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Virus Hepatitis

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UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS
January 12 - January 17, 1948

No. 185

Monday, January 12

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns' Quarters, U. H.

9:15 - Fracture Rounds; A. A Zierold and Staff; Ward A; Minneapolis General Hospital.

10:00 - 12:00 Neurology Ward Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - 11:50 Physical Medicine Conference; Reflex Sympathetic Distrophy; Frederic J. Kottke; E-101, U. H.

11:00 - 11:50 Roentgenology-Medicine Conference; Staff; Veterans' Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and D. State; Eustis Amphitheater, U. H.

12:15 - 1:20 Pediatric Seminar; Psychological Problems of the Adolescent; Audrey Arkola; 6th Floor Seminar Room, U. H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; M-435, U. H.

12:30 - 1:20 Pathology Seminar; Relation of Extra Gastric Tumors to Gastric Acidity. Suad Niazu; 104 I. A.

12:30 - 1:30 Physiology Seminar; Histological Evidence of Allergic Mechanisms in Neurotropic Virus Diseases; Berry Campbell; 214 M. H.

12:30 - 1:50 Surgery Grand Rounds; A. A. Zierold, Clarence Dennis and Staff; Minneapolis G neral Hospital.

4:00 - 5:00 School of Public Health Seminar; Subject to be announced; 113 MeS.

Tuesday, January 13

8:30 - 10:20 Surgery Reading Conference; Lyle Hay; Small Conference Room, Bldg. I, Veterans' Hospital.

9:00 - 9:50 Roentgenology Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and Nathanial Lufkin; Veterans' Hospital

12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans' Hospital.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U.H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans' Hospital.

4:00 - 5:30 Surgery-Physiology Conference; O. H. Wangensteen and M. L. Visscher; Eustis Amphitheater, U. H.

5:00 - 5:50 Roentgenology Diagnosis Conference; J. Richards Aurelius and Staff of Ancker Hospital; M-515, U. H.

Wednesday, January 14

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker and Joe R. Brown; Veterans' Hospital.

11:00 - 11:50 Pathology-Medicine-Surgery Conference; Subject to be announced; E. T. Bell, O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

4:00 - 5:00 Infectious Disease Routes; Todd Amphitheater, General Hospital, Veterans' Hospital.

Thursday, January 15

8:15 - 9:00 Roentgenology-Surgical-Pathology Conference; Walter Walker and H. M. Stauffer; M-515, U. H.

8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans' Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans' Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and D. State; Eustis Amphitheater, U. H.

12:00 - 12:50 Physiological Chemistry Seminar; The Uptake of Radioactive Phosphorus by the Calcified Tissues of Normal and Choline Deficient Rats; Arthur Lindenbaum; 214 M. H.

1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.

1:30 - 3:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor West Wing, U.H.

4:00 - 4:50 Bacteriology Seminar; Energy Release from Food; Upjohn Co. film; 214 M. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 5:50 Roentgenology Seminar; Subject to be announced; Robert S. Leighton; M-515, U. H.

7:00 - 8:00 Urology-Roentgenology Conference; H. M. Stauffer and George Eaves; M-515, U. H.

Friday, January 16

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphi., U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphi., U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Staff; Veterans' Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, A. V. Stoesser and Staffs; Minneapolis General Hospital.

11:30 - 12:50 University of Minnesota Hospitals General Staff Meeting; The Possibilities and Limitations of Roentgen Diagnosis; Leo G. Rigler; New Powell Hall Amphitheater.

1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

3:00 - 3:50 Surgery Literature Conference; Clarence Dennis and Staff; Minneapolis General Hospital.

Saturday, January 17

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 21, U. H.

8:00 - 9:30 Psychiatry and Neurology Grand Rounds; Staff; University Hospitals.

9:00 - 9:50 Surgery-Roentgenology Conference; O. H. Wantensteen, L. G. Rigler, and Staff; Todd Amphitheater, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-515, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; M-515, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:00 - 12:20 Anatomy Seminar; Progress in Neuroanatomy during 1947; A. T. Rasmussen; A review of recent work on Cutaneous Localization of the Cerebellar Cortex; Berry Campbell: 226 I. A.

II. THE ETIOLOGY AND EPIDEMIOLOGY OF VIRUS HEPATITIS

Hendrik DeKruif

Introduction

Epidemic jaundice has been recognized by medical men as a disease of troops during wars of the past century. At the same time, although a fatal type of parenchymal necrosis of the liver was known to pathologists, this was not associated with epidemic or sporadic jaundice until 1890[1]. The important interrelationships of these several forms of jaundice were obscured, nevertheless, for half a century more by the predominant belief - originating from Virchow and shared even by many medical officers in the early part of World War II - that the primary lesion was "catarrhal" inflammation of the ampulla of Vater. With the advent of the use of syringes and needles, and later of blood substitutes, on a large scale, still another form of jaundice has appeared and further confused the picture. Recent advances made during the last war have (a) established with fair assurance the virus etiology of the various forms; (b) qualitatively identified non-fatal forms with the fatal form both pathologically[1] and epidemiologically[2]. It is the purpose of this paper to summarize a few of the important properties of the virus presumed to be the etiological agent, and to discuss the possible identity of etiology of the various forms.

Etiology

In the first place, many of the manipulations necessary for thorough etiological study have not been accomplished. The virus has not been observed with the electron microscope[3,14], nor has tissue culture been successful[2]. Many animal transmission experiments, reviewed by MacCallum in 1944[4], have yielded a few apparently positive results. Andersen[5] (1937-8) thought that the Denmark epidemic of infectious hepatitis might be derived from porcine hepatitis. He first accomplished two serial passages in young, slightly underfed pigs by mixing jaundiced pig liver with their mash; and later repeated the experiment (two passages in pigs) starting with duodenal drainage from an early human case. The critical experiment of passage back to man was not accomplished. From an epidemic near Leipsig in 1942, German investigators[6], using urine and duodenal fluid from early cases, apparently accomplished nine passages in canaries. Serial passages in chick embryos were also made[7]. MacCallum and Miles[8] in 1946 used blood and fecal filtrates from infectious hepatitis cases to inoculate young Wistar rats on a diet (4% casein) just deficient enough in certain amino acids to produce microscopic liver lesions in the controls. After three blind passages using the rat organs (liver, spleen), liver necrosis began to appear and then also lymph node hemorrhage (not found in fatal human cases), until by the 14th passage severe lesions were produced in rats on the deficient diet for only seven days. Normally fed rats were not successfully inoculated. None of the above experiments have been confirmed, to my knowledge, although active work on this important problem is being done by the army with the cooperation of the Wild Life Division of the Department of Agriculture. The shortcomings of these experiments may be due to the possibility that many species have their own virus hepatitis, and that the virus homologous for the animal used creeps into an inadequately controlled experiment.

Secondly, attempts to devise a specific serologic test for hepatitis have been no more successful than the animal transmission experiments. Eaton, Murphy and Hanford[9] demonstrated in convalescent serum from patients with homologous serum jaundice an antibody which would fix complement in the presence of antigen prepared either from normal human liver tissue or from liver tissue of fatal human hepatitis. They described this as a heterogenetic antibody, different from the Forssman antibody of infectious mononucleosis in its alcohol solubility and adsorption of red cells of certain species, from reagin of syphilis on the basis of negative re-

actions of the sera of Wasserman - positive luetics, but not definitely different from the antibody found in serum sickness.

Until further fundamental work has been done, therefore, our knowledge of the etiology of hepatitis must be limited to results of human transmission experiments and of direct observation of epidemics. The work on human transmission[10] was done mainly during the last war on small groups of volunteer soldiers and conscientious objectors. The infectiousness of the agent has been fairly well demonstrated by serial passages - three with material from infectious hepatitis and two with material from homologous serum jaundice - as well as by takes with very small (0.003cc serum) doses. Furthermore the agent passes through Seitz EK filters, resists heating to 56° for 30-60 minutes[11, 2], repeated freezing and thawing, and standing at room temperature for a year[3]. In drinking water its resistance to chlorination was found to be somewhat greater than that of the common intestinal pathogens[12]. If there is an appreciable amount of organic material in the water, this must first be eliminated by coagulation and filtration to reduce the B.O.D.; and then concentrations of chlorine after ½ hour must be 1.1 ppm total and 0.4 ppm free. A method for inactivating the agent in plasma has been suggested by Levinson[13]. He showed that one-second exposure of a thin stream of plasma to ultraviolet light did not render the plasma harmful on reinjection into the same species. Oliphant was unable to infect human volunteers with previously icterogenic plasma after such irratiation[14]. Since screening of donors by histories and simple laboratory tests is no guarantee of the freedom of their blood from this virus, such an approach to the problem of homologous serum jaundice would seem logical.

Some of the apparent differences between the naturally acquired disease and the homologous serum form can best be shown in Table I. The natural and artificial forms have been thought of as distinct diseases on the basis of absence of heterologous immunity and differences in incubation period, clinical onset, mortality rates, and percentage of naturally occurring secondary cases[3]. However, Neefe also points out that, although the onset of the disease tends to be sudden in the natural form and is often insidious in the artificail form, one cannot be certain of the origin of an individual case from either history or type of onset. Evidence for the occurrence of natural secondary spread from homologous serum jaundice is not clear cut. Freeman[15] mentions a 36-fold increase of jaundice in the non-vaccinated population of an army camp during the Yellow Fever Vaccine epidemic, and also describes second and third waves at intervals of thirty days. From the distribution of these cases in barracks, however, there could have occurred a separate epidemic of infectious hepatitis. Granted then that all cases of epidemic hepatitis are by definition a "naturally occurring secondary cases", and that secondary spread from homologous serum jaundice has not been proven, the mere portal of entry may account for the presence or absence of virus in the feces.

Differences in mortality rates may also not represent etiological differences. The rate of 0.2% in the large Yellow Fever Vaccine epidemic is approximately the same as the general rate for infectious hepatitis. The higher mortality in wounded soldiers infected by plasma may be related to a poor nutritional state and negative nitrogen balance. The high rates among English children who contracted the disease from measles and mumps convalescent sera seems better explained as the result of a virulent variant.

Homologous immunity has been shown to last for one to one and a half years, at least[16]; but experimental results[17,18] have conflicted on the existence of cross-immunity between the two forms. Neefe's experiments showed susceptibility to challenge with "infectious hepatitis" virus 400 days after homologous serum (plasma and yellow fever vaccine) infections and 200 days after negative challenge with icterogenic plasma. Oliphant found that 10 of 10 previous

cases of Yellow Fever Vaccine jaundice were immune to inoculation with early infectious hepatitis serum; whereas this serum infected 4 of 11 controls. It should be recalled, though, that the source of the Yellow Fever Vaccine hepatitis was probably catarrhal jaundice in Johns Hopkins Medical students[2]. Here again, the important factor would seem to be variation in the virus rather than portal of entry. Confusing factors are lack of knowledge of the true source of the virus, and of the general immune pattern.

Finally, the previously stressed difference in incubation periods has recently been minimized in importance by Aycock and Oren[19], who have tabulated (Table II) examples of prolongation of incubation period (in other diseases as well as in hepatitis) by admixture of immune serum with the etiological agent. For significant numbers they have lumped all the human transmission experiments and show definite prolongation by the parenteral route over the oral. On this basis they suggest that infectious hepatitis may be a reservoir for the artificial form, homologous serum jaundice. It is difficult to see how this disease could have arisen phylogenetically with a distinct etiology in the short time that syringes and needles have found use en masse.

Epidemiology

The epidemiology of the two forms of the disease should, with the reservations imposed by Aycock above, be considered separately because of their portals of entry. Infectious hepatitis has no climatic or seasonal limitations. Racially, the negro seems to be more resistant than the white. Epidemics in Iceland[20] and Denmark[5] have had a much higher incidence in rural than in urban districts, and Andersen has interpreted this as favoring the theory of fecal-oral spread over droplet spread. Persons aged 5 to 30 show the greatest susceptibility[21], but more of the cases in children are mild and non-icteric. Epidemics spread characteristically through families, summer camps, orphan asylums, and military units of company strength, and occur usually where there is breakdown of good general sanitation. They often begin and spread slowly, because of the long incubation period, but gross contamination of a water supply can cause a great concentration of cases all at once. The military importance of infectious hepatitis was only too obvious to many medical officers; it has involved 40 - 50% of commands in an illness requiring around six weeks' hospitalization. About 10% of cases relapsed or became subacute or chronic. Some of these may yet become important to civilian medicine as cholangiolitic cirrhosis[21]. In military experience, the disease often was accompanied by such intestinal infections as amebic dysentery and salmonellosis. Epidemics have been attributed to milk and food[10] as well as to water. The possibility of droplet spread has not been ruled out. Precautions to prevent spread of infectious hepatitis should include avoidance of contact, sterilization of trays and eating utensils, personal hygiene and stool precautions similar to those used for typhoid fever, screening from flies - all for at least a month after onset of the disease. Protection of specimens and avoidance of use as blood donors are obvious additional steps. Spread through hospital wards has not been a feature of the disease. Immune serum globulin given in the incubation period has prevented the disease during epidemics in Pennsylvania, the middle east, and in New Haven[22].

Homologous serum jaundice, on the other hand, is spread only by means of human blood, plasma, serum and lymph[22]. Such small doses can be infective that transmission can result from incomplete sterilization of syringes and needles in large diabetic and syphilis clinics, and probably even by finger-puncture needles used for hematological work. The late form of post arsphenamine jaundice - (approximately half the cases of jaundice following arsphenamine) is now thought to be at lease partly due to hepatitis virus. Thus precautions to take to prevent this disease are (a) sterilization

of instruments after each use by boiling, not merely by soaking in disinfectant solutions such as mercuric chloride or alcohol; (b) no use as blood donor for at least a year, and preferably not at all. Immune serum globulin, given to a large number of patients during the incubation period, has not prevented nor modified the disease, but has prolonged the incubation period[23]. Susceptibility to the serum-transmitted form increases with age, in contrast to the natural form, a point of importance to civilian blood substitute therapy.

In Germany in 1883-1884 an epidemic of hepatitis with incubation period of 1-2 months, was caused by "humanized" vaccinia lymph[15]. More recent epidemics resulting from transfer with blood derivatives are tabulated (Table III). In 1937 Findlay recognized that jaundice was being transmitted with Yellow Fever Vaccine, but thought that the agent was derived from serum used in the attenuation of the Yellow Fever virus. Later the human serum used to facilitate lyophilization of the final product was incriminated[2]. An interesting feature of these epidemics is the moderate (10-50 donor) size of the pools that have been most infective. Individial units are often infective, of course; but are less important as a cause of great numbers of cases. Huge pools of the type used in the American Red Cross fractionation program (50,000 donors) have not been infective, possibly because of the more certain admixture of antibodies. Immune globulin alone has not transmitted the disease[22]. Human albumin can be heated to 60° C for 10 hours to inactivate the virus. It is hoped that some such treatment as ultraviolet irradiation will be found as safe and effective in the case of whole blood and plasma.

Table I

	Infectious Hepatitis	Homologous Serum Jaundice
I Incubation Period	17-43 days	60-150 days
II Onset	Sudden, c̄ high fever	sometimes insidious
III Secondary cases (Naturally occurring)	all	???
IV Mortality	0.2%	0.2% to 6-19% (British)
V Viremia	late incubation period early active disease healthy carriers	Most of incubation pd. during active disease healthy carriers.
VI Transmission	orally and parenterally	parenterally; ??? orally
VII Virus in feces	yes	Not demonstrated
VIII Immunity		
Homologous	yes	yes
Heterologous	??	??
IX Y - Globulin	prevents	lengthens incubation

Table II

Variation of Incubation Period[19]

Agent	Added Immune Bodies or Route of Inoculation	Incubation Period	Percent Prolongation
I Poliomyelitis	Normal Monkey serum	8.3	72
	human convalescent serum	14.3	
II Influenza	1:800 Y - Globulin	6.2	
	1:100 Y - Globulin	8.7	40
III Homologous*	Controls	34.1	
Serum jaundice	Y - Globulin	52.8	55
IV Infectious Hepatitis	Feces, serum-enterally	28.4	
	serum parenterally	61.6	117
V Homologous Serum jaundice	Feces, serum-enterally	46.1	
	serum-parenterally	87.8	90
IV & V	Feces - enterally	29.9	
	serum - enterally	38.8	30

* (23) 29 j : 2406 $\bar{p}$ Y - globulin
23 j : 2374 in controls

Table III

Epidemics of Homologous Serum Jaundice

	Source	Material	Immunized	Jaundiced	Mortality	Incubation Period, days	Dose of icterogenic serum(cc)	Rx of serum	Size of pools
I	Bremen 1883-4 (Hirsch)	humanized vaccinia lymph	1289	191	?	60	?	glyceri nated	?
II	England 1938	Measles convalescent serum	107	44	10	?	4.5	?	?
III	Russia 1940	Sandfly fever; human immune serum	500	92	1+	63-146	0.01	?	?
IV	England 1941	Mumps convalescent serum	165	79	?	58-86	?	Merthiolate 1:2000	11
V	U.S. Army 1942	Serum J.H. Med. Stud. (endemic inf. hepatitis)	2,954,000	26,771	0.2%	?90	0.003	57°C for 30-60	13
VI	England 1943	Measles Convalescent serum	109	37	8	16-161	10	Phenol 0.25% ether 0.25%	?

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