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Infectious Hepatitis

Evidence for Two Distinctive Clinical, Epidemiological, and Immunological Types of Infection

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The identification of two types of infectious hepatitis with distinctive clinical, epidemiological, and immunological features provided an explanation for the occurrence of second attacks of the disease. One type resembled classical infectious hepatitis (IH); it was characterized by an incubation period of 30 to 38 days, a relatively short period of abnormal serum transaminase activity (3 to 19 days), a consistently abnormal thymol turbidity, and a high degree of contagion. The other type resembled serum hepatitis (SH); it was characterized by a longer incubation period (41 to 108 days), a longer period of abnormal transaminase activity (35 to 200 days) and a relatively normal thymol turbidity. Contrary to commonly accepted concepts, the SH type was moderately contagious. Patients with IH type were later proved to be immune to the same type. Patients with the SH type were not immune to the IH type infection.

Infectious hepatitis has been recognized as an endemic disease at the Willowbrook State School, Staten Island, NY, since 1953. As a result of this endemic environment, 1,153 cases of infectious hepatitis with jaundice were observed to have been transmitted by natural contact in this institution during the past 12 years. Second attacks with jaundice have occurred in 63 patients or 5.5% of this group. In most instances the second attack of jaundice occurred within one year but occasionally as late as four and seven years after the first attack. One possible explanation for second attacks would be the existence of multiple types of infectious hepatitis virus, immunologically separate and distinct. Examples of this phenomenon have been observed in enterovirus, adenovirus, and myxovirus infections. The studies reported in this communication provide evidence for the presence of two distinctive clinical, epidemiological, and immunological types of infectious hepatitis.

The nature of the endemic situation at the Willowbrook State School has been described in detail in previous reports.[1-3] Briefly, infectious hepatitis was first noticed among Willowbrook patients as early as 1949. From 1949 to 1963 the patient population increased from a mere 200 to over 6,000. As the population increased and new susceptible children were admitted, hepatitis found a continuous foothold. Attempts to relieve overcrowding have now reduced this population to approximately 5,400 mentally retarded patients, predominantly children, who are distributed among 24 buildings. The constant admission of many susceptible children and the natural transmission of the disease via the intestinal-oral route have been responsible for the continuing endemic situation. Many of the patients are incapable of being toilet trained and prone to put everything that they pick up into their mouths. This intensifies the problem of control. Under the chronic circumstance of multiple and repeated natural exposure, it has been shown that most newly admitted children become infected within the first 6 to 12 months of residence in the institution.

For editorial comment see page 406.

Prior experience indicated that γ-globulin did not prevent hepatitis infection; it attenuated the disease. Eleven separate dosage trials with γ-globulin have been undertaken since 1956 in an attempt to reduce the number of clinical cases of infectious hepatitis in the institution. The direct measurable result of these programs was a reduction of approximately 85% of icteric hepatitis among patients and employees at Willowbrook. With the realization that subclinical cases persisted and were contagious, elimination of the disease could not be accomplished. In the absence of an effective vaccine, the study on the natural history of infectious hepatitis in this institution was therefore considered an important step toward better understanding and future control of this infection. The benefits of such a program to the entire institution were obvious. It

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remained then to assess the risks and the benefits to the children who would be active participants in the study.

The decision to propose the controlled infection of a small number of newly admitted children was based on the following considerations:

1. It was well recognized that infectious hepatitis was a mild and relatively benign disease in children as compared with adults; most cases were anicteric and asymptomatic. Experience at Willowbrook indicated that the disease observed at this institution was especially mild. Consequently, only the Willowbrook strains of infectious hepatitis virus would be used for the study.

2. The study group would include only children whose parents gave written consent after being informed of the details, potential risks, and potential benefits of the investigation.

3. The study would be carried out in a special isolation unit with special medical and nursing personnel to provide close observation and optimum care. Thus, these children would be protected from other endemic diseases in the institution, such as shigellosis, parasitic infections, respiratory infections, and other infectious diseases. Experience has indicated that the children in the special isolation unit were subjected to *less* risk than the children who were admitted directly to the institutional wards.

4. It is important to emphasize that the studies were to be carried out at the Willowbrook State School because of the local endemic situation, and *not* because the children were mentally retarded.

Observations on approximately 250 children who acquired artificially induced hepatitis in the Willowbrook study since 1956 revealed that the experimental disease was generally milder than the observed natural infection. In fact, many cases would have gone unrecognized if it had not been for careful daily observation and serial biochemical tests of liver function.

The studies were reviewed and sanctioned by the University Committee on Human Experimentation, by the New York State Department of Mental Hygiene, and by the Armed Forces Epidemiological Board. The Willowbrook studies have been conducted in accordance with the World Medical Association's Draft Code of Ethics on Human Experimentation.[4] The guidelines which were adopted for the study at its inception in 1956 conform with the following general principles of the Code of Ethics: (1) that where children are to be the subject of an experiment, the nature, the reason, and risks of it should be fully explained to their parents or lawful guardians, who should have complete freedom to make a decision on behalf of the children; (2) that children in institutions and not under the care of relatives should not be the subject of human experiment; (3) that the experiment should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man; (4) that during the course of the experiment the subject of it should be free to withdraw from it at any time; (5) that the investigator, or investigating committee, or any scientifically or medically qualified person associated with him or the committee should be free to discontinue the experiment if in his or their judgment it may, if continued, be harmful to the subject of the experiment; (6) that any risk to which the subject of an experiment may be exposed should be carefully assessed in terms of direct benefit to himself or indirect benefit to others, on the assumption that the risks have been explained to, and freely accepted by, the subject of the experiment.

Materials and Methods

The children in the various study groups were 3 to 10 years of age. They were admitted directly to a special isolation facility capable of housing up to 16 children. The number of children included in each study generally ranged between 6 and 14. They had no contact with the rest of the institution and were cared for by physicians, nurses, and attendants who had minimal contact with other patients and personnel.

Source of Hepatitis Virus.—Blood serum from patients in the Willowbrook study provided the source of infectious virus. The material was tested for safety to rule out the presence of adventitious bacterial viral, or mycotic agents. The serum was inoculated into suckling mice and into the following tissue cultures: rhesus monkey kidney, human embryonic lung fibroblasts, and the WISH strain of continuous human amnion cells. No cytopathic changes were seen in tissue cultures and no illness was observed in the animals.

Biochemical Tests of Liver Function.—In addition to careful clinical observation for presence of jaundice, hepatomegaly, and other manifestations of hepatitis, tests of the following were performed at periodic intervals: serum bilirubin, thymol turbidity, serum glutamic oxalacetic transaminase (SGOT) and bilirubin in the urine. Blood was obtained before exposure and at weekly intervals or more often thereafter. The following methods were employed: serum bilirubin(Malloy and Evelyn[5]), thymol turbidity (Maclagan[6]) and SGOT (Karmen[7]). A result was considered abnormal if the serum bilirubin value was more than 1.0 mg/100 ml; the thymol turbidity more than 6 units, and for the purpose of the present study if the SGOT was 100 units or more.

Criteria for Diagnosis of Hepatitis.—The occurrence of clinical jaundice associated with an abnormal serum bilirubin and an abnormal SGOT was required for a diagnosis of hepatitis with jaundice. The diagnosis of hepatitis without jaundice was reserved for cases in which the serum bilirubin value was less than 1.0 mg/100 ml but in which a crescendo-like rise in SGOT activity exceeded 100 units.

Definition of Incubation Period.—The method of determining the incubation period of infectious hepatitis has varied in many studies. Most often, it has been measured as the number of days between ex-

posure and either onset of symptoms or onset of jaundice. It is well known that jaundice may occur as early as two days or as late as two weeks after the first sign of illness. Moreover, experience at Willowbrook indicated that most cases of infectious hepatitis were anicteric and asymptomatic. Consequently, under the conditions of the present study the incubation period was usually defined as the number of days between exposure and first evidence of abnormal serum transaminase activity as indicated by a SGOT level above 100 units.

The evidence for the presence of two types of infectious hepatitis was accumulated from a series of seven separate trials which were carried out during the period from September 1964 to January 1967.

First Trial

Willowbrook serum pool No. 5 (WSP-5) was used for the first trial. It was prepared from specimens obtained three to seven days before onset of jaundice in 27 Willowbrook study patients. On Sept. 23, 1964, WSP-5 was fed to 11 of 13 newly admitted subjects in a dose of 1.0 ml. Two children served as controls. All subjects were intimately exposed to each other but were isolated from other Willowbrook patients.

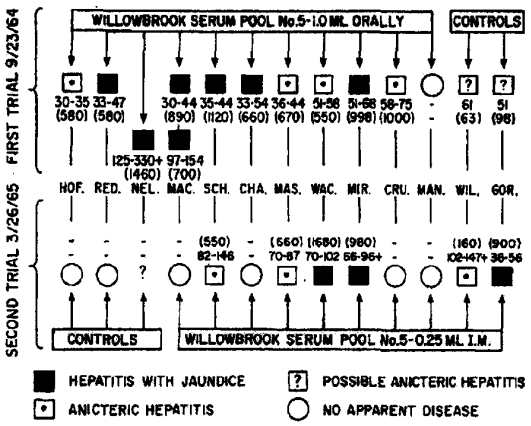
Results.—As indicated in Fig 1, oral administration of WSP-5 was followed by hepatitis in ten of 11 subjects. The incubation periods ranged between 30 and 36 days in six children, and between 51 and 58 days in three; in one child evidence of hepatitis was first detectable on the 125th day. Patient Mac had a spontaneous second attack of hepatitis on the 97th day, 67 days after onset of the first attack. At least one of the two unfed controls may have had possible anicteric hepatitis. Jaundice was observed in six of ten subjects with hepatitis.

Second Trial

The second trial was undertaken to study the problem of second attacks of hepatitis. On March 26, 1965, WSP-5 was given to ten of 13 subjects who had participated in the first trial six months previously. The dose was 0.25 ml intramuscularly. Three additional subjects were uninoculated controls. All 13 subjects were isolated from other Willowbrook patients from the beginning of the first trial until the termination of the second trial.

Results.—As indicated in Fig 1, hepatitis was observed in six of ten subjects who were inoculated with WSP-5. The incubation periods ranged between 38 and 102 days. The occurrence of hepatitis in four subjects (Sch, Mas, Wac, and Mir) represented second attacks.

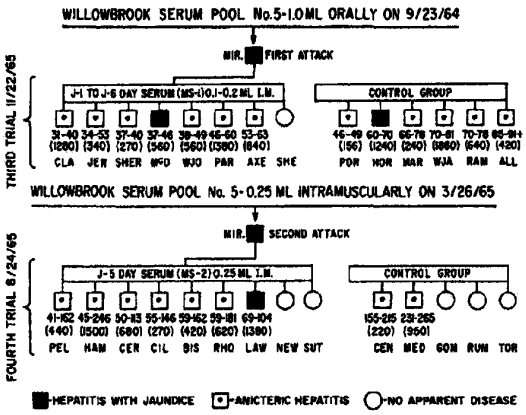
As indicated in Fig 1, the following differences were apparent when the results of the first two trials were compared: (1) During the first attack of hepatitis in four subjects (Sch, Mas, Wac, and Mir) the incubation period ranged between 35 and 51 days; it was longer during the second attack, ranging between 66 and 82 days. (2) Duration of abnormal SGOT activity was relatively short (5 to 17 days)



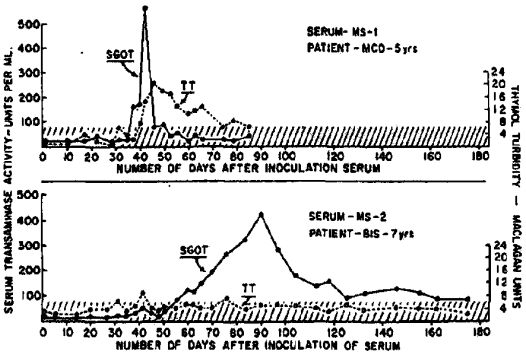
1. *First trial*, occurrence of first attack of hepatitis after subjects were fed Willowbrook serum pool No. 5 (WSP-5). *Second trial*, occurrence of second attacks of hepatitis in same subjects following inoculation of WSP-5 six months later. First number indicates first day SGOT exceeded 100 units/ml; second number, first day SGOT declined to levels below 100 units; numbers in parentheses, peak SGOT levels.

in most patients during the first trial; it was much longer (17 to 64 days) during the second trial. These findings suggested the possibility that the two attacks of hepatitis were caused by two different viruses.

During the course of the first two trials, serial samples of serum were obtained before and after onset of first and second attacks of hepatitis in individual subjects. This material was stored in the deep freeze at −20 C. Serum specimens from subject Mir were selected for special study. It was postu-



2. *Third trial*, occurrence of hepatitis in subjects who received serum (MS-1) obtained from patient Mir during first trial. Note onset of hepatitis after relatively short incubation period: relatively short period of abnormal transaminase activity; and high attack rate in control group. *Fourth trial*, occurrence of hepatitis in subjects who received serum (MS-2) from patient Mir during second trial. Note longer incubation period, longer period of abnormal transaminase activity, and contact infection in two of five control subjects.



3. Pattern of serum transaminase (SGOT) and thymol turbidity (TT) activity response after inoculation of serum from first attack (MS-1) and second attack (MS-2). Note spiking rise and precipitous fall of SGOT and abnormal TT activity following MS-1 infection. In contrast, note gradual rise and prolongation of SGOT activity and normal TT following MS-2 infection.

lated that blood obtained during the week prior to onset of the first attack of jaundice should contain the virus responsible for the first attack. It was also postulated that blood obtained six months later should contain neutralizing antibody against the virus responsible for the first attack, and consequently, if the second attack serum were infectious, it would suggest the presence of an immunologically distinct type of virus.

The serum specimens obtained from subject Mir prior to the first attack were pooled and designated MS-1. This material was used for the third trial. The serum specimens from the same subject immediately before the second attack were designated MS-2 and were used for the fourth trial.

Third Trial

Fourteen newly admitted subjects participated in the third trial. On Nov 22, 1965, a pool of MS-1 serum was given intramuscularly to eight subjects; the dose was 0.1 to 0.2 ml. Six subjects were uninoculated controls. All children were intimately exposed to each other during the course of the trial.

Results.—The results of the third trial are shown in Fig 2 and Table 1. Hepatitis was observed in seven of eight subjects who were inoculated with MS-1 serum; the incubation periods ranged between 31 and 53 days. A transient jaundice with a slight elevation of serum bilirubin (1.4 mg/100 ml) was present for one day in one patient, subject McD. The remaining six children had anicteric hepatitis. The results of serial biochemical tests of liver function in the seven inoculated children infected with MS-1 serum are listed in Table 1 which shows (1) the spiking rise and precipitous fall in SGOT activity and (2) the presence of abnormal thymol turbidity in all seven patients.

All six subjects in the uninoculated, intimately exposed control group contracted hepatitis 46 to 85 days after the beginning of the third trial. Jaundice was observed in only one of the six control children (Hor). The observation of contact infection after 46 days indicated that hepatitis caused by MS-1 serum had an incubation period of 31 to 38 days.

Fourth Trial

Fourteen newly admitted children participated in the fourth trial. On Aug 24, 1965, MS-2 serum was given intramuscularly to nine subjects; the dose was 0.25 ml. The specimen of MS-2 serum was obtained five days before onset of the second attack of jaundice. Five subjects were uninoculated controls. All 14 children were intimately exposed to each other during the course of the trial.

Results.—As indicated in Fig 2 and Table 2, hepatitis was observed in seven of nine subjects who were inoculated with MS-2 serum. The incubation periods ranged between 41 and 69 days. Jaundice

Table 1.—Serial Liver Function Tests in Seven Children Infected With MS-1 Hepatitis Serum

Day After Exposure	CLA		JEN		SHER		MCD		W JO		PAR		AXE	
	TT*	SGOT†	TT	SGOT	TT	SGOT	TT	SGOT	TT	SGOT	TT	SGOT	TT	SGOT
0	4	34	2.5	14	3	19	<1.2	21	<1.2	16	4.0	26	2.5	26
10	2.7	27	1.2	20	3.2	28	<1.2	20	<1.2	16	1.8	27	3	27
16	2.5	28	4	34	4.2	42	3.5	18	<1.2	21	3	21	2.1	27
22	2.7	20	5.7	27	8.7	42	2.1	42	1.8	26	2.7	20	3	22
28	6.2	84	<1.2	50	7.5	27	1.2	16	2.1	18	3	16	7.5	24
31	6.5	1,280	2.1	40	4.5	20	5.7	21	1.8	12	5	21	6	16
34	...	...	8	310	...	...	...	...	...	...	...	...	...	...
35	12.5	120	12.5	160	13.7	24	3.2	24	2.1	14	4.2	10	6.5	20
37	11.2	170	15.5	340	6.2	270	2.1	170	1.2	86	2.1	17	...	...
40	12.5	56	25	138	7.5	84	7.5	180	3	560	4.2	40	5	14
42	10	39	25	140	8.2	40	14.8	560	7.5	420	7	22	4.5	19
46	6.5	48	22	91	10	34	21	75	6.7	114	5	128	1.2	20
49	6.2	29	27	126	7.7	27	18	84	5.5	51	3	750	7	21
51	...	...	...	...	...	...	...	...	...	...	7	1,380	...	...
52	...	...	...	...	...	...	...	...	...	...	7.5	940	...	...
53	...	...	21	64	8.5	50	17.5	39	13.4	56	9.2	740	11	840
55	...	...	...	...	...	...	13	48	...	...	13	600	...	...
56	8	49	22.2	34	8.5	41	...	...	11.7	46	11	480	16	560
58	...	...	...	...	...	...	...	...	...	...	...	...	15	138
60	4.2	21	17.5	44	8.7	35	10.5	20	11.2	44	9.5	60	22	106
63	7	42	16.4	57	11	18	11.5	42	8.7	18	13	34	16.5	49

*Thymol turbidity, units.
†Serum glutamic oxaloacetic transaminase, units/ml.

occurred in one patient, Law, on the 83rd day, 14 days after first evidence of abnormal SGOT activity (> 100 units). The remaining six children had anicteric hepatitis. The results of serial tests of liver function shown in Table 2 reveal a gradual rise and a prolonged persistence of SGOT activity. Thymol turbidity was normal in five of seven subjects.

Anicteric hepatitis was observed in two of the five uninoculated control subjects, 155 and 231 days after the beginning of the fourth trial. Hepatitis occurred in contact Cen, 86 days after onset of the disease in subject Law. Hepatitis in contact Med occurred 76 days after onset of hepatitis in contact Cen.

A comparison of the results of the third and fourth trials revealed the following differences: (1) Incubation period ranged from 31 to 38 days (mean of 35 days) following MS-1 infection, as compared with 41 to 69 days (mean of 54 days) following MS-2 infection. (2) Abnormal serum transaminase activity was relatively short (3 to 19 days) following MS-1 infection and relatively long (35 to 200 days) after MS-2 infection. (3) Thymol turbidity was consistently abnormal after MS-1 infection; it was frequently normal after MS-2 infection. (4) Contagion—MS-1 infection was highly contagious for all six presumably susceptible contacts; MS-2 infection was less contagious, spreading to only two of five presumably susceptible contacts.

The striking contrast in the pattern of SGOT and thymol turbidity response is illustrated in Fig 3. MS-1 infection in subject McD (third trial) is characterized by a spiking rise in SGOT activity followed by a rise in thymol turbidity. In contrast, MS-2 infection in patient Bis (fourth trial) is characterized by a normal thymol turbidity and a gradual, prolonged rise in SGOT activity.

The results of the first and third trials clearly demonstrated that infectious hepatitis virus MS-1 type was infectious by mouth and the disease was highly contagious. The results of the fourth trial indicated that infectious hepatitis MS-2 type was less contagious but it did spread to susceptible contacts. The fifth and sixth trials were designed to test the infectivity of MS-2 serum by mouth. The sera to be tested were obtained from subjects Ham and Pel who had a typical MS-2 type infection (fourth trial).

Fifth Trial

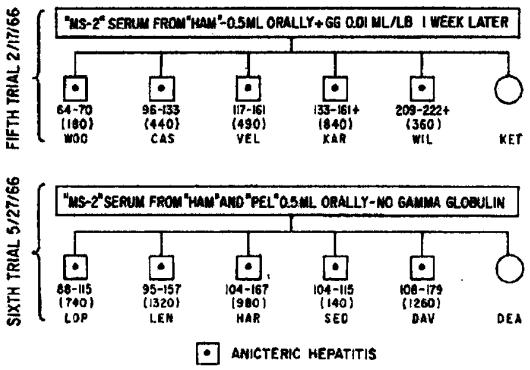
Nine newly admitted children participated in the fifth trial. On Feb 17, 1966, MS-2 type serum obtained from subject Ham was given to six subjects. The dose was 0.5 ml by mouth; three children were unfed controls. One week later the six children received γ-globulin, 0.01 ml per pound of body weight intramuscularly. The use of γ-globulin was a precautionary measure because of limited experience with MS-2 type of infectious hepatitis virus.

Results.—The results of the fifth trial are shown in Fig 4. Anicteric hepatitis was observed in five of

Table 2.—Serial Liver Function Tests in Seven Children Infected With MS-2 Hepatitis Serum

Day After Exposure	PEL		HAM		CER		CIL		BIS		RHO		LAW	
	TT*	SGOT†	TT	SGOT	TT	SGOT	TT	SGOT	TT	SGOT	TT	SGOT	TT	SGOT
0	4.9	16	3	16	1.2	10	<1.2	34	3	12	2.1	18	1.2	8
6	6.7	<8	2	16	2	12	1.2	30	1.2	12	3	21	4	20
14	7	16	4.2	19	4.2	12	1.5	16	1.2	<8	2.2	10	2.2	16
20	9.5	15	7.5	34	3	9	1.2	26	3.7	14	3	18	4	10
27	5.7	20	2	19	1.5	8	<1.2	19	3.5	10	3.5	18	1.5	11
31	6.5	18	3.7	20	6	11	1.5	18	6.2	16	3.5	13	3	8
34	4.2	31	3	41	1.7	10	<1.2	16	3.2	14	2.5	15	2.2	4
37	6.7	50	3	52	3	18	<1.2	28	4.7	31	3.2	26	3.2	21
41	8	129	6.5	54	3	15	1.2	33	8.2	41	4.2	26	2.7	12
45	5.5	340	6.5	111	<1.2	30	<1.2	37	4	32	3.2	29	<1.2	15
48	7.7	410	1.5	150	3	89	<1.2	50	3.2	22	2.7	25	4	15
50	7.7	350	4.2	380	4	152	<1.2	80	4.2	40	2.5	31	2.5	20
55	5.5	440	2.5	950	13	680	1.2	180	4	78	2.5	60	1.2	61
59	6.7	410	8.2	1,120	20.2	420	<1.2	240	5	119	4	124	2.5	56
62	5.5	340	5.5	1,390	22	200	2.5	200	5	112	5.2	160	3.5	49
66	6.2	420	6	1,500	10.5	120	3	140	4.2	140	3	150	2.1	84
69	7.7	340	5	1,320	7.5	150	3	220	4.5	190	3	410	4.5	120
76	5.2	250	5.2	940	4.2	150	3.7	270	6.7	260	5.5	620	10	750
83	6.5	200	2.1	760	3.2	510	<1.2	180	3.7	320	2.1	480	15	1,060
90	8.7	410	3	560	6	340	2.1	260	5	420	5	580	11.5	1,250
97	6.5	270	2.5	200	6.2	200	4.2	220	5.2	280	4.2	400	13.7	1,380
104	7	220	5	110	7.2	140	2.5	166	5	176	6.2	620	9	120
113	6.2	188	3	170	10	78	<1.2	210	4.5	142	6.7	560	6.5	94
118	6.2	176	2.5	190	5.5	56	<1.2	184	3	156	4	440	6	42
126	4.5	120	2.1	140	5.5	14	1.8	146	5.7	96	7.5	132	...	...
132	5	124	2.5	144	5	20	2.5	180	4	106	3.5	112	2.1	14
146	5	124	4	490	3.5	34	7.5	90	5	124	7	340	3.2	20
150	...	...	<1.2	670	...	...	...	...	...	...	3	132	...	...
155	6	148	4.7	420	7	27	5.7	84	5	112	6	160	4	22
162	7.5	74	2.5	220	5	27	5.2	98	4	88	10	160	4.5	22
174	6.2	140	3.2	170	1.2	32	6	94	2.7	84	6.5	172	...	...
181	5	54	1.8	126	2.5	14	1.8	36	2.1	27	4.2	84	...	...
189	5	114	2.1	118	...	...	...	...	2.1	76	4.5	106	4	15

*Thymol turbidity, units.
†Serum glutamic oxaloacetic transaminase, units/ml.



4. *Fifth and sixth trials*, oral administration of MS-2 serum followed by anicteric hepatitis in ten of 12 subjects after long incubation periods. First number indicates first day that SGOT exceeded 100 units/ml; second number, first day the SGOT declined to levels below 100 units; numbers in parentheses, peak SGOT levels.

six presumably susceptible subjects. The incubation periods ranged between 64 and 209 days. The duration of abnormal SGOT activity was prolonged and the thymol turbidity response was normal in three of five subjects with hepatitis. All children were clinically normal. They were asymptomatic and they gained weight. Hepatitis was not observed in the three children who were unfed controls.

Sixth Trial

The fifth trial indicated that infectious hepatitis virus MS-2 type was infective by mouth. It was considered important to confirm this observation. Accordingly, on May 27, 1966, MS-2 type serum from subjects Ham and Pel was given to six presumably susceptible newly admitted subjects; the dose was 0.5 ml by mouth. Gamma globulin was not administered.

Results.—As indicated in Fig 4, the results of the sixth trial were similar to the fifth trial. Anicteric asymptomatic hepatitis was observed in five of six subjects after prolonged incubation periods ranging between 88 and 108 days. The SGOT activity was prolonged and the thymol turbidity response was compatible with a MS-2 type of infection.

The previous six trials provided evidence for two types of infectious hepatitis with distinctive clinical and epidemiological features. The seventh trial was designed to study the immunological aspects of the disease following MS-1 type infection (third trial) and MS-2 type infection (fourth trial).

Seventh Trial

The sixteen subjects who participated in the seventh trial included eight children from the third trial and eight children from the fourth trial. The entire group was isolated from other institutional patients during the entire period of the study. On March 28, 1966, four months after the third trial and seven months after the fourth trial, all 16 subjects were inoculated with infectious hepatitis serum, MS-1 type; the dose was 0.2 ml. intramuscularly.

Results.—Evidence for homologous immunity following MS-1 infection is presented in Fig 5. The initial inoculation of MS-1 serum on Nov 22, 1965, had been followed by infectious hepatitis in seven of eight subjects; the pattern of serum transaminase and thymol turbidity activity was typical of MS-1 infection. Subsequent challenge with infectious MS-1 serum on March 28, 1966, revealed no evidence of hepatitis with or without jaundice; all eight subjects were immune.

Lack of heterologous immunity in subjects first infected with MS-2 virus is shown in Fig 6. The initial inoculation of MS-2 serum on Aug 24, 1965, was followed by infectious hepatitis in six of eight subjects; the pattern of transaminase and thymol turbidity activity was typical of MS-2 infection. Subsequent challenge with infectious MS-1 serum on March 28, 1966, was followed by hepatitis in all eight subjects. The pattern of the SGOT and thymol turbidity response in this second attack was characteristic for MS-1 type of infection. Thus, inoculation of MS-1 serum was followed by hepatitis in five of six subjects who had a previous infection caused by MS-2 serum (Fig 6). In contrast, the same MS-1 serum produced no evidence of infection in seven subjects who had a previous attack

	RESULTS OF INOCULATION WITH MS-1 SERUM (11/22/65)				RESULTS OF CHALLENGE WITH MS-1 SERUM (3/28/66)
SUBJECT	TYPE OF HEPATITIS	ABNORMAL SGOT ACTIVITY PEAK LEVEL UNITS/ML	ABNORMAL SGOT ACTIVITY DURATION DAYS	PEAK THYMOL TURBIDITY UNITS/ML	TYPE OF HEPATITIS
AXE	⊡	840	10	22.0	○
MAR	⊡	240	12	13.5	○
MCD	■	560	9	21.0	○
JEN	⊡	340	19	27.0	○
SHR	⊡	270	3	10.0	○
WJA	⊡	1880	11	15.0	○
WJO	⊡	560	11	13.4	○
SHE	○	-	-	-	○

■ HEPATITIS WITH JAUNDICE ⊡ ANICTERIC HEPATITIS ○ NONE

5. Evidence for homologous immunity following MS-1 hepatitis infection.

	RESULTS OF INOCULATION WITH MS-2 SERUM (8/24/65)				RESULTS OF CHALLENGE WITH MS-1 SERUM (3/28/66)			
SUBJECT	TYPE OF HEPATITIS	ABNORMAL SGOT ACTIVITY PEAK LEVEL UNITS/ML	ABNORMAL SGOT ACTIVITY DURATION DAYS	PEAK THYMOL TURBIDITY UNITS/ML	TYPE OF HEPATITIS	ABNORMAL SGOT ACTIVITY PEAK LEVEL UNITS/ML	ABNORMAL SGOT ACTIVITY DURATION DAYS	PEAK THYMOL TURBIDITY UNITS/ML
RHO	⊡	620	122	5.5	■	1500	15	32.0
PEL	⊡	440	121	8.0	⊡	830	15	15.5
CER	⊡	680	63	22.0	⊡	510	14	20.0
BIS	⊡	420	103	5.0	○	-	-	-
HAM	⊡	1500	200	7.5	⊡	1360	15	25.0
MED	⊡	950	34	7.5	■	1040	17	40.0
SUT	○	-	-	-	⊡	380	14	15.7
GOM	○	-	-	-	■	750	14	21.2

■ HEPATITIS WITH JAUNDICE ⊡ ANICTERIC HEPATITIS ○ NONE

6. Evidence for lack of heterologous immunity following MS-2 hepatitis infection.

of hepatitis caused by MS-1 serum (Fig 5). These observations indicate that the two types of hepatitis virus are immunologically distinct.

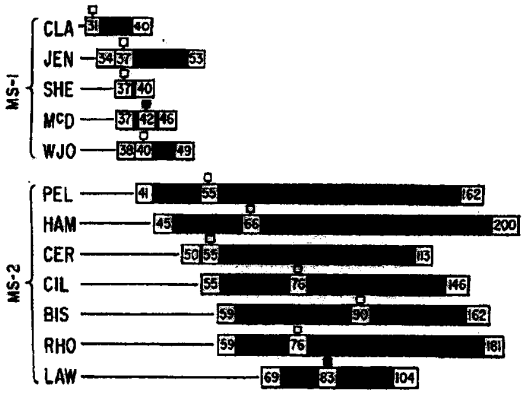
Comment

The data accumulated during the course of these studies confirm the presence of two types of infectious hepatitis in Willowbrook. In the series of seven trials it has been possible to identify distinctive clinical, epidemiological, and immunological features characteristic of each type of infection. The two types of hepatitis were caused by two different viruses, designated as MS-1 and MS-2. MS-1 virus was derived from the serum of a patient during the first attack of hepatitis; MS-2 virus was derived from the serum of the same patient six months later.

The disease associated with MS-1 virus infection is undoubtedly the classical type of infectious hepatitis, a disease also known under the following aliases: infective hepatitis, IH hepatitis, virus A hepatitis, and in former years, acute catarrhal jaundice and epidemic jaundice. The disease associated with MS-2 virus infection resembles serum hepatitis which has also been referred to as homologous serum jaundice, SH hepatitis, virus B hepatitis, post-transfusion hepatitis, and postvaccinial hepatitis. A comparison of the incubation period, thymol turbidity pattern, and epidemiological and immunological aspects provides evidence supporting the relationship of MS-1 to infectious hepatitis (IH) and MS-2 to serum hepatitis (SH).

Incubation Period.—The incubation period of infectious hepatitis has been reported to range between 15 and 50 days[1,8-11]; the mean is approximately 30 to 35 days. In contrast, the incubation period of serum hepatitis has been observed to be much longer, generally ranging between 43 and 180 days with most cases occurring between 60 and 90 days.[9,11,12] In natural disease, especially infectious hepatitis, the limits of the incubation period are often ill-defined because the precise time of infection is unknown. Incubation periods following MS-1 and MS-2 types of infection are charted in Fig 7. Two types of incubation period have been recorded: (1) the interval between the time of exposure and first sign of hepatic involvement, as indicated by an increase in SGOT above 100 units/ml; and (2) the interval between time of exposure and peak SGOT or onset of jaundice. Experience at Willowbrook has indicated that onset of jaundice generally occurs at the time of peak transaminase activity. As indicated in Fig 7, the incubation period following MS-1 infection was 31 to 42 days; the mean was 37 days. In contrast, MS-2 infection occurred after an incubation period of 55 to 90 days; the mean was 71 days. The similarity of MS-1 to IH and MS-2 to SH is obvious.

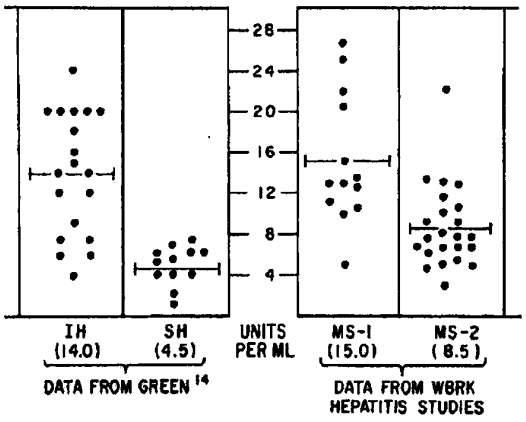
The mode of transmission did not affect the incubation period of MS-1 type of infection; it was essentially the same following oral and parenteral exposure. On the other hand, the incubation period



7. Comparison of incubation period and abnormal SGOT activity following MS-1 and MS-2 hepatitis infection. Note relatively long incubation period, more prolonged period of abnormal SGOT activity following MS-2 infection, also delay in onset of jaundice or peak SGOT activity following MS-2 infection. First number indicates time interval in days, from exposure to first increase in SGOT above 100 units; black square, day of onset of jaundice; white square, day of peak transaminase; last number, first day the SGOT declined to levels below 100 units.

of MS-2 type of infection was longer following oral exposure (sixth trial) than parenteral inoculation (fourth trial).

Thymol Turbidity Pattern.—Reports by Neefe[13] and by Green[14] have indicated that the thymol turbidity test is often negative in serum hepatitis. Neefe stated that "In two small but closely comparable groups of patients with induced virus IH hepatitis and virus SH hepatitis, respectively, the responses to the serum colloidal gold and the thymol (turbidity and flocculation) tests were less in



8. Comparison of peak thymol turbidity levels within two weeks after onset of jaundice in 19 patients with infectious hepatitis (IH), 12 patients with serum hepatitis (SH), 13 Willowbrook patients with infectious hepatitis (MS-1 type), and 23 Willowbrook patients with infectious hepatitis (MS-2 type). Note similarity in thymol turbidity response between IH and MS-1 and between SH and MS-2.

degree and duration in the virus SH hepatitis than in the other group." Green described the thymol turbidity pattern in 12 cases of serum hepatitis and 19 cases of infectious hepatitis. His data, charted in Fig 8, support Neefe's observations. As indicated in Fig 8, the thymol turbidity test in serum hepatitis was relatively normal within the first two weeks after onset of jaundice; the mean level was 4.5 Maclagan units/ml. In contrast, it was increased significantly in infectious hepatitis; the mean level was 14.0 units. The data from the Willowbrook studies, charted alongside Green's data in Fig 8, highlight the striking similarity between IH and MS-1 type hepatitis and SH and MS-2 type hepatitis.

SGOT Activity.—The striking contrast between the SGOT pattern in MS-1 infection as compared with MS-2 infection is illustrated in Fig 3 and 7. In future studies it will be important to accumulate comparable data for typical cases of infectious hepatitis and serum hepatitis. The spiking rise in SGOT activity and its short duration in MS-1 infection may be indicative of infectious hepatitis. On the other hand, serum hepatitis may be characterized by a gradual rise and a prolongation of SGOT activity.

Epidemiological Aspects.—It is well recognized that infectious hepatitis is a contagious disease and that the most common mode of transmission is via the intestinal-oral route. Contact infection usually occurs under conditions which favor crowding and close association. The evidence that MS-1 type of hepatitis was highly contagious was presented in the third trial (Fig 2); all six contacts contracted MS-1 type hepatitis after exposure to children with MS-1 type of infection. This phenomenon is characteristic of IH type of hepatitis.

The most widely accepted concept of the spread of serum hepatitis supports the parenteral mode of transmission of infective blood or blood products. A limited number of trials in volunteers indicated that serum hepatitis virus was not infective by mouth.[11,15] The results of these studies suggested that serum hepatitis was rarely transmitted through personal contact.

The observation that MS-2 type hepatitis was communicable (Fig 2) and infective by mouth (Fig 4) would not be compatible with the prevailing view that serum hepatitis is not contagious after intimate contact. On the other hand, these findings would be compatible with reports by Findlay and Martin,[16] by Freeman,[17] and especially by Mirick and Shank,[18] who described an epidemic of serum hepatitis in 272 persons who had been inoculated with human plasma. The incubation period was long; it ranged from 49 to 125 days (average 79 days). Thirty additional cases of serum hepatitis were observed in uninoculated personnel who had been in intimate contact with plasma-inoculated personnel. The epidemiological aspects of MS-2 hepatitis in Willowbrook are similar to the epidemic of serum hepatitis described by Mirick and Shank.

Although both types of virus were infective by mouth, it was clear that MS-1 was more highly infectious than MS-2. During the course of the first trial (Fig 1) the two viruses were inadvertently fed as components of Willowbrook serum pool No. 5. Of ten subjects who acquired hepatitis, nine had a typical MS-1 or IH type of disease. In one patient, Nel, hepatitis occurred after an incubation period of 125 days; the disease was a typical MS-2 type of infection. It is likely that patient Nel was immune to IH before exposure to the serum pool. In four subjects (Sch, Mas, Wac, and Mir) the phenomenon of interference may have been responsible for the occurrence of only one infection, MS-1 type. In contrast, subject Mac had a double infection caused by MS-1 after 30 days and MS-2 after 97 days. There was no evidence of interference in this patient.

Immunological Aspects.—The immunological aspects of MS-1 and IH hepatitis and MS-2 and SH hepatitis are essentially the same. Studies by Neefe and associates[11] and by Havens[18] confirmed the existence of homologous immunity following IH and SH hepatitis. In contrast, there was no evidence of cross immunity between the two types of hepatitis. The same phenomenon has been observed following MS-1 and MS-2 infection (Fig 5 and 6).

Clinical Aspects.—It was impossible to differentiate between the two types of hepatitis on the basis of clinical manifestations alone without the aid of serial laboratory determinations. During the course of the seven trials, MS-1 type hepatitis was observed in 29 subjects; ten were jaundiced and 19 were anicteric. MS-2 type hepatitis was observed in 27 subjects; six were icteric and 21 anicteric. Jaundice in both groups was mild, the bilirubin value ranging between 1.0 and 3.0 mg/100 ml; it subsided after one to ten days, average of five days for both groups. There was no correlation between persistence of abnormal enzyme activity and presence of clinical symptoms. The children were asymptomatic and gained weight in spite of a prolonged elevation of SGOT. The weight gain during a 25-week period of observation was 0.9 to 3.6 kg (2 to 8 lb), average 2 kg (4.5 lb), for the MS-1 group. During a 30-week period of observation, the weight gain in children in the MS-2 group ranged between 1.8 and 3.6 kg (4 and 8 lb), average 2.7 kg (6 lb).

Conclusions

The evidence presented in the foregoing discussion indicates that the two types of infectious hepatitis in Willowbrook are examples of infectious hepatitis and serum hepatitis with distinctive clinical, epidemiological, and immunological features. This phenomenon is a logical explanation for the occurrence of second attacks of hepatitis in this institution.

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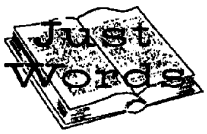

It takes little linguistic sophistication to be ready with a spontaneous verdict on whether a particular English word is of Romance or Teutonic origin. The verdict may be wrong, but generally it is ready—spontaneously so. On the other hand, whether a Latin word reached us by way of French or directly is a matter on which we feel obliged to consult a dictionary, except when its sojourn in French has left unmistakable marks on its spelling and its pronunciation or both. That this latter matter, which by rights ought to concern only the abstrusely learned, should have a bearing on our spelling is most unfortunate. It does though.

Our suffixes "-nt" ("-nce") and "-ble" ("-bility") are preceded by "-a-" or "-e-" and "-a-" or "-i-" reflecting a Latin pattern in which verbs in *-are* formed *-ant-* and *-abil-* while verbs from other classes formed *-ent-* and *-ibil-*. Our pronunciation does not differentiate between the forms in *-a-* and those in *-e-* or *-i-*, and in deciding which spelling to use in a given word we rely (to put it somewhat mystically) on our awareness of Latin as Latin is alive in English.

This would be fine if there were not things like "resistant" (with "-a-") but "resistible" (with "-i-"), while "existent" and "existible" (if we want such a thing) do follow the pattern. Here is an English irregularity which has no English cause, only a French one, for French differentiates in pronunciation (and spelling) between *-ible* and *-able*, but neither in pronunciation nor in spelling (with some exceptions that have no bearing on our problem) between *-ant* and *-ent*.

I can spell "existent" because I know English and am aware of the Latinity that is alive in English. I can spell "resistant" because I know French or (since that is no consistent guide) because I have learned it by rote. Actually, when I am tired I can't spell it. When I am tired I have to look up "defendant" and "assistant" (but "consistent") and "ascendent" and "ascendant". . . .

This is a nuisance. If I were a dictator with full spelling-reform powers, I would send all spelling-reformers to Siberia, though I myself would become guilty of spelling reform to the extent of straightening out the "ent-ant" mess. While at it, I would do a little repair work in the matter of the shaky distinction between "-ceed" in "proceed" and "-cede" in "recede" (and possibly cut out one "m" in "commence").

ALEXANDER GODE, PHD