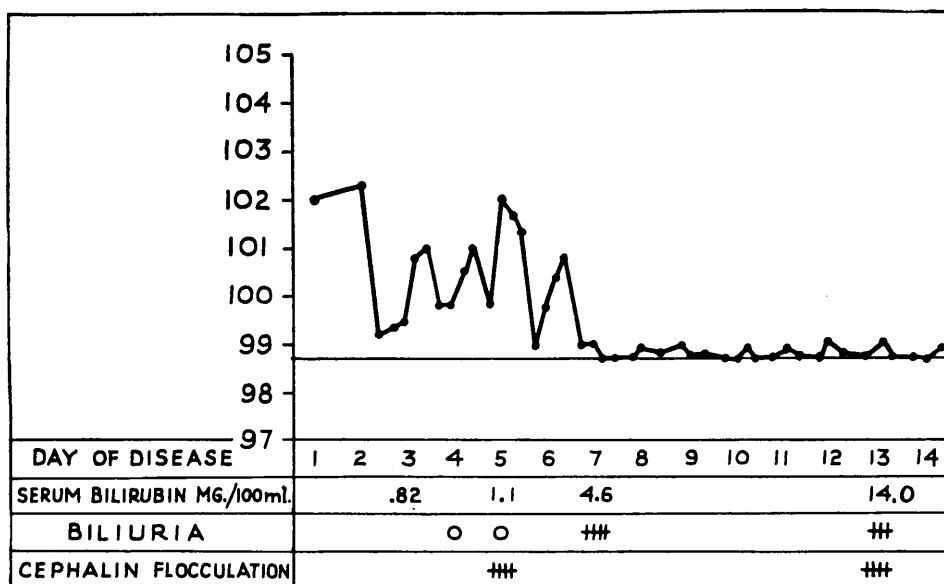


FIG. 2.

Clinical course of volunteer BD. The 7-day period of pre-icteric fever is evident. Rectal temperatures are recorded.

The 2 controls, living in close proximity to the other members of the experimental group, have also remained well.

It is to be noted that *Sal. cholera suis* was isolated from the blood of 2 of the 5 experimental cases induced by feeding icterogenic agent. We have presumed that this organism is a secondary invader, for salmonella infections had been present in Institution N, where these men were quartered, prior to the feeding experiments. It recalls the association of salmonella infections and epidemic hepatitis previously described by French Army workers in 1916,²² and subsequently discussed by others.^{23,24}

One case of acute hepatitis with moderately severe jaundice appeared among the personnel of Institution N, 51 days after the beginning of the experiments there and 31 days after the appearance of the first case among the human volunteers fed icterogenic material. This patient had worked at night

at the same desk occupied originally by the first patient to contract the disease experimentally. Although this patient with the "naturally acquired" disease was away on trips before the onset of his disease it is difficult to regard him as an imported case of hepatitis. It is as yet too early to postulate the exact significance of these events.

Summary. An experiment on the transmission of infectious hepatitis has been carried out among 19 volunteers at 2 institutions. At one of the institutions 3 different samples of serum containing the icterogenic agent were inoculated intracutaneously into 5 human subjects, and the disease was produced in 3 after incubation periods of 56 to 70 (avg 64) days.

At another institution other samples of serum and also specimens of feces (and urine) were fed to 9 human subjects, and the disease was produced in 5 after an incubation period of 20 to 84 (avg 37) days by both of these materials.

One case of "naturally acquired" hepatitis has appeared among the institutional personnel 51 days after the beginning of the experiment and 31 days after the appearance of the first experimental case.

²² Sarrailhé, A., and Clunet, J., *Bull. et Mem. Soc. de hôp.*, Paris, 1916, 3s, 40, 563.

²³ Wilcox, W. H., *Brit. M. J.*, London, 1919, 1, 639.

²⁴ Klemperer, P., Killiam, J. A., and Heyd, C. G., *Arch. Pathol. and Lab. Med.*, 1926, 2, 631.