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FINAL REPORT

A THREE YEAR SURVEY OF VIRAL HEPATITIS IN WEST LONDON (1972-1975)

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A THREE YEAR SURVEY OF VIRAL HEPATITIS IN WEST LONDON (1972-1975)

Report to the Research Division,
Department of Health and Social Security
Part III An analysis of 368 patients
tested for serological markers of both
hepatitis A and hepatitis B virus infection.

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A THREE YEAR SURVEY OF VIRAL HEPATITIS IN WEST LONDON (1972 - 1975)

Report to the Research Division, Department of Health and Social Security.
Part III - An analysis of 368 patients tested for Serological Markers of both hepatitis A and hepatitis B virus infection.

1. INTRODUCTION

The first two parts of this report described 455 patients with acute viral hepatitis who were tested for hepatitis B surface antigen. In 368 of these patients sufficient serum was available for further tests.

The possibility that acute viral hepatitis might be due to more than two viruses was suggested by reports of multiple episodes of hepatitis in drug addicts (Havens, 1956; Iwarson, Lundin, Holmgren and Hermondsson, 1973). A significant proportion of transfusion associated hepatitis cannot be serologically attributed to hepatitis B, hepatitis A, cytomegalo virus or Epstein Barr virus infection (Hollinger, Aach, Gitnick, Roch and Melnick, 1973). These observations have led to the term non-A, non-B hepatitis which may occur sporadically (Villarejos, Visona, Eduarte, Provost and Hilleman, 1975).

It therefore appeared appropriate to investigate our patients with available serum samples for serological evidence of recent infection to both hepatitis A and hepatitis B to establish the relative importance of the three types of hepatitis and to examine clinical and epidemiological data in relation to each type of hepatitis.

2. METHODS AND PATIENTS

Details of the diagnostic criteria by which patients were included in the survey, the biochemical tests performed and the serological method for detecting hepatitis B surface antigen have been described in Part I of the report. The hepatitis B core, whole and immunoglobulin M specific antibody were measured by a competitive radioimmunoassay technique (CORAB, Abbotts Laboratories) as was the antibody to the hepatitis A virus (HAV-AB, Abbott Laboratories). The immunoglobulin M specific antibody to hepatitis A virus was determined with an immunosorbent assay (Duermeyer, van der Veen and Koster, 1978).

Stored aliquots of acute and convalescent sera from the 368 patients were tested for hepatitis B core and hepatitis A virus antibody under code. All sera positive for either hepatitis A or hepatitis B core antibody were further tested for the IgM specific fraction to determine whether or not the antibody detected indicated a recent infection by the virus concerned. The presence of hepatitis B surface antigen or hepatitis B core immunoglobulin M specific antibody was accepted as evidence of recent infection with hepatitis B. The finding of hepatitis A virus immunoglobulin M antibody in the acute sera or the appearance of whole antibody between the acute and convalescent samples indicated recent exposure to hepatitis A.

Patients without serological markers of recent infection with either hepatitis A or hepatitis B were retested for immunoglobulin G and M antibodies to Epstein Barr virus and cytomegalo virus. Statistical methods were those used in Parts I and II of the report. Wilcoxon's rank sum test was used to compare the age medians of the three types of hepatitis.

3. RESULTS

3.1 Serology

Of the 93 hepatitis B surface antigen positive patients found during the course of the survey, 88 had sufficient acute and convalescent serum to be re-examined and tested for hepatitis B surface antibody and hepatitis A virus antibody (figure 1). There were 42 who had hepatitis A virus antibody. One of these had antibody of the immunoglobulin M class suggesting recent coincident infection with hepatitis A.

Only 28 (32 %) of the 88 hepatitis B surface antigen positive patients developed surface antibody. However, relatively few of the patients were followed up after they recovered from their illness and ceased to have detectable quantities of antigen in their serum.

There were 11 patients among the 280 hepatitis B surface antigen negative patients who were found to have immunoglobulin M specific hepatitis B core antibody. Five of these developed hepatitis B surface antibody (figure 2). One of the 11 patients had evidence of recent infection with hepatitis A as indicated by the presence of immunoglobulin M specific antibody to hepatitis A. Thus, altogether there were 98 patients (27 %) in whom it was thought that hepatitis B infection alone was the cause of their illness (Table I).

Two hundred and fifteen patients (59 %) had hepatitis A virus immunoglobulin M specific antibody in either their acute or both acute and convalescent sera or showed seroconversion to the whole antibody (2 patients) indicating that they were suffering from hepatitis A.

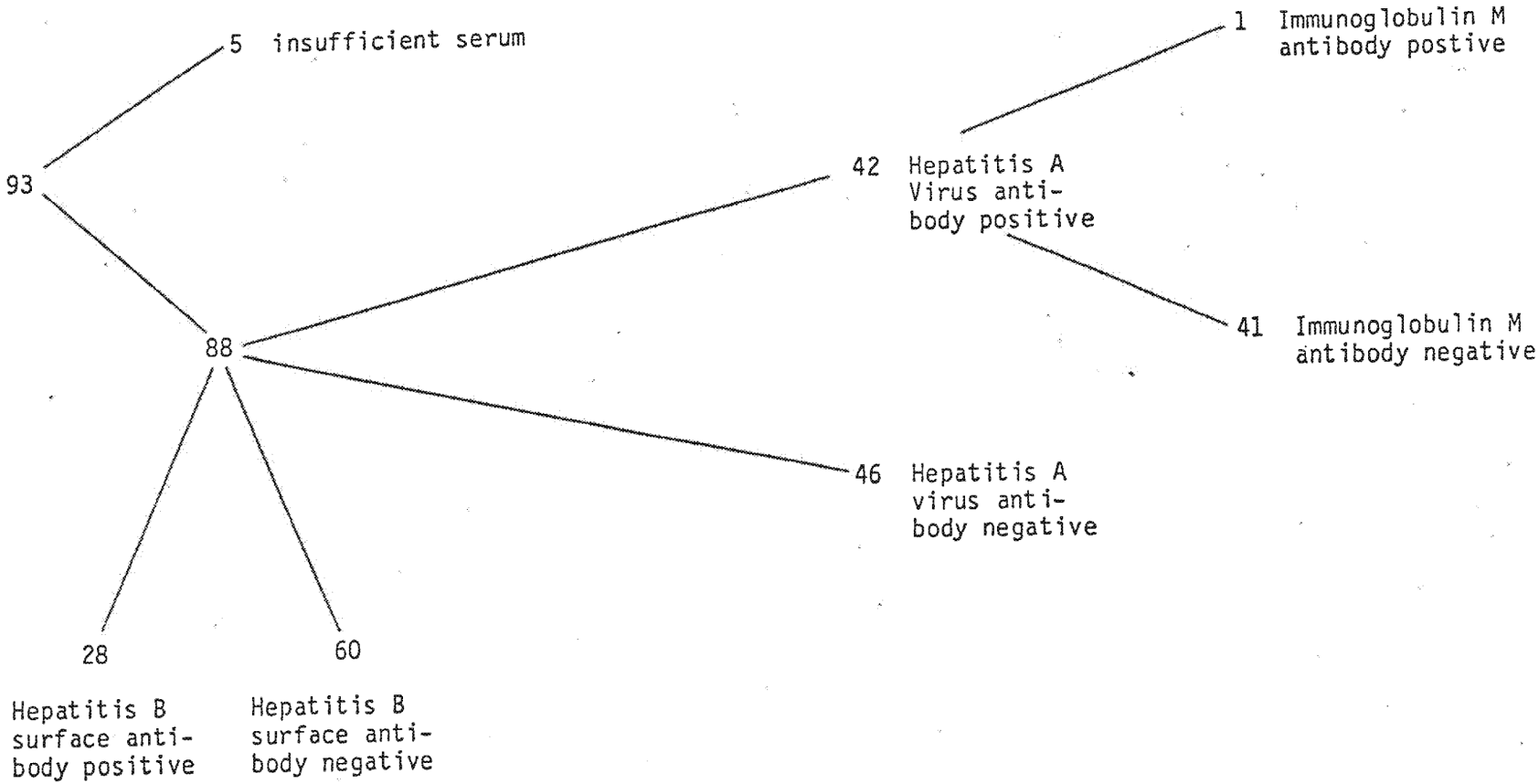

Figure 1 Scheme of serological tests performed in 93 hepatitis B surface antigen postive patients

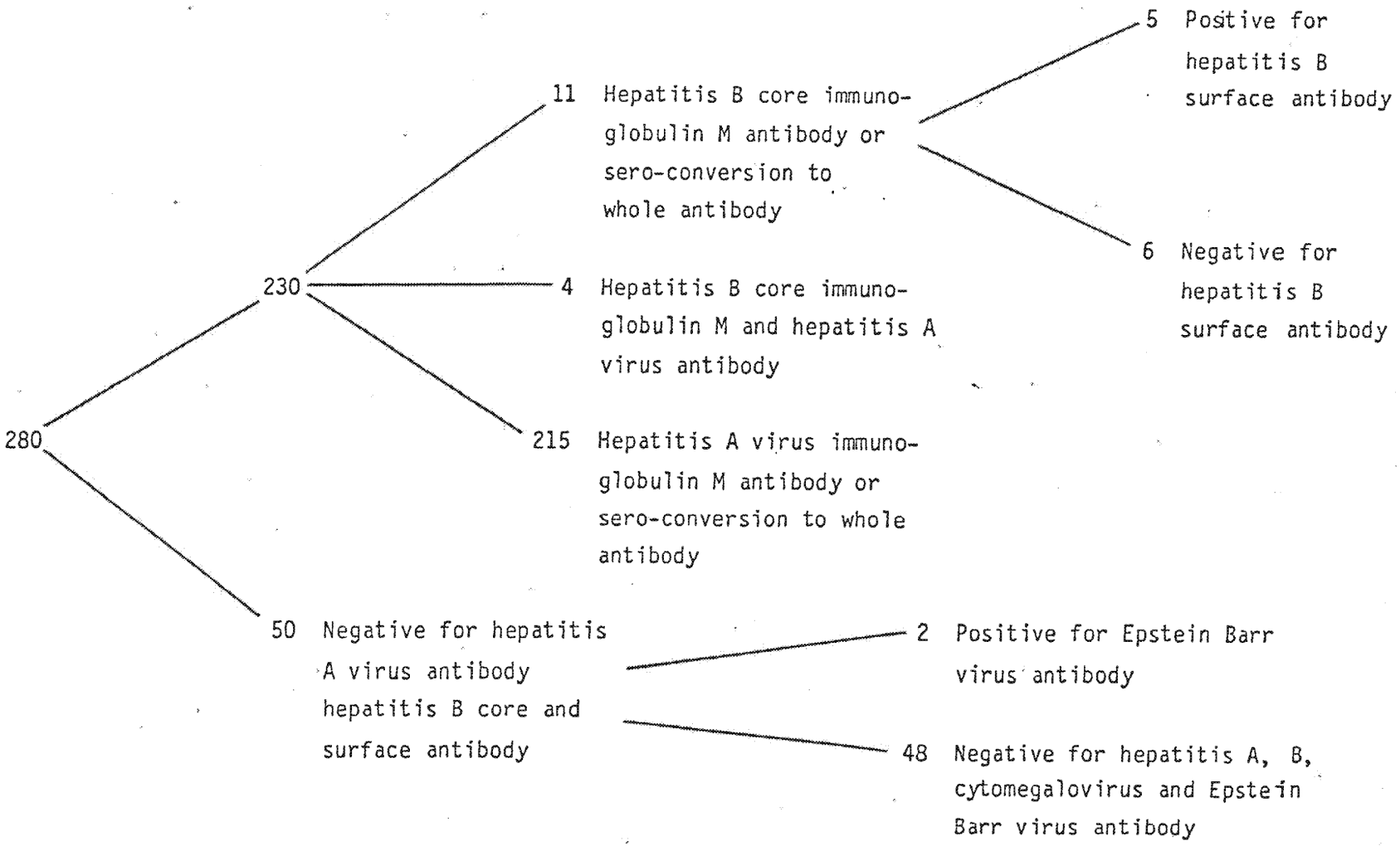

Figure 2 Scheme of serological tests performed in 280 hepatitis B surface antigen negative patients

Table I Classification of 368 patients tested for serological evidence of hepatitis A and hepatitis B

Hepatitis A			
	Immunoglobulin M antibody or sero-conversion to the whole antibody		215
Hepatitis B			
	Hepatitis B surface antigen alone	87	
	Hepatitis B core immunoglobulin M antibody or sero-conversion to the whole antibody	11	98
Hepatitis A and B			
	Hepatitis B core and hepatitis A virus immunoglobulin M antibody	4	
	Hepatitis B surface antigen and hepatitis A virus immunoglobulin M antibody	1	5
Non-A, non-B hepatitis			
	Negative serology	16	
	Hepatitis A virus whole antibody only	32	48
Epstein Barr virus antibody			2*
			368

*Two patients with evidence of Epstein Barr virus infection were excluded from the 50 patients who showed no evidence of recent infection with hepatitis A or B.

In addition to the hepatitis B surface antigen positive patient with hepatitis A virus immunoglobulin M antibody, there were 4 hepatitis B surface antigen negative patients with both immunoglobulin M specific hepatitis B core antibody and immunoglobulin M specific hepatitis A virus antibody in the acute phase of the illness. Hence 5 patients showed evidence of recent exposure to both hepatitis A and hepatitis B.

Two of the 50 remaining patients showed a 4-fold or greater increase in the titre of the immunoglobulin G antibody to the Epstein Barr virus between the acute and convalescent samples of serum. Even though the immunoglobulin M antibody to the Epstein Barr virus was not found in these 2 patients, their illness may have been due to this virus and they were therefore excluded. Sixteen of the remaining patients had no serological markers of hepatitis A or B and 32 showed evidence of previous but not recent infection with hepatitis A. Thus, 48 (13 %) of the 366 patients were accepted as suffering from non-A, non-B hepatitis.

3.2 Epidemiological, Clinical and Biochemical Comparison between the Types of Hepatitis

The sections dealing with incidence, age, sex and seasonal distribution include all 366 patients tested for serological markers of hepatitis A and hepatitis B. Thereafter, the analysis is confined to the 361 patients who were classified as having had hepatitis A, hepatitis B and non-A, non-B hepatitis and compared with respect to clinical and epidemiological factors.

3.2.1 Incidence

Hepatitis A accounted for 215 (59 %) of the 366 patients tested, whilst hepatitis B was the cause of the illness in 98 (27 %). In 48 patients (13 %) there was no evidence of recent infection with either virus or with cytomegalo virus or with the Epstein Barr virus (Table II). In the remaining 5 patients there was evidence of recent exposure to both hepatitis A and B. Thus hepatitis A, hepatitis B and non-A, non-B hepatitis occurred in a ratio of approximately 4:2:1.

Of the 266 adults 112 (42 %) had hepatitis A, 98 (37 %) had hepatitis B, 46 (18 %) had non-A, non-B hepatitis and 5 (3 %) had both hepatitis A and hepatitis B infection. Thus among the adults the ratio was very approximately 2:2:1.

There were 100 children under the age of 15 of whom 98 had hepatitis A and formed 46 % of all patients with hepatitis A. Only 2 children had non-A, non-B hepatitis and no child suffered from hepatitis B.

3.2.2 Age Distribution

The age distribution of the patients with hepatitis A differed markedly from that found in patients with either hepatitis B or non-A, non-B hepatitis. The numbers of patients with hepatitis A diminished rapidly with age (Table III, Figure 3). Well over half (58 %) with this type of hepatitis were aged 19 or less. The median age for the hepatitis A patients was 17 (range 3-64) years (Table IV). This was significantly lower than the median age of the hepatitis B patients ($p < 0.0001$) and the patients with non-A, non-B hepatitis ($p < 0.005$).

Table II Incidence of hepatitis A, hepatitis B and non-A, non-B hepatitis in 366 patients tested

Type of hepatitis	Children	Adults	Total	Percentage of all 366 patients
A	98	117	215	58.7
B	0	98	98	26.8
Non-A, non B	2	46	48	13.1
A and B	0	5	5	1.4
TOTAL	100	266	366	100.0

Table III. Age distribution according to type of hepatitis in 366 patients

Age Group (years)	Type of hepatitis				
	A	B	Non-A, non-B	A + B	Total
≤ 9	65	0	1	0	66
10-19	59	14	3	2	78
20-29	46	40	21	2	109
30-39	23	27	8	0	58
40-49	13	13	7	1	34
50-59	6	3	6	0	15
≥ 60	3	1	2	0	6
TOTAL	215	98	48	5	366

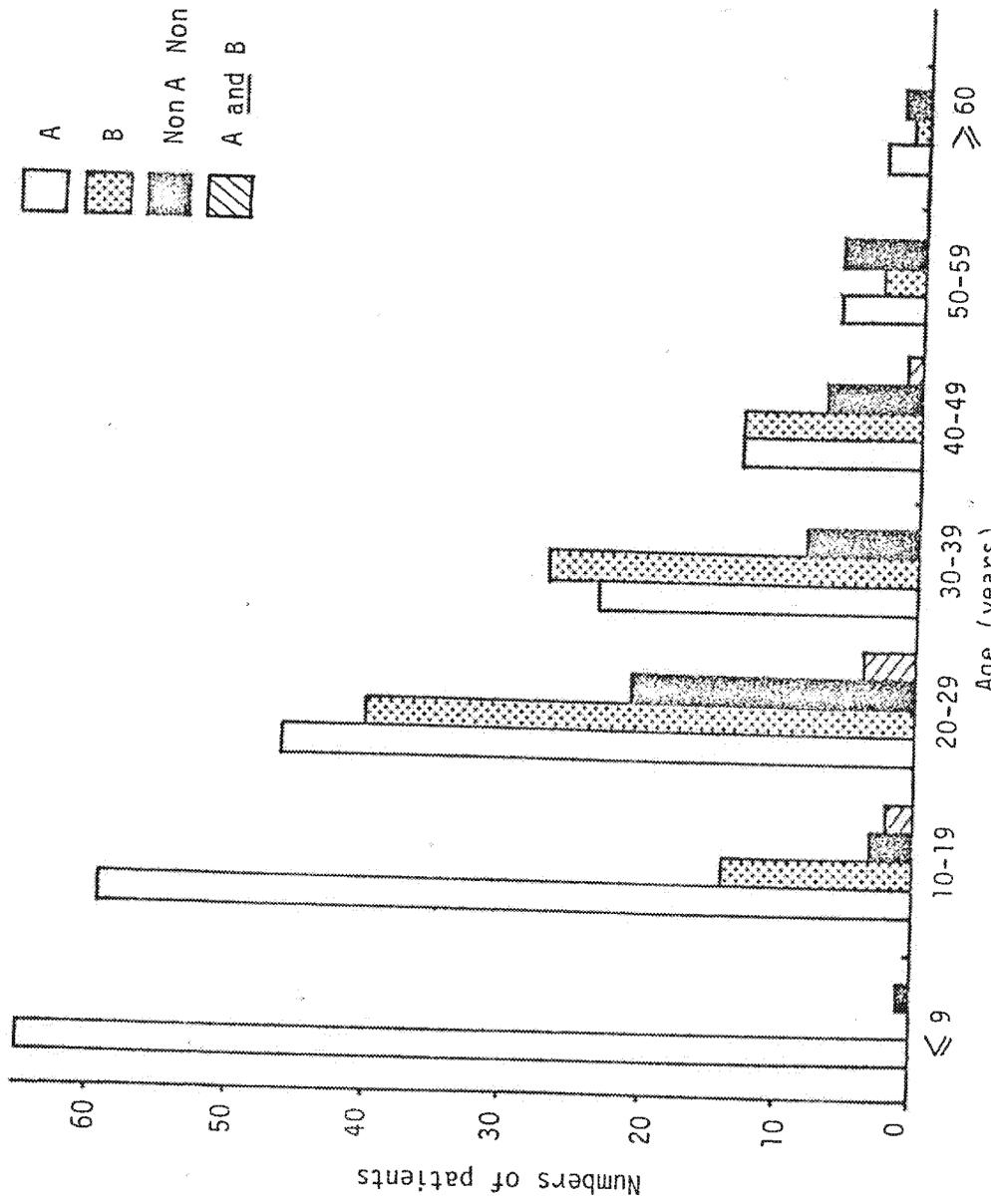

Figure 3 Age distribution of 366 patients tested for serological markers of hepatitis A and hepatitis B.

Table IV Age medians and ranges in relation to type of hepatitis

Hepatitis	Age in years		Number of patients
	Median	Range	
A children	8	3-14	98
A adults and children	17	3-64	215
A adults	27	16-64	117
B adults	26.5	16-60	98
Non-A, non-B adults and children	28	9-64	48

Hepatitis A versus B: Standardized normal deviation = 6.79, $p < 0.00001$

Hepatitis A versus Non-A, non-B: Standardized normal deviation = 2.84, $p < 0.005$

(Wilcoxon's rank sum test)

The numbers of patients with hepatitis B and non-A, non-B hepatitis rose to a peak in the twenties and then gradually declined in the older age groups. Two thirds (67/98) of the patients with hepatitis B were aged between 20 and 39 years. The youngest patient with hepatitis B was 16 years.

Although the age distribution of the non-A, non-B hepatitis patients was more similar to that of hepatitis B than hepatitis A, there were 4 times as many patients aged 50 years or over (17 %) compared with either hepatitis B or hepatitis A (4 % respectively). The median age of the hepatitis B patients was 26.5 (range 16 to 60) years and did not differ significantly from that of the non-A, non-B hepatitis patients, which was 28 (range 9 to 64) years. Interestingly, the median age of the hepatitis A adults, 27 (range 15 to 64) years was almost identical to that of the hepatitis B patients.

3.2.3 Sex Distribution

More males than females suffered from each type of hepatitis (Table V). The ratio of male to female in the 366 tested patients was 1.7 to 1. The excess of males was particularly marked among the hepatitis B patients in whom the ratio of men to women was 2.6 to 1 which increased to 4.5 to 1 in those aged 30 years or more. Thus there were more men with hepatitis B than men with hepatitis A or non-A, non-B hepatitis, $p < 0.02$. In both hepatitis B and non-A, non-B hepatitis more than half the men were 30 years or over. The women patients tended to be younger. Just over two thirds of the women with hepatitis B and non-A, non-B hepatitis and approximately four fifths of the females with hepatitis A were below the age of 30 years. Under the age of 15 years the male to female ratio was closer to unity (1.13 to 1).

Table V. Age and sex distribution of 366 patients according to type of hepatitis

Sex	Age	A	B	Non-A, non-B	A and B	Total
	⩽14	52	0	1	0	53
	15-19	14	8	1	1	24
MALE	20-29	30	27	9	2	68
	30-39	14	22	6	0	42
	⩾40	15	14	11	1	41
	TOTAL	125	71	28	4	228
	⩽14	46	0	1	0	47
	15-19	12	6	1	1	20
FEMALE	20-29	16	13	12	0	41
	30-39	9	5	2	0	16
	⩾40	7	3	4	0	14
	TOTAL	90	27	20	1	138
MALE	% aged <30 yrs	23.2%	50.7%	60.7%	-	36.4%
FEMALE	% aged <30 yrs	17.8%	29.6%	30.0%	-	21.7%
Ratio of male: female		1.4:1	2.6:1	1.4:1		1.7:1

Hepatitis B versus A and non-A, non-B Chi square$_2$ = 5.6, $p < 0.02$

3.2.4 Seasonal Distribution of 361 Patients with Hepatitis A, Hepatitis B and non-A, non-B Hepatitis

Most cases of hepatitis A occurred in the spring, particularly in the months March and April (Table VI, Figure 4). There were 2 smaller peaks, the first in June and the second in September and October. The small peak in June was mainly due to a large number of cases that occurred in 1972 connected with the outbreak in Ealing in March and April of the same year. There were no peaks in 1973, the year with the least number of patients suffering from hepatitis A.

The distribution of the hepatitis B patients was more even but there was a definite rise towards the end of the year which occurred each year.

The number of patients with non-A, non-B hepatitis varied little from month to month although there was a slight reduction in the summer months of June, July and August.

3.2.5 Comparison of Epidemiological Group with Type of Hepatitis

The majority of those patients assigned to the oral epidemiological group (described in Part I) proved to have hepatitis A. Fifty-seven of the 62 patients in this group (92 %) had hepatitis A (Table VII). The other epidemiological groups could not be associated with any particular type of hepatitis. In 158 patients with hepatitis A there was either a history of a therapeutic injection without a close contact, in 71, or with a close contact with another person suffering from jaundice, in 32. In a further 55 patients there was no history of exposure in either way. Thus only a quarter (57/215) of all the hepatitis A patients were identified on epidemiological grounds with reasonable certainty. Proportionally fewer of the patients found to have hepatitis A serologically

Table VI Monthly distribution according to type of hepatitis among 361 patients

Month	A	B	Non-A, non-B	TOTAL
January	9	7	4	20
February	21	7	4	32
March	41	7	5	53
April	31	10	5	46
May	18	5	4	27
June	23	9	2	34
July	11	7	3	21
August	9	4	2	15
September	18	9	6	33
October	18	12	5	35
November	5	13	4	22
December	11	8	4	23
TOTAL	215	98	48	361

Table VII Association of hepatitis A with oral epidemiological group

	Type of hepatitis				Type of hepatitis as a percentage of each epidemiological group		
Epidemiological Group	A	B	Non-A, non-B	Total	A	B	Non-A, non-B
Oral	57	2	3	62	91.9	3.2	4.8
Parenteral	71	43	22	136	52.2	31.6	16.2
Equivocal	32	17	5	54	59.3	31.5	16.2
Not known	55	36	18	109	50.1	33.0	16.5
TOTAL	215	98	48	361	59.6	27.1	13.3
Percentage with history of injection	47.9	61.2	56.2	52.6			

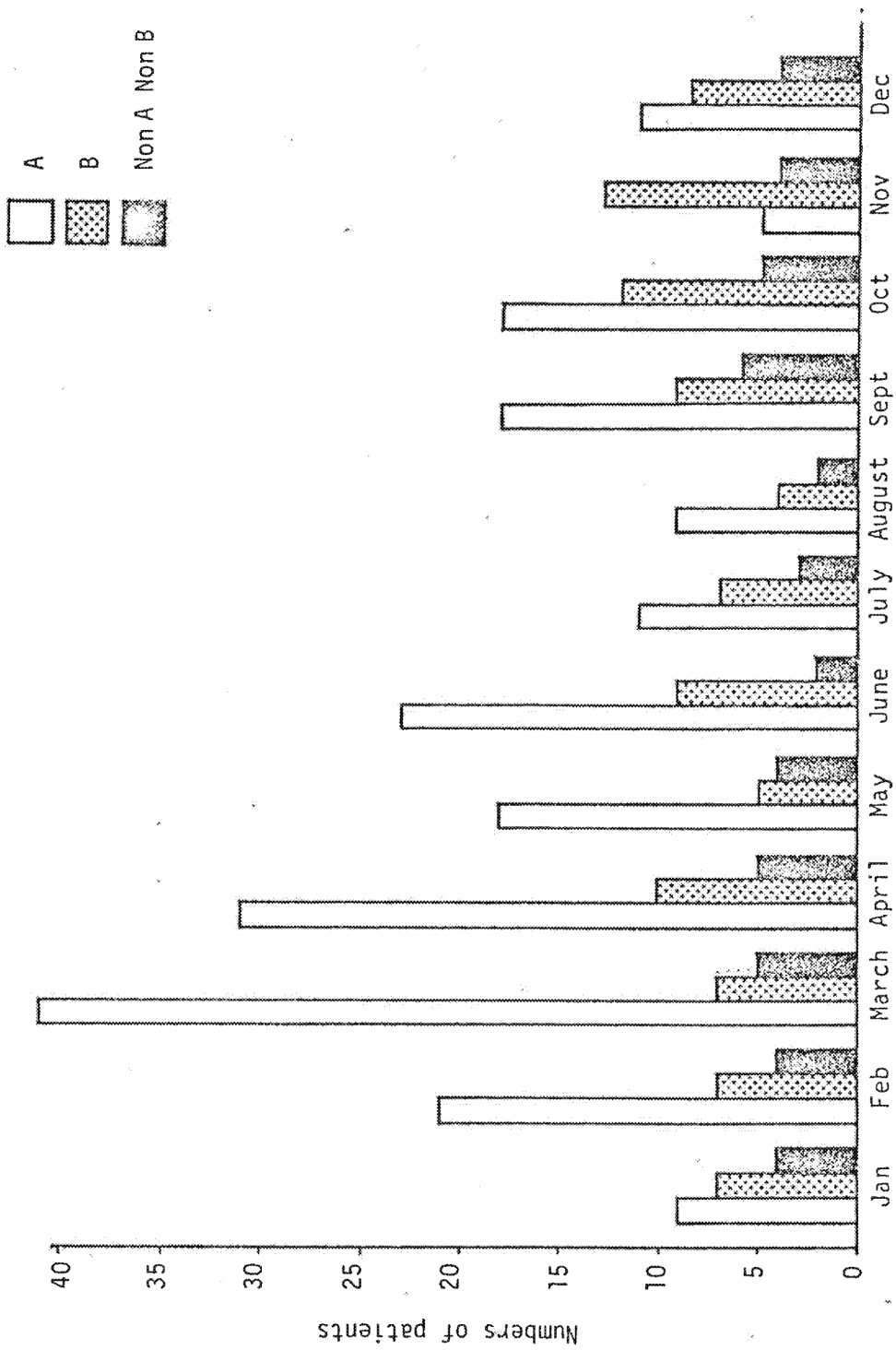

Figure 4 Seasonal distribution of 361 patients with hepatitis A, hepatitis B and non A, non B hepatitis.

gave a history of injection prior to their illness compared with those who had hepatitis B or non-A, non-B hepatitis.

3.2.6 Clinical Features

The clinical picture was closely similar in all 3 forms of viral hepatitis. However, 4 of the features, namely duration of jaundice, the occurrence of fever, arthralgia and rash, were affected by the type of hepatitis and age but not by sex.

In 8 of the 361 patients jaundice was not observed. Four of these anicteric patients had non-A, non-B hepatitis, one of whom was a child; two adults and one child had hepatitis A and the remaining adult had hepatitis B.

3.2.6.1 Duration of Jaundice

This varied from one day to over 3 months. Patients with hepatitis B experienced a significantly longer period of jaundice ($p < 0.025$) compared with adults suffering with non-A, non-B hepatitis (Table VIII, Figure 5).

Approximately 60 % (56/92) of the hepatitis B patients were jaundiced for 4 weeks or more and over half of these patients remained jaundiced for more than 6 weeks. The median duration of jaundice in these patients was 30 days. Patients with non-A, non-B hepatitis were more fortunate. One third (15/44) of them were either not jaundiced or jaundiced for 2 weeks or less and the median duration for these patients was 24 days. Although adults with hepatitis A tended to be jaundiced for longer periods than adults with non-A, non-B hepatitis, the difference did not reach significance.

Table VIII Duration of jaundice in 244 adults and type of hepatitis

Duration of jaundice (weeks)	Type of hepatitis			TOTAL
	A	B	Non-A, non-B	
<2	27	14	12	53
2-4	32	21	15	68
4-6	33	27	9	69
>6	20	29	5	54
TOTAL	112	91	41	244
Median duration in days	28	30	24	
Percentage jaundiced for <2 weeks	24.1	15.4	29.3	21.7
Percentage jaundiced for >6 weeks	17.8	31.9	12.2	22.1

Hepatitis A versus B	Not significant
Hepatitis A versus non-A, non-B	Not significant
Hepatitis B versus non-A, non-B	Chi square$_4$ = 9.5, $p < 0.025$

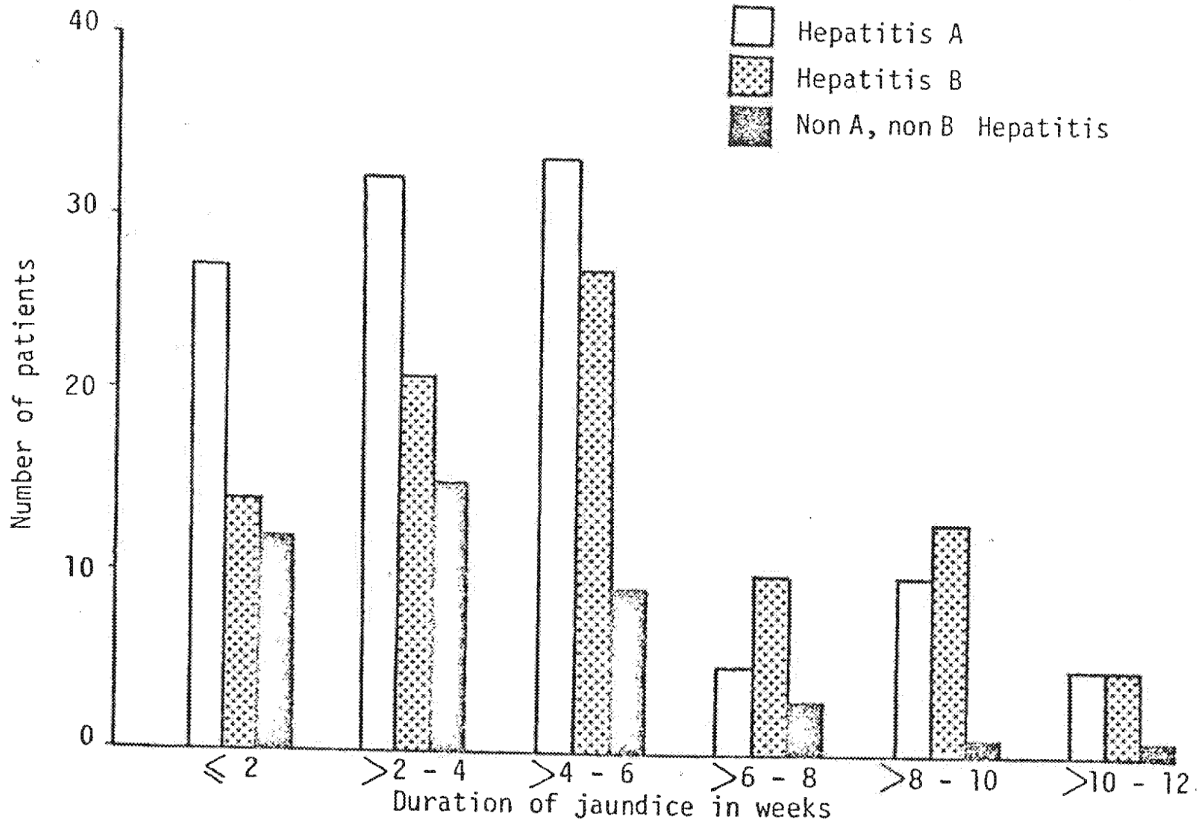

Figure 5 Type of hepatitis and duration of jaundice in adults

The lengths of jaundice for both hepatitis A and hepatitis B showed a bimodal pattern with peaks of patients between the fourth and sixth weeks and a smaller rise between the eighth and tenth week.

Of the 2 children with non-A, non-B hepatitis, one was anicteric and the other was jaundiced for less than 2 weeks.

3.2.6.2 Duration of Jaundice and Age in Hepatitis A Patients

There was a close association between the duration of jaundice and age in the hepatitis A patients, $p < 0.001$, (Table IX, Figure 6). The children had the shortest period of jaundice with an average length of 14 days, almost half the average of the adults. The older adults suffered the longest duration of jaundice (median 30 days) although this was not much longer than that experienced by the younger adults (median 25 days).

The period of jaundice also increased with age among the patients with hepatitis B but the association was not so marked, $p < 0.025$. Approximately half the patients (49 %) aged 30 years or more were jaundiced for longer than 6 weeks compared with less than a fifth (18 %) of those aged between 15 and 29 years. The association between age and length of jaundice could not be demonstrated in the non-A, non-B hepatitis patients, possibly because they were a smaller group.

Table IX. Association of age with duration of jaundice in patients with hepatitis A and hepatitis B

Hepatitis A

Age (years)	Duration of jaundice (weeks)				TOTAL	Median (days)
	<2	2-4	4-6	>6		
⩽14	55	27	8	2	94	14
15-29	19	22	21	7	70	25
⩾30	8	10	12	13	43	30
TOTAL	82	59	41	22	207	

Chi square$_6$ = 49.8, $p < 0.001$

Hepatitis B

15-29	10	15	16	9	50	28
⩾30	4	6	11	20	41	40
TOTAL	14	21	27	29	91	

Chi square$_3$ = 10.7, $p < 0.025$

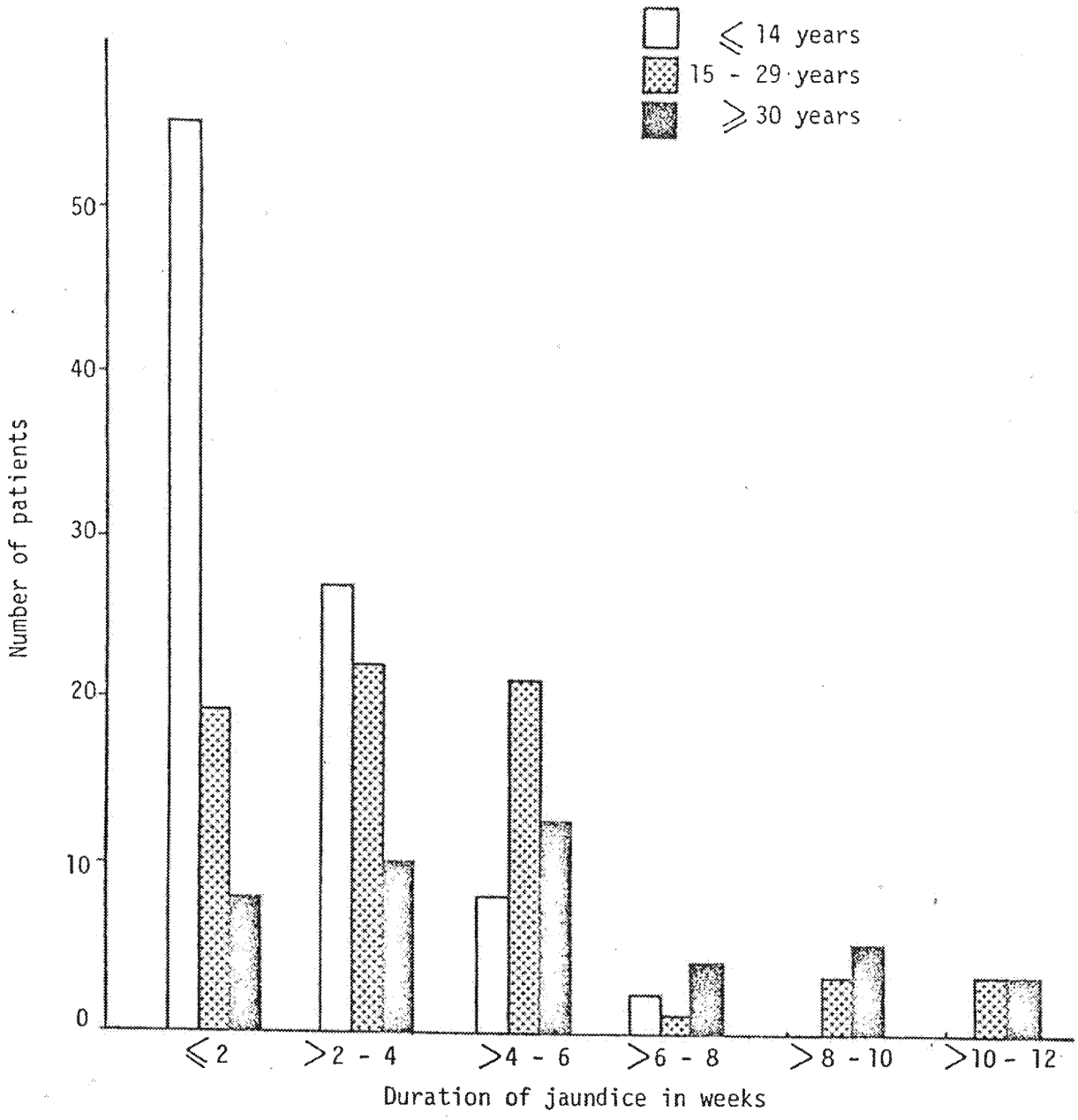

Figure 6 Association of age with duration of jaundice in hepatitis A patients

3.2.6.3 Fever

Nearly three quarters of all the patients had fever. Those with hepatitis B were least likely and those with hepatitis A most likely to have fever early in their illness (Table X), $p < 0.01$. Sixty-one per cent (56/92) of the hepatitis B patients and 83 per cent (95/115) of the hepatitis A adults experienced fever. The hepatitis A children were less commonly affected (76 %). The duration of fever did not differ significantly between the disease groups.

3.2.6.4 Arthralgia

Slightly more than one third (93/252) of all the adults complained of joint pains during their illness. Those with non-A, non-B hepatitis were least affected (12/44) whilst the patients with hepatitis B tended to suffer for longer than adults with hepatitis A or non-A, non-B hepatitis. This association did not reach statistical significance. Only 18 per cent of the children with hepatitis admitted to joint pains and neither of the 2 children with non-A, non-B hepatitis had arthralgia.

Among the patients with hepatitis A there was a highly significant association with age (Table XI). The percentage with arthralgia increases linearly with age and the chi square for a linear trend in the percentages for each group was 18.6 which indicated a strong linear relationship ($p < 0.001$). There was no association between the presence or absence of arthralgia and the severity of the illness as judged by the peak bilirubin in any of the 3 types of hepatitis. Both small and large joints were affected. No patient had a true arthritis or reported swelling of the joints.

Table X Type of hepatitis and presence and duration of fever

Adults

Duration of fever (days)	Type of hepatitis			TOTAL
	A	B	Non-A, non-B	
None	20	36	13	69
1-7	78	42	25	145
⩾8	17	14	7	38
TOTAL	115	92	45	252
Percentage with fever	82.6	60.8	71.1	72.6
Percentage with fever ⩾ 8 days	14.8	15.2	15.6	15.1

$$\text{Chi square}_4 = 12.2,\ p < 0.01$$

Children

Duration of fever (days)	Type of hepatitis		
	A (Percentage)		Non-A, non-B
None	23	(24.2)	1
1-7	67	(70.5)	1
⩾8	5	(5.3)	
TOTAL	95		2

3.2.6.5 Skin Rash

Just under a quarter (80/347) of all the patients reported a skin rash which usually occurred early in the illness. The majority described an erythematous maculopapular eruption whilst some had an urticarial type of rash. Neither lasted more than 2-3 days. There appeared to be a definite association between the type of hepatitis and the occurrence of a rash, $p < 0.02$ (Table XII). Almost a third (30/94) of the patients with hepatitis B had a rash compared with a tenth (5/45) of the non-A, non-B hepatitis and a fifth (24/117) of the hepatitis A patients. The presence of a rash was not related to age in the hepatitis A patients nor to the severity of the hepatitis as judged by peak bilirubin levels. Both the children with non-A, non-B hepatitis developed a rash.

3.2.7 Biochemical Results

The recorded peak level of serum bilirubin and peak levels of enzymes released into the blood as a result of damage to the liver during the course of viral hepatitis may be affected by the timing of the blood samples. Account was therefore taken of the time interval between the onset of jaundice, or of the illness, and the peak levels recorded, when comparing the different types of hepatitis.

During the course of the survey there was a change in the units of measurement of the serum bilirubin. The serum bilirubin levels are therefore given in micromoles per litre and milligrammes per 100 millilitres.

3.2.7.1 Peak Serum Bilirubin Levels

The highest serum bilirubin level recorded was 1370 micromoles per litre (80 milligrammes per 100 millilitres). This level was in a patient who became uraemic and so was omitted from the analysis. The next highest reading was 537 micromoles per litre (33.5 milligrammes per 100 millilitres).

Table XI Association of age with arthralgia in patients with hepatitis A

Age (years)	No Arthralgia	Arthralgia	Total	Percentage with Arthralgia
⩽14	78	17	95	17.9
15-29	50	22	72	30.6
⩾30	20	24	44	54.5
TOTAL	148	63	211	29.9

$\text{Chi square}_2 = 19.3$, $p < 0.001$

The peak serum bilirubin was compared between the 3 types of viral hepatitis in 182 adults and 71 children in whom the time from the onset of the jaundice to the first blood test was less than one week. In the adults the peak bilirubin was significantly correlated with the type of hepatitis, $p < 0.001$ (Table XIII, Figure 7).

Over half (34/62) of the patients with hepatitis B had a peak bilirubin of 173 micromoles per litre (10.1 milligrammes per 100 millilitres) or more with a median peak of 187 micromoles per litre (10.9 milligrammes per 100 millilitres). By contrast, well over half (21/36) of the non-A, non-B adult patients had a peak bilirubin of less than 86 micromoles per litre (5 milligrammes per 100 millilitres) and the median level was 77 micromoles per litre (4.5 milligrammes per 100 millilitres). Exactly half (42/84) of the adults with hepatitis A had peak bilirubin levels between 87 and 172 micromoles per litre (5.1 to 10.0 milligrammes per 100 millilitres) and the corresponding median level was 120 micromoles per litre (7.0 milligrammes per 100 millilitres).

In the patients with hepatitis A age was closely correlated with the peak bilirubin level, p being less than 0.001 (Table XIV, Figure 8). Only one of 71 children under 15 years of age had a bilirubin level of greater than 172 micromoles per litre (10 milligrammes per 100 millilitres) compared with 12 (40 %) of 30 adults aged 30 years or over. These differences are reflected in the increasing median levels for the 3 age groups. A similar trend was evident in the hepatitis B patients but only just reached significance ($p < 0.05$). The difference was largely confined to the patients with bilirubin levels above 172 micromoles per litre (10 milligrammes per 100 millilitres). Forty-four per cent of the hepatitis B patients aged 30 years or more had a peak bilirubin level of greater than 258 micromoles per litre (15 milligrammes per 100 millilitres) compared with 16 per cent of those aged between 15 and 29 years.

Table XII Association of skin rash with type of hepatitis

Adults

Skin rash	Type of hepatitis			TOTAL
	A	B	Non-A, non-B	
Absent	93	64	40	197
Present	24	30	5	59
TOTAL	117	94	45	256
Percentage with skin rash	20.5	31.9	11.1	23.0

$\text{Chi square}_2 = 8.2,\ p < 0.02$

Children

Skin rash	Type of hepatitis	
	A (Percentage)	Non-A, non-B
Absent	70 (76.9)	0
Present	21 (23.1)	2
TOTAL	91	2

Table XIII Association between peak serum bilirubin and type of hepatitis in 182 adults (time of onset of jaundice to first blood sample one week or less)

Peak serum bilirubin (micromoles per litre)*	Type of hepatitis			TOTAL
	A	B	Non-A, non-B	
⩽86	20	12	21	53
87-172	42	16	8	66
173-258	18	17	6	41
⩾259	4	17	1	22
TOTAL	84	62	36	182
Median peak serum bilirubin (micromoles per litre)	120	187	77	
Percentage with bilirubin ⩽86 micromoles	23.8	19.4	58.3	29.1
Percentage with bilirubin >172 micromoles per litre or more	26.2	54.8	19.4	34.6

$\text{Chi square}_6 = 41.24,\ p < 0.001$

Two way comparisons

Non-A, non-B versus hepatitis A $\text{Chi square}_3 = 13.9,\ p < 0.001$

Hepatitis A versus hepatitis B $\text{Chi square}_3 = 18.9,\ p < 0.001$

* 86 micromoles per litre = 5 milligrammes per 100 millilitres

172 micromoles per litre = 10 milligrammes per 100 millilitres

258 micromoles per litre = 15 milligrammes per 100 millilitres

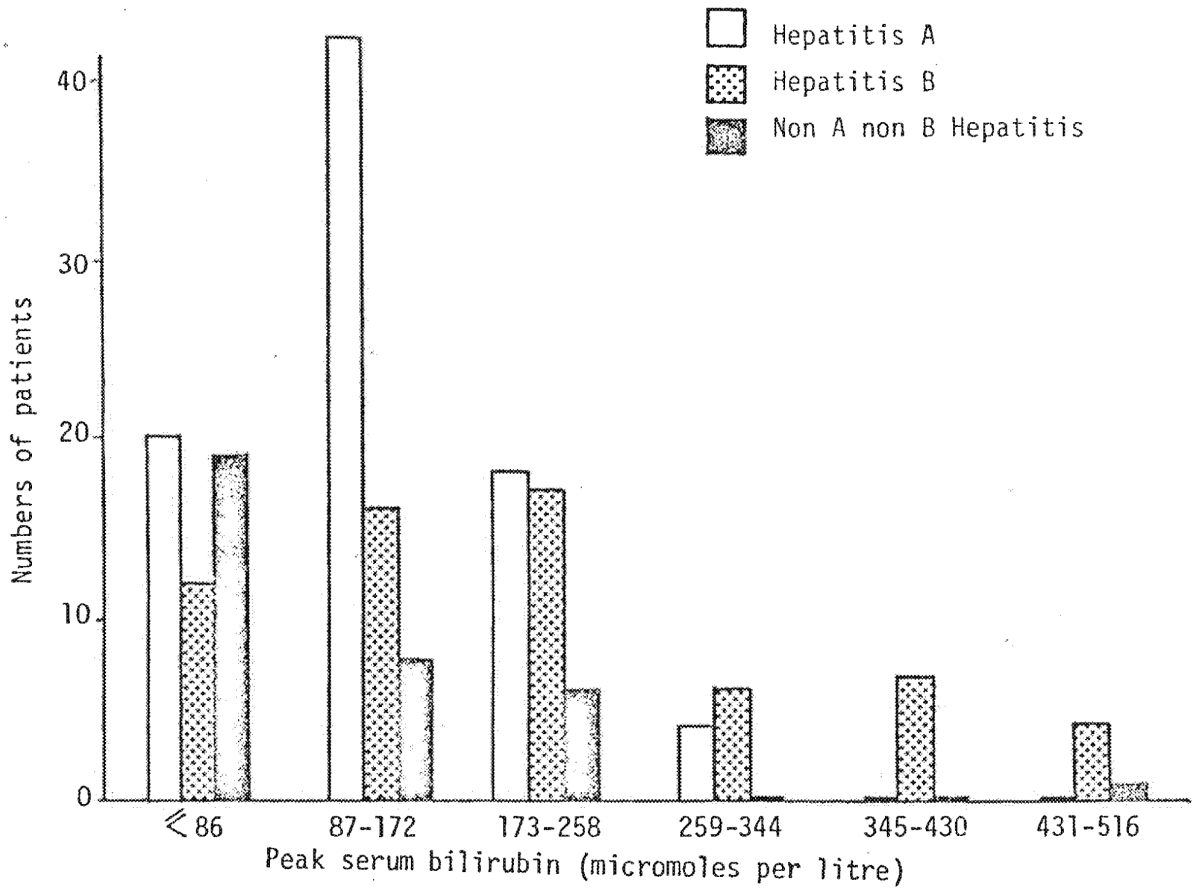

Figure 7 Association between peak serum bilirubin and type of hepatitis in adults (time from onset of symptoms to first blood test, one week or less)

Table XIV Association of age with peak serum bilirubin level (time from onset of jaundice to first blood test one week or less)

Hepatitis A

Age (years)	Peak serum bilirubin (Micromoles per litre)			TOTAL	Median level (micromoles per litre)
	⩽86	87-172	>172		
⩽14	41	29	1	71	82.6
15-29	15	29	10	54	113.5
⩾30	5	13	12	30	142.2
TOTAL	61	71	23	155	

Chi square$_4$ = 34.7, $p < 0.001$

Hepatitis B

Age (years)	Peak serum bilirubin (Micromoles per litre)				TOTAL	Median level (micromoles per litre
	<86	87-172	173-258	>258		
15-29	7	10	14	6	37	179.9
⩾30	5	6	3	11	25	218
TOTAL	12	16	17	17	62	
Percentage ⩾ 30 years	41.7	37.5	17.6	64.7	40.3	

Chi square$_3$ = 7.90, $p < 0.05$

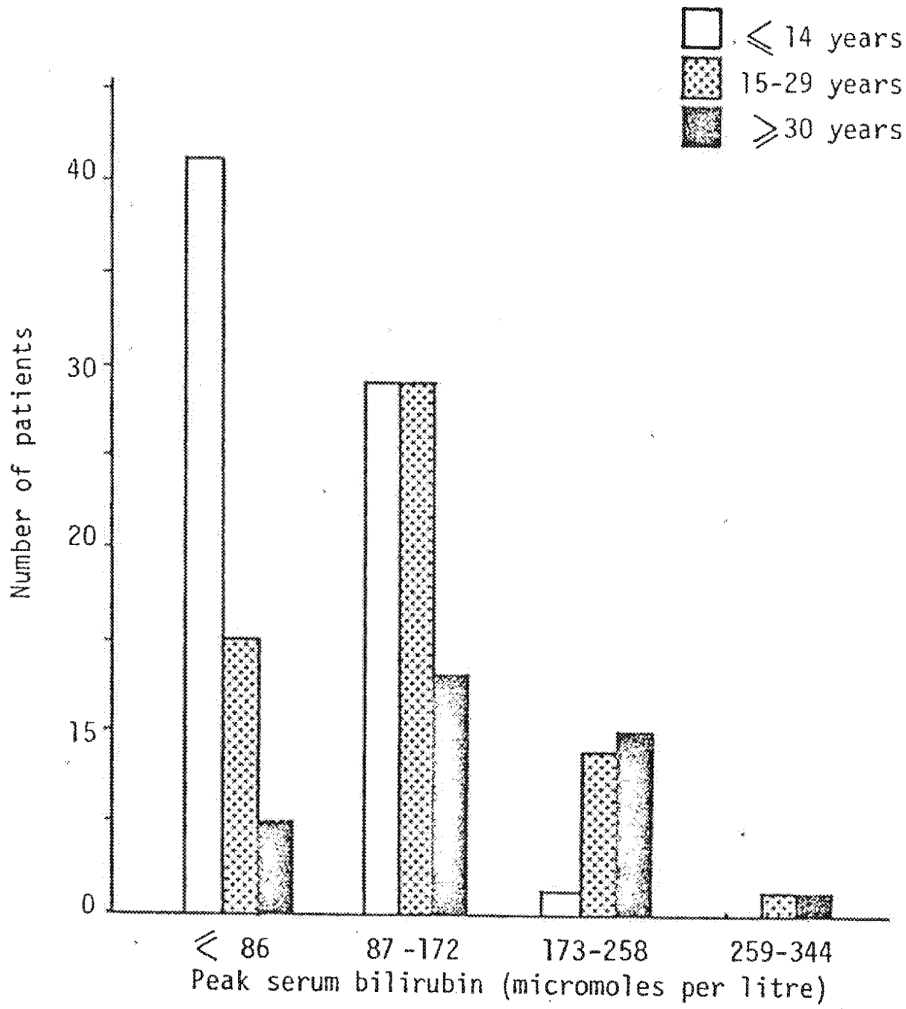

Figure 8 Association between peak serum bilirubin and age in patients with hepatitis A.

There were no significant differences in the height of the peak bilirubin between the sexes either in adults or children with each type of hepatitis.

3.2.7.2 Peak Serum Alanine Aminotransferase Levels

There was a strong association, $p < 0.001$, between the type of hepatitis and the height of the peak serum alanine aminotransferase level in adults (Table XV, Figure 9). When blood was obtained within 14 days of the onset of the illness, 37 per cent (17/46) of the hepatitis B patients had an alanine aminotransferase level of more than 1200 international units per litre compared with 16 per cent (5/31) of patients with non-A, non-B hepatitis. Over half (17/31) of the non-A, non-B patients had levels below 400 international units per litre. These differences were reflected in the medians for the peak alanine aminotransferase for hepatitis B and non-A, non-B hepatitis which were 981 and 337 international units per litre respectively. There was an even more marked difference in the peak levels between hepatitis B and non-A, non-B hepatitis adults when the first blood sample was taken later than the fifteenth day after the onset of the illness (Table XVI). In 69 per cent (20/29) of the hepatitis B patients the peak alanine aminotransferase level was 800 international units or more compared with only 12 per cent (1/8) of the non-A, non-B patients and 16 per cent (3/19) of the hepatitis A adults. Thus the hepatitis B patients had significantly higher peak alanine aminotransferase levels than non-A, non-B hepatitis adults irrespective of the timing of the first blood sample. The peak levels in the hepatitis A adults (median 917 international units per litre) were similar to those in the hepatitis B patients but the levels in the hepatitis B patients remained elevated for a longer period than in the adults with hepatitis A.

Table XV Association of peak alanine aminotransferase levels with type of hepatitis in 153 adults (interval of 2 weeks or less between the first symptom and the first blood test)

Peak serum alanine aminotransferase (international units per litre)	Type of hepatitis			TOTAL
	A	B	Non-A, non-B	
<400	13	4	17	34
401-800	19	15	5	39
801-1200	18	12	4	34
1201-1600	11	10	1	22
>1600	13	7	4	24
TOTAL	74	48	31	153
Percentage with peak serum alanine aminotransferase <400 international units per litre	17.6	8.7	54.8	22.5
Percentage with peak serum alanine aminotransferase >1200 international units per litre	32.4	37.0	16.1	30.5
Median peak serum alanine aminotransferase (international units per litre)	917	981	337	

$\text{Chi square}_6 = 24.7,\ p < 0.001$

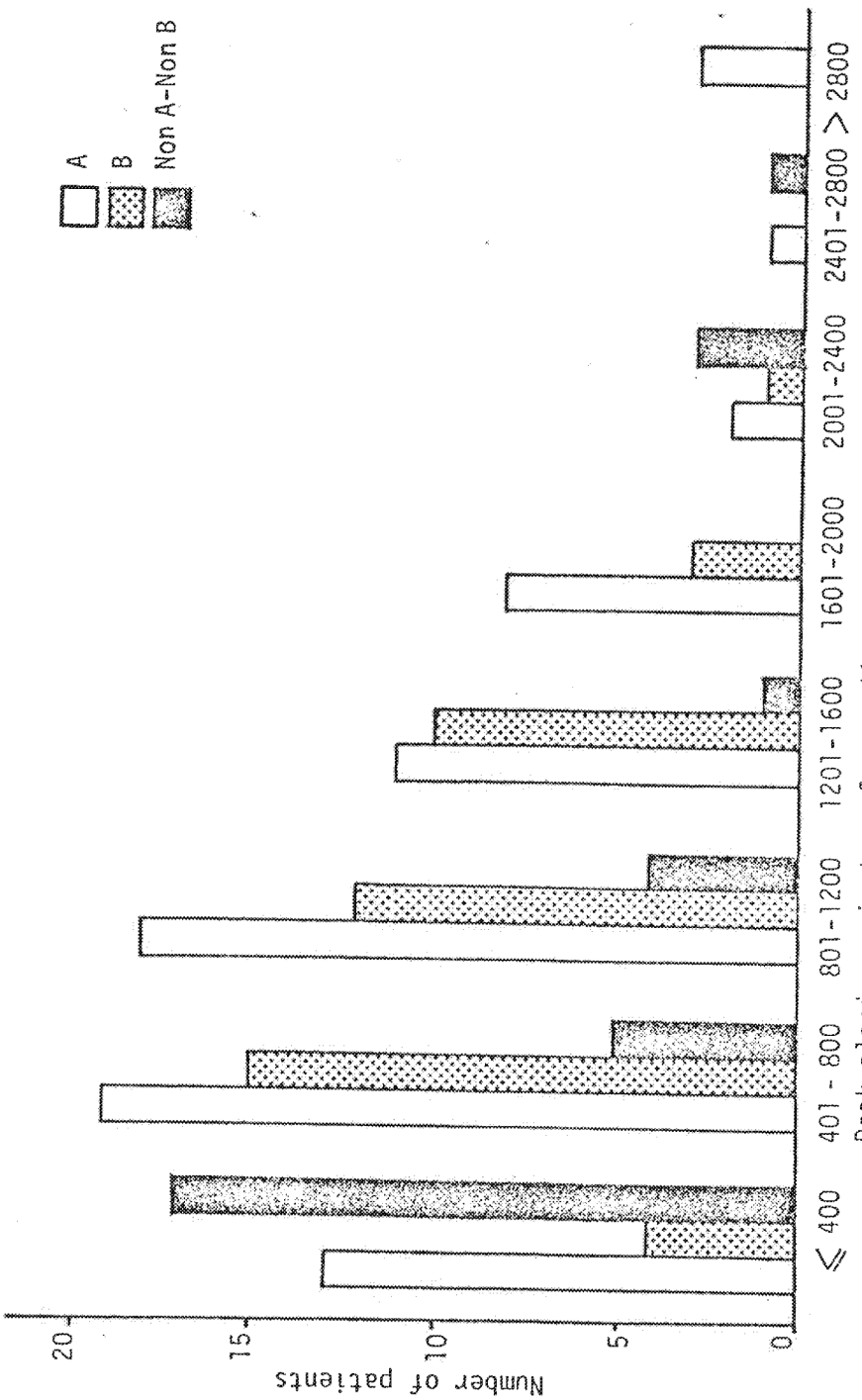

Figure 9 Relationship between peak serum alanine aminotransferase and type of hepatitis (time from onset of symptoms to first blood test 2 weeks or less)

Table XVI Relationship between peak alanine aminotransferase and type of hepatitis in 56 adults (interval of more than 2 weeks between the first symptom and the first blood test)

Peak serum alanine aminotransferase (international units per litre)	Type of hepatitis			TOTAL
	A	B	Non-A, non-B	
⩽400	9	2	6	17
401-800	7	7	1	15
>800	3	20	1	24
TOTAL	19	29	8	56
Percentage with peak alanine amino-transferase >800 international units per litre	15.8	69.0	12.5	42.9

Chi square$_2$ (last 2 rows combined) = 17.7, $p < 0.001$

3.2.8 Travel Abroad

Two fifths of all the patients (145/361) had travelled abroad during the 6 months prior to their illness (Table XVII). Slightly more adults with hepatitis A and non-A, non-B hepatitis gave a history of travel than patients with hepatitis B. Moreover, of those with hepatitis B significantly fewer (16/98) visited a semi and/or a non-industrialised country compared to adults with hepatitis A (37/117) or non-A, non-B hepatitis (12/46), $p < 0.05$.

Less than a third of the children with hepatitis A had travelled overseas before their illness, but of those that had, 70 per cent (22/31) had been to a non-industrialised country. Many were children of Asian immigrants who had visited the Indian sub-continent with their parents to see relatives. One of the 2 children with non-A, non-B hepatitis also visited a non-industrialised country.

Children with hepatitis A who developed their illness between the months of September and December were much more likely to have travelled abroad before their illness (Table XVIII). Over two thirds (68 %) of those who developed symptoms in the last 4 months of the year had travelled abroad compared with a fifth (21 %) who became ill during the first 8 months of the year ($p < 0.001$). This association was also true for adults with hepatitis A but the relationship was not so strong ($p < 0.05$). Two thirds (67 %) of those who developed hepatitis in the last 4 months had been abroad compared with two fifths who became ill in the first 8 months.

There was no such association in the patients with hepatitis B. Slightly more of the adults who contracted non-A, non-B hepatitis in the first 8 months of the year had been abroad prior to their illness, compared with those who became ill during the remaining months of the year.

Table XVII The relationship between travel abroad and type of hepatitis

a) Adults and children

Travel Abroad in previous 6 months	Type of hepatitis					TOTAL
	A		B	Non-A, non-B		
	Adults	Children		Adults	Children	
None	61	67	61	26	1	216
Industrial[1]	19	5	21	8	0	53
Semi-industrial[2]	11	4	3	8	0	26
Non-industrial[3]	9	22	5	3	1	40
More than one type	17	0	8	1	0	26
TOTAL	117	98	98	46	2	361
Percentage who travelled	47.9	31.6	37.8	43.5		40.2

b) Adults only

Travel to a semi- or non-industrial country	Type of hepatitis			TOTAL
	A	B	Non-A, non-B	
No	80	82	34	196
Yes	37	16	12	65
TOTAL	117	98	46	216

Chi square$_2$ = 6.7, $p < 0.05$

1 Australia, Canada, France, Germany, Iceland, Italy, Netherlands, Russia, Scandinavia, Switzerland, U.S.A.

2 Barbados, Brazil, Greece, Hong Kong, Israel, Lebanon, Mexico, Poland, Spain, Yugoslavia

3 Algeria, India, Iran, Morocco, Nepal, Pakistan, Persian Gulf, Thailand, Tunisia

Table XVIII Association between travel and hepatitis A in the last 4 months of the year

Month of first symptom	Travel abroad within 6 months of the illness		TOTAL	Percentage Abroad
	No	Yes		
Hepatitis A children				
January to August	60	16	76	21.1
September to December	7	15	22	68.2
TOTAL	67	31	98	31.6
Percentage September to December	10.4	48.4	22.4	

Chi square = 15.4, $p < 0.001$

Hepatitis A adults				
January to August	51	36	87	41.4
September to December	10	20	30	66.7
TOTAL	61	56	117	47.9
Percentage September to December	16.4	35.7	25.6	

Chi square = 4.7, $p < 0.05$

3.2.9 Injection Experience

Approximately one half (190/361) of all the patients had received an injection during the 6 months prior to their illness. Patients with hepatitis B were more likely to have had an injection but this did not reach statistical significance.

All 15 of the adults who gave a history of a non-therapeutic injection had hepatitis B. Of these, 13 were drug addicts which was highly significant compared with the other types of hepatitis ($p < 0.0001$). The 2 patients who were not addicts had been tattooed. One of these had also had his ear pierced as had one of the addicts.

3.2.10 Family Size

There was a strong relationship between family size and the type of hepatitis, $p < 0.01$ (Table XIX). More than half of the patients with hepatitis B (53/98) and adults with non-A, non-B hepatitis (25/44) lived alone or with 1 or 2 others. Only a third of the adults with hepatitis A (42/117) came from a single or small family whereas over half (64/117) lived in a medium size family of 4 to 6 persons. Surprisingly, a greater proportion of the patients with hepatitis B (18 %) lived in a large household with at least 6 others, compared with the other 2 types of hepatitis. The outbreak of hepatitis B among members of a commune in Richmond probably accounts for this.

Comparison between hepatitis B and non-A, non-B hepatitis revealed no significant difference in family sizes. Combining these 2 groups and comparing them with the hepatitis A adults shows a highly significant difference, $\text{chi square}_2 = 16.5$, $p < 0.001$.

Table XIX Association of family size with type of hepatitis

Adults

Family size (number of persons)	Type of hepatitis			TOTAL
	A	B	Non-A, non-B	
1 - 3	42	53	25	120
4 - 6	64	27	16	107
⩾7	11	18	5	34
TOTAL	117	98	46	261
Percentage with family size 1-3	35.9	54.1	54.3	45.0
Percentage with family size 7 or more	9.4	18.4	10.9	13.0

$$\text{Chi square}_4 = 18.2,\ p < 0.01$$

Children

Family size (number of persons)	Type of hepatitis		Percentage of hepatitis A Total
	A	Non-A, non-B	
1 - 3	3	1	3.1
4 - 6	71	1	72.4
⩾7	24	0	24.5
TOTAL	98	2	100

Nearly three quarters (71/98) of the children with hepatitis A lived in families with 4 or 5 others and over a fifth (24/98) came from large households. Only 3 lived in small households. One child with hepatitis A was living in an institution when he contracted the illness.

3.2.11 Consumption of Communal Meals

There was no evidence to suggest that the consumption of meals prepared communally in canteens and other public eating places was associated with any particular type of hepatitis. However, fewer patients with non-A, non-B hepatitis ate regular canteen or restaurant meals. As would be expected, a high proportion of children ate in school canteens.

3.2.12 History of Previous Jaundice

There was a history of previous jaundice in 12 of the 98 patients with hepatitis B and 7 (15 %) of the 46 adult patients with non-A, non-B hepatitis (Table XX). None of the hepatitis A adults nor any of the children had had a previous episode of jaundice.

Eight of the 12 hepatitis B patients and 6 of the 7 patients with non-A, non-B hepatitis had evidence of previous infection with hepatitis A. Their serum contained whole but not immunoglobulin M specific antibody to hepatitis A. All but 2 of the 8 hepatitis B patients with serological evidence of hepatitis A in the past had been jaundiced more than 5 years before. The remaining 2 had been jaundiced within 6 months of their current illness. Possibly they had acquired hepatitis A and hepatitis B about the same time.

Interestingly, the 4 hepatitis B patients without serological evidence of previous hepatitis A infection had also been jaundiced within 8 months of their current

Table XX Association of history of previous jaundice with type of hepatitis in adults

Previous jaundice	Hepatitis			TOTAL
	A	B	Non-A, non-B	
None	117	86	39	242
6 months or less	0	6	0	6
5 years or more	0	6	7	13
TOTAL	117	98	46	261
Percentage with previous jaundice	0	12.2	15.2	7.3

Chi square$_4$ = 17.1, $p < 0.001$

illness. It was not possible to determine if this had been due to non-A, non-B hepatitis.

The one patient with non-A, non-B hepatitis without serological evidence of previous hepatitis A infection had been jaundiced 20 years before, in his youth.

None of the non-A, non B patients had hepatitis B surface or core antibody in their serum.

3.2.13 Whole Antibody to Hepatitis A Virus in relation to Age and Sex among Patients with Hepatitis B and non-A, non-B Hepatitis

Half the patients with hepatitis B (48/98) and two thirds of those with non-A, non-B hepatitis (31/48) had whole antibody to hepatitis A virus indicating previous infection with hepatitis A. There was a highly significant association between the percentage who were positive and increasing age, $p < 0.001$, in the patients with hepatitis B (Table XXI). Patients with non-A, non-B hepatitis showed a trend in the same direction but this was not statistically significant.

Although there was no clear association with sex, more males than females with hepatitis B had whole antibody to hepatitis A suggesting that in this group men were more likely to have been exposed to hepatitis A.

3.2.14 Birth Place and Type of Hepatitis

Twenty per cent of all the adults (52/261) and 12 of the 100 children were born outside the United Kingdom (Table XXII). Those who had hepatitis B were most likely to have been born abroad, roughly 3 out of every 10 patients. Only 2 out of every 10 adults with non-A, non-B hepatitis and

Table XXI Association between the presence of whole antibody to hepatitis A virus and age in patients with hepatitis B and non-A, non-B hepatitis

Hepatitis B

Age (years)	Whole antibody to hepatitis A virus		TOTAL	Percentage with whole antibody to hepatitis A virus
	Present	Absent		
15-29	17	37	54	31.5
⩾30	31	13	44	70.5
TOTAL	48	50	98	

Chi square$_1$ = 13.2, $p < 0.001$

Non-A, non-B hepatitis

Age (years)	Whole antibody to hepatitis A virus		TOTAL	Percentage with whole antibody to hepatitis A virus
	Present	Absent		
⩽14	0	2	2	-
15-29	15	8	23	62.5
⩾30	17	6	23	73.9
TOTAL	32	16	48	66.7

Not significant

Table XXII Relationship between birth place and type of hepatitis

Birth Place	Type of hepatitis					TOTAL
	A		B	Non-A, non-B		
	Adults	Children		Adults	Children	
United Kingdom	104	87	68	37	1	297
Abroad	13	11	30	9	1	64
TOTAL	117	98	98	46	2	361
Percentage born abroad	11.1	11.2	30.6	19.6	-	17.7

Chi square_2 (adults) = 12.7, $p < 0.01$

only 1 out of every 10 hepatitis A patients, irrespective of age, had been born outside the United Kingdom. The difference between the adults was statistically significant at the one per cent level.

One of the 2 children with non-A, non-B hepatitis was born in the United Kingdom.

Among the patients with hepatitis B a higher proportion (73 %) of those who had been born abroad compared with those who had been born in this country (38 %) had whole antibody to hepatitis A virus indicating previous infection, $p < 0.005$ (Table XXIII). This finding was not unexpected as many of those born abroad came from the Indian sub-continent where they were likely to have been exposed to hepatitis A at a very early age. Patients with non-A, non-B hepatitis showed a similar but not significant trend.

3.2.15 Occupation of the Patient and Type of Hepatitis

There was no obvious association between the present or previous accupation of the patient and the type of hepatitis suffered.

There were 24 patients who were unemployed at the time of their illness, 15 had hepatitis B, 6 had hepatitis A and there were 2 with non-A, non-B hepatitis (Table XXIV). Thus there were more unemployed patients with hepatitis B (15 %) compared with hepatitis A (6 %) or non-A, non-B hepatitis (4 %), $p < 0.05$. Seven of the 15 unemployed hepatitis B patients admitted to addiction. There were no addicts with hepatitis A or non-A, non-B hepatitis.

Table XXIII Whole antibody to hepatitis A virus according to birth place in patients with hepatitis B and non-A, non-B hepatitis

Hepatitis B

Birth Place	Whole antibody to hepatitis A virus		TOTAL	Percentage with whole antibody to hepatitis A virus
	Present	Absent		
United Kingdom	26	42	68	38.2
Abroad	22	8	30	73.3
TOTAL	48	50	98	51.0

Chi square$_1$ = 8.9, $p < 0.005$

Non-A, non-B hepatitis

Birth Place	Whole antibody to hepatitis A virus		TOTAL	Percentage with whole antibody to hepatitis A virus
	Present	Absent		
United Kindom	23	15	38	60.5
Abroad	9	1	10	90.0
TOTAL	32	16	48	66.7

Not significant

Table XXIV Association between unemployment, addiction and hepatitis B

	Type of hepatitis				TOTAL	Percentage with hepatitis
	A	B		Non-A, non-B		
		Addicts	Non-Addicts	TOTAL		
Unemployed	7	7	8	15	2	24	62.5
Employed	110	6	77	83	44	237	32.5
TOTAL	117	13	85	98	46	261	
Percentage unemployed	6.0	66.6	9.4	15.3	4.3	9.2	

Comparison between unemployed adults in the 3 types of hepatitis: Chi square$_2$ = 7.1, $p < 0.05$

3.2.16 Home Amenities

There was no association between any particular type of hepatitis and the sharing of kitchen, toilet, bathroom or hot water facilities. Less than 5 per cent shared either a kitchen or the hot water facilities available in the accommodation occupied.

Between 7 and 11 per cent of all patients shared either a toilet or bathroom. These proportions were similar to those in the local community.

4. DISCUSSION

The survey demonstrated that hepatitis A remains the most common type of hepatitis in urban areas of the United Kingdom. It accounted for 59 per cent of detectable cases. It was more than twice as common as hepatitis B and four times as frequent as non-A, non-B hepatitis. Children under the age of 15 years predominantly suffered from hepatitis A. They accounted for nearly half of all the patients who were detected with this type of hepatitis. These findings were based on serological tests performed in 366 patients who were selected, according to the availability of suitable serum samples, from 489 patients identified as suffering from acute viral hepatitis during the 3 years of the survey. Compared with other age groups, fewer children under the age of 5 years could be adequately tested serologically, owing to the difficulty of obtaining a sufficient volume of blood for both biochemical and serological tests. As most of the children that were tested proved to have hepatitis A, this form of hepatitis may have been underrepresented in the group of patients who were investigated in more detail serologically. Nevertheless, the error was unlikely to have been very great as the number of children under the age of 5 years formed only 5 per cent of all the patients with viral hepatitis in the survey.

The incidence of hepatitis A declined rapidly with age (Figure 3) but cases occurred even in the middle aged or elderly who had escaped infection earlier in their lives. This is in keeping with a study of hepatitis A antibody in 95 London blood donors, reported by Banatvala and Thorogood (1980). They found that a third had evidence of previous infection with hepatitis A compared with 14 per cent of 70 students. The relationship with age was further emphasised by their observation that 77 per cent of the subjects they studied over the age of 30 years had antibody to hepatitis A. In the survey a larger

percentage of patients with hepatitis B (70 %) and non-A, non-B hepatitis (74 %) over the age of 30 years had hepatitis antibody compared with those under this age, 31 and 65 per cent respectively. These figures agree with Banatvala and Thorogood's data.

There are few studies of endemic or sporadic hepatitis that can be directly compared with this survey. Villarejos and his colleagues, who examined endemic hepatitis in Costa Rica, found that 25 (54 %) of 46 patients developed antibody to hepatitis A (Villarejos, Provost, Ittensohn, McLean and Hilleman, 1976). It is surprising that in a single source epidemic among 135 naval recruits in California sero-conversion to hepatitis A virus antibody occurred in only 25, or 19 per cent (Routenberg, Dienstag, Harrison, Kilpatrick, Hooper, Purcell and Fornes, 1974). A prospective study of 155 patients admitted to the University Hospitals of Düsseldorf, Essen, Marburg and Tübingen with acute viral hepatitis between 1978 and 1980 revealed that 23 (15 %) were suffering from hepatitis A. However, of 168 children admitted to another German hospital, 134 (80 %) were suffering from hepatitis A (Frösner, Deinhardt, Schomerus, Wiedman, Dolle, Altdorfer, Schmid and Franzen, 1980). In another consecutive series of 541 hospital patients admitted to hospital in Milan, 102 (19 %) had hepatitis A (Caredda, Mornforte, Rossi, Loperz and Moroni, 1981). In the United States, 31 per cent of 198 sporadic cases of acute viral hepatitis in the general community of six sentinal counties were due to hepatitis A (Maynard, 1980). Thus the proportion of patients found to be suffering from hepatitis A may depend on whether or not the information is based on a hospital series or a community study, the age structure of the patients investigated, the presence or absence of an epidemic or local outbreak as well as previous exposure, which may vary from one geographical location to another. Hence

the varying figures need careful interpretation. It is interesting to note that the percentage found to have hepatitis A in the Costa Rica study was closely similar to that observed in West London, despite obvious differences in the standard of living and social circumstances between the two populations.

Hepatitis B occurred in 27 per cent of the survey patients and appeared to be a disease of adults. No child under the age of 15 years was affected. This is in accord with a previous report from Scotland. None of the 77 patients under the age of 20 years admitted to hospital with acute viral hepatitis in Western Scotland between 1969 and 1970 was found to have hepatitis B surface antigenaemia (Ross and McMichael, 1970). However, the serum of the patients was tested by immunoelectrophoresis which is a relatively insensitive technique. Frösner, Deinhardt, Schomerus, Wiedman, Dolle, Altdorfer, Schmid and Franzen (1980) recorded that 14 per cent of 168 children admitted to a hospital in Germany had hepatitis B using a sensitive method for detecting the hepatitis B surface antigen. This was much lower than the 56 per cent found among patients of mixed age who were admitted to another group of hospitals in that country. Other work in Western communities has shown that hepatitis B in children is largely confined to special circumstances, such as compromised host defences associated with other diseases or their treatment (World Health Organisation, 1977). Transmission from mother to child may also be important in this context (Schweitzer, Wing, McPeak and Spears, 1972; Schweitzer, Mosley, Ashcavai, Edwards and Oberly, 1973) but appears to be relatively rare in developed countries in contrast to non-industrialised regions of the world where it may account for the large numbers of carriers reported in these areas (World Health Organisation Technical Report Series No. 602, 1977).

A small but significant proportion (13 %) of the 366 patients studied in detail serologically, proved by exclusion to have had non-A, non-B hepatitis. A surprisingly similar percentage, 14 per cent (10/73) of patients has been reported with this form of hepatitis in a consecutive series of patients admitted to hospital in Denmark (Kryger, Aldershvile, Christofferson, Hardt, Juhl, Mathieson, Nielson, Poulsen and members of the Copenhagen Hepatitis Acuta Programme, 1980). Likewise Villarejos and his colleagues found 11 of 103 patients whose illness could not be attributed to hepatitis A, hepatitis B or infectious mononucleosis in Costa Rica (Villarejos, Visona, Eduarte, Provost and Hilleman, 1975). In neither of these surveys nor in the present study did the administration of blood or its products appear to be important in the transmission of non-A, non-B hepatitis. This is in marked contrast to the experience in the United States of America where this type of hepatitis is thought to be the major cause of post transfusion hepatitis at the present time (Alter, 1980).

Dienstag, Alaama, Mosley, Redeker and Purcell (1977) have estimated that non-A, non-B hepatitis may also be the cause of 25 per cent of sporadic viral hepatitis in the United States. This report is consistent with the 30 per cent found by Frösner, Deinhardt, Schomerus, Wiedman, Dolle, Altdorfer, Schmid and Franzen (1980) in Germany and the 31 per cent reported by Maynard (1980) in the United States. Only 2 of the 100 children studied serologically in West London had non-A, non-B hepatitis which did not appear to be a significant cause of viral hepatitis under the age of 15 years. Studies in Melbourne have drawn similar conclusions (Lucas, Gust, McCrorie, Lehman, Dimitrakakis and Locarnini, 1980).

4.1 Age Distribution

Nearly all the children tested serologically had hepatitis A and the incidence of hepatitis A fell progressively with each decade (Figure 3). The fall implies a gradual acquisition of immunity with age although the absolute number of patients in the older age group with hepatitis A was surprisingly large. In underdeveloped areas of the world, where hygiene and sanitation are poor, 95 per cent of children have acquired antibody to hepatitis A by the age of 15 years (Villarejos, Provost, Ittensohn, McLean and Hilleman, 1976). Thus the present survey reflects the trend in Western industrialised countries for hepatitis to affect the older age group as a result of improved living conditions.

Since 1966, in both Canada and the United States, there has been a shift in the age structure of reported cases in favour of young adults. A relatively high proportion of notifications in Canada between 1967 and 1969 were in the 20 to 29 year age group (Epidemiological Bulletin, Canada, 1971) although those aged 5 to 9 years still formed the largest group in some years. Over the same period in the United States the age of highest prevalence shifted from children between 5 and 14 years to those aged 15 to 24 years. This was due to an absolute increase in the numbers of young adults contracting hepatitis. From 1973 to 1977 the reported incidence of hepatitis A declined in all age groups. The peak incidence occurred in the 15 to 24 years age group and was 2 to 3 times greater than in children aged between 5 and 14 years. By contrast, hepatitis B increased over the same period, particularly among young adults aged between 25 and 29 years (Centre for Disease Control, Hepatitis Surveillance, 1979). Likewise in Sweden an increased incidence of hepatitis has been observed in young adults (Ringertz, 1971). In the present study both hepatitis B and non-A, non-B hepatitis occurred most frequently in the third decade and would appear to

be the cause of the peak of cases in this age group. More than twice as many men as women had hepatitis B in their twenties whereas slightly more women than men of the same age had non-A, non-B hepatitis.

Dienstag, Alaama, Mosley, Redeker and Purcell (1977) have also reported an excess of women with non-A, non-B hepatitis, the majority of whom were over the age of 35 years in a study carried out in Los Angeles. No reason was established for this distribution. In Costa Rica children seem just as commonly affected as adults (Villarejos, Provost, Ittensohn, McLean and Hilleman, 1976).

4.2 Sex Distribution

Males predominated at all ages in the survey (Table V). The ratio of males to females increased with age in all three types of hepatitis. This trend was most marked in the patients with hepatitis B. The Registrar General's Statistical Review of England and Wales for 1972 and 1973 and the Statistics of Infectious Diseases for 1974 and 1975 show the ratio of males to females notified as suffering from viral hepatitis to fluctuate around unity. It is difficult to explain why the survey findings were at variance with the national statistics. Possibly hepatitis B, which has been shown in several studies to affect men more frequently than women, is more prevalent in the metropolitan area such as London than in the country as a whole and this may have influenced the figures in the survey. Alternatively, the male patients with hepatitis B admitted to hospital may not have been reported as frequently. Unfortunately, the national figures were not broken down into the various types of hepatitis.

It is now well recognised that hepatitis B surface antigen positive acute viral hepatitis is more common in males (London, Sutnick and Blumberg, 1969; Cossart and Vahrman, 1970; Farrow, Holborow, Johnson, Lamb, Stewart, Taylor

and Zuckerman, 1970; Blumberg, Sutnick, London and Melartin, 1972). Of the 93 patients positive for hepatitis B surface antigen in the survey, 69 (74 %) were males and the ratio of men to women reached 5 to 1 over the age of 30 years. Similar, though slightly lower, ratios were found among the 366 patients tested for serological evidence of both hepatitis A and hepatitis B. The predominance of men with hepatitis B may be due to social factors such as drug abuse (Cherubin, Hargrove and Prince, 1970) or promiscuous sexual habits, whether they be heterosexual (Vahrman, 1970) or homosexual (Mirick and Shank, 1959; Fulford, Dane, Catterall, Woolf and Denning, 1973; Vahrman, 1973).

The ratio of men to women with hepatitis A and non-A, non-B hepatitis was much lower than in patients with hepatitis B, 1.6 and 1.4 to 1 respectively. This suggests that the social factors which are important in the transmission of hepatitis B do not operate or are much less important among adults with hepatitis A or non-A, non-B hepatitis. Women tend to marry earlier than men and possibly this diminishes their chance of close social and sexual contacts outside their families and hence the risk of acquiring hepatitis from such contacts.

Among the children in the survey tested serologically, the ratio of boys to girls was close to unity (1.13 to 1). All but 2 had hepatitis A. In most epidemics or point source outbreaks in the United Kingdom the two sexes have been affected more or less equally (Morgan and Brown, 1927; Booth and O'Kell, 1927; Pickles, 1930; Lisney, 1944; Bothwell, Martin, Macara, Skone and Wofinden, 1963; Burns, 1967; Rowland and Skone, 1972). Such outbreaks were most likely due to hepatitis A and involved large numbers of children. Thus in both endemic and epidemic circumstances, sexual status does not appear to affect the transmission of hepatitis A in children.

4.3 Clinical Features

The clinical picture was closely similar in all three types of viral hepatitis. A syndrome resembling serum sickness consisting of joint and skin manifestations has been recognised during the prodromal period of acute viral hepatitis. It was first mentioned by Graves (1843) and has been associated with hepatitis B infection (Alpert, Isselbacher and Schur, 1971; Onion, Crumpacker and Gilliland, 1971; Zuckerman, Darnell and Scalise, 1976). A third of the patients in the survey complained of arthralgia with or without myalgia early in their illness. A similar incidence has been observed by Koff (1971). Contrary to previous reports there was no association between arthralgia and type of hepatitis suffered although the symptoms lasted longer in patients with hepatitis B.

There was a clear linear association between arthralgia and age in hepatitis A patients in the survey ($p < 0.01$), but there was no correlation between this symptom and the severity of the illness as judged by the peak serum bilirubin level. Possibly the joints of older patients are more susceptible to damage from circulating immune complexes or the immune response is in some way different in older subjects.

Just under a quarter of the patients reported a skin rash early in the illness, generally lasting 2 to 3 days. It was most frequent (32 %) in hepatitis B and least common (11 %) in those with non-A, non-B hepatitis ($p < 0.02$). Duffy, Lidsky, Sharp, Davis, Person, Hollinger and Min (1976) record that skin lesions may occur with or without joint lesions and consist of an erythematous macular or maculopapular eruption lasting days or occasionally weeks. Urticaria, erythema multiforme-like rashes and even purpura have been described (Krugman and Gocke, 1978). These cutaneous manifestations are usually mild, brief and self limiting as appeared to be the case in this survey.

4.4 Severity of Viral Hepatitis

The severity appeared to depend on two major factors, the type of hepatitis and the age of the patient.

4.4.1 Type of Hepatitis

It has been widely accepted that hepatitis B is the most severe form of hepatitis (Editorial, Lancet, 1970; Rosenheim, 1972; Sherlock, 1972). Nevertheless, there have been few detailed reports since the work of Krugman, Giles and Hammond (1967) on children in an institution for the mentally handicapped. They showed that children with the MS-2 strain of hepatitis, subsequently identified as hepatitis B (Giles, McCollum, Berndtson and Krugman, 1969), had a longer duration of elevated serum transaminase activity than those with the MS-1 strain or hepatitis A. Wewalka (1972) found that the average duration of jaundice, as well as the duration of raised serum transaminase levels was significantly greater in hepatitis B surface antigen positive patients. Likewise Cossart and Vahrman (1970) observed that elevated transaminase levels lasted more than 8 weeks in 90 per cent of the patients with hepatitis B surface antigen negative. Conversely there are also reports that hepatitis A is frequently a sub-clinical or unrecognised illness (Szmuness, Dienstag, Purcell, Harley, Stevens and Wong, 1976; Villarejos, Provost, Ittensohn, McLean and Hilleman, 1976), though whether or not this is more frequent than in hepatitis B remains uncertain.

In this investigation adults with hepatitis B had a more prolonged duration of jaundice, a higher peak serum bilirubin and a higher peak serum alanine aminotransferase level than adults suffering from either hepatitis A or non-A, non-B hepatitis. Comparison between hepatitis B and non-A, non-B hepatitis revealed the largest differences. The duration of jaundice was significantly longer ($p < 0.025$) and the peak serum bilirubin and alanine aminotransferase

significantly higher ($p < 0.001$) in patients with hepatitis B. These findings are in keeping with reports that non-A, non-B hepatitis following transfusion of blood or its products, or associated with drug addiction, is a much milder disease than hepatitis B (Purcell, Alter and Dienstag, 1976; Craske, Dilling and Stern, 1975; Berman, Alter, Ishak, Purcell and Jones, 1979; Kryger, Aldershvile, Christofferson, Hardt, Juhul, Mathieson, Nielson, Poulsen and the Copenhagen Hepatitis Acuta Programme, 1980; Norkrans, Frosner, Hermondsson and Iwarson, 1980). Although adults with hepatitis B were more ill than adults with hepatitis A, as judged by the same criteria, the differences were smaller. The duration of jaundice was only slightly longer in the patients with hepatitis B.

The peak serum bilirubin was very significantly higher ($p < 0.001$) as was the peak serum alanine aminotransferase level beyond the second week of the illness. The peak alanine aminotransferase level in the first 2 weeks of the illness was only a little higher than in those with hepatitis A. The slightly longer duration of jaundice and higher levels of alanine aminotransferase later in the illness indicate that hepatitis B is a more prolonged illness than hepatitis A, a difference which is independent of age.

The differences between hepatitis A and non-A, non-B hepatitis were also less marked than between hepatitis B and non-A, non-B hepatitis. Both the peak bilirubin and the peak alanine aminotransferase were significantly higher in adults with hepatitis A ($p < 0.001$). But the duration of the pre-icteric illness and the length of jaundice were not significantly longer than in patients with non-A, non-B hepatitis. Nevertheless, one third of the patients with non-A, non-B hepatitis were not jaundiced or were jaundiced for less than 2 weeks compared with a quarter of the hepatitis A patients. This was reflected in the median period of jaundice which was substantially shorter in those with non-A, non-B hepatitis.

In conclusion, hepatitis B appears to be the most severe form of hepatitis in adults but is closely followed by hepatitis A. Generally non-A, non-B hepatitis is a much milder disease.

4.4.2 Effect of Age

Both Capps, Bennett, Mills, Ettinger, Drake and Stokes (1955) and Harris and Beveridge (1967) have drawn attention to the fact that infective hepatitis is mild, short lived illness in children. At the Willowbrook State School clinical and biochemical indicators in children with hepatitis A virus infection returned to normal within 2 to 3 weeks of the onset of the acute illness (Krugman, Ward and Giles, 1962). However, it has been alleged that there is no evidence that hepatitis A increases in severity with age (Mowat, 1980).

In this study there was a clear association between the severity of the illness and increasing age in both hepatitis A and hepatitis B. The trend was most evident among the patients with hepatitis A. Children with this type of infection had the shortest duration of jaundice. The median duration in them was 14 days compared with 30 days in those aged 30 years or more ($p < 0.001$). Similarly there was a highly significant increase in peak bilirubin levels ($p < 0.001$) and peak alanine aminotransferase levels ($p < 0.05$) with rising age. Since children form the bulk of patients with hepatitis A in outbreaks and epidemics it is not surprising that hepatitis A has been generally accepted as much more mild illness than hepatitis B (Dienstag, 1980). This finding is in line with the mildness of other viral illnesses in children.

The relation between age and severity of the illness was not so marked in patients with hepatitis B. The duration of jaundice was significantly prolonged in those over the age of 30 years compared with those aged between 15 and 29 years ($p < 0.025$). Likewise the peak serum bilirubin

was higher ($p < 0.05$) in the older patients. The peak serum alanine aminotransferase showed the same trend, but did not reach statistical significance. In neither hepatitis A nor hepatitis B did age appear to have any influence on the duration of the pre-icteric illness.

In the patients with non-A, non-B hepatitis no association could be demonstrated between any of the clinical or biochemical criteria of severity and age. This may have been due to the smaller number of patients and the general mildness of this type of hepatitis.

In all types of hepatitis neither the peak serum bilirubin nor the duration of jaundice differed significantly between the sexes. The aminotransferase levels tended to be higher in the males, but again this difference did not reach statistical significance. However, London, Drew, Blumberg, Grossman and Lyons (1977) have recorded more serious sequelae from hepatitis B infection and higher frequency of symptomless carriers in males.

4.5 Hepatitis A Virus Antibody

In the survey the presence of immunoglobulin M specific antibody to the hepatitis A virus was accepted as evidence of a recent infection with this virus. The detection of whole antibody alone indicated a past infection.

Approximately a half of the patients with hepatitis B and two thirds of those with non-A, non-B hepatitis had whole antibody to hepatitis A in their serum. Only a small proportion gave a history of previous jaundice (12 % of the hepatitis B patients and 15 % of the non-A, non-B patients). Eight of the 12 patients with hepatitis B and 6 of the 7 non-A, non-B patients with a history of previous jaundice had hepatitis A virus antibody. In 6 of the 12 hepatitis B patients the jaundice had occurred within 6 months of the

current illness and in 4 of these 6 the hepatitis A virus antibody was absent. Thus they had either had non-A, non-B hepatitis or some other cause of jaundice. Alternatively, it was connected with their current illness but there was no way of ascertaining the true cause. All 6 who had been jaundiced at least 5 years or more before had hepatitis A virus antibody as had the 6 patients with non-A, non-B hepatitis.

In conclusion the survey revealed that the majority of previous hepatitis A infection in patients presenting with hepatitis B and non-A, non-B hepatitis had been either inapparent or forgotten. Where jaundice had been recalled, the attack had commonly occurred in childhood.

Patients with hepatitis B born abroad were more likely to have had a previous infection with hepatitis A than those born in the United Kingdom, $p < 0.005$ (Table XXIII). Many of the patients were from the Indian sub-continent or had come from the Mediterranean region. It is likely that most had been infected in early childhood as is common in poorer parts of the world.

The proportion of patients with whole antibody to hepatitis A virus was greater in this survey than reported among blood donors in the United Kingdom by Banatvala and Thorogood (1980). This difference may have been due to the greater number of older persons in the survey population whose social habits exposed them to a greater risk of viral hepatitis of all types.

4.6 Predisposing Factors

A number of factors have traditionally been associated with an increased risk of viral hepatitis. These include a history of skin puncture within 6 months of the illness,

close contact with another person suffering from viral hepatitis within 60 days of the illness, travel to under-developed countries with a high prevalence of endemic hepatitis, living in overcrowded dwellings, exposure to poor sanitary conditions and low socio-economic status. In the survey some of these factors appeared to be more closely associated with one particular type of hepatitis than another.

4.6.1 Injection Exposure

As expected from the finding of Cherubin, Hargrove and Prince (1970) and confirmed by many other groups of workers, there was a high incidence of hepatitis B infection among the addicts. All 13 addicts who were included with the 366 patients tested for the hepatitis A antibody, were positive for the hepatitis B surface antigen. Hepatitis B infection may also be contracted as a result of tattooing (Mowat, Albert-Recht, Brunt and Walker, 1973). In the present series only 2 of the 6 men so exposed were hepatitis B surface antigen positive, a proportion which was not significantly different to that found among all the patients tested.

Our findings suggest that post-transfusion hepatitis due to either hepatitis B or non-A, non-B hepatitis is a relatively infrequent cause of hepatitis in the community. This bears out the findings of a prospective study of post-transfusion hepatitis carried out in London at about the same period (Medical Research Council Working Party on Post-Transfusion Hepatitis, 1974). That investigation revealed that frank hepatitis developed in only one per cent of patients who were transfused although 4.5 per cent had sustained increases in alanine aminotransferase which may indicate sub-clinical hepatitis (Bang, Ruegsegger, Lay and Laduc, 1959).

4.6.2 History of Contact

The importance of children in the spread of viral hepatitis was noted by Hirsch (1886) who referred to an outbreak in Birmingham between September and November 1882. Pickles (1939), in his classic studies, traced the spread of the disease in children living in villages in Wensleydale and suggested that schools provided the circumstances for close contact between children of different families who passed the infection from one to the other. Rowland and Skone (1972) have emphasised that faecal-oral spread of viral hepatitis occurs largely within families during epidemics. In the Bristol outbreak, 37 per cent of 2,107 patients were members of a family with one or more cases and 10.3 per cent of the adults and 39.6 per cent of the children in contact with cases in the home developed infective hepatitis (Bothwell, Martin, Macara, Skone, Wofinden, 1963).

Well over half of the children with serologically proven hepatitis A in the survey gave a history of contact with another person who was jaundiced or who had known viral hepatitis within 60 days of the onset of their illness compared with just over a quarter of adults with hepatitis A and a fifth of those with hepatitis B. In half the children the contact was within the family. This supports the view that close contact within families particularly between children remains a most important factor in the spread of hepatitis A infection.

The household contacts among the patients with hepatitis B were between males, 6 of whom were addicts who lived in small groups. In them the history of contact was complicated by their sharing of syringes and apparatus in connection with their drug habit. However, there were 2 female consorts who disclaimed addiction who developed hepatitis B. In them close social and probably sexual contact played a more important role in the transmission of this disease as has been reported between spouses (Hersh, Melnick, Goyal and

Hollinger, 1971). Likewise there were 3 male homosexuals with household contacts and presumably they contracted their disease in a similar manner.

There were 7 patients suffering from non-A, non-B hepatitis who gave a history of close social contact with another patient with jaundice. Four were within the same household which indicates that family contact may also play a role in the transmission of this type of hepatitis as suggested by Villarejos, Ittensohn, McLean and Hilleman (1976). These workers reported 4 families, each with several cases involving both children and adults with non-A, non-B hepatitis in a prospective survey of endemic hepatitis in Costa Rica.

4.6.3 Travel

Travel to a foreign country did not appear to play an important role in the development of viral hepatitis. Only two fifths of the 361 patients gave a history of travel overseas within 6 months of their illness. However, of the 145 patients who did travel, 92 (63 %) had visited a semi or non-industrialised country where the prevalence of viral hepatitis would be expected to be higher than in the United Kingdom. Furthermore, the proportion of adults with hepatitis A who had travelled to such countries (32 %) was significantly greater than the corresponding proportion of adults with hepatitis B (16 %), $p < 0.05$.

The incidence of hepatitis A rose during the last 4 months of the year particularly between September and October, following a fall in numbers over the summer months. Those who became ill during the autumn were more likely to have travelled to a semi or non-industrialised country compared with those who developed hepatitis earlier in the year. This was most marked among the children ($p < 0.001$). Thus

the autumn rise in hepatitis A appeared to be largely due to returned travellers who had acquired their infection abroad. Similar observations have been reported from Germany (Frösner, Roggendorf, Frösner, Gerth, Borst, Blochinger and Schmid, 1981).

4.6.4 Density of Occupation and Family Size

In an urban society, such as exists in the suburbs of London, the size of homes does not vary very greatly. Thus the density of occupation and family size are closely linked and are therefore best considered together.

The attack rate of infectious hepatitis, expressed as the number of cases per thousand of the population has been shown to vary directly with the population density defined as the average number of persons per room (Burns, 1967; Rowland and Skone, 1971). In the survey the density of occupation was likewise given by averageing the number of persons per room. The children on the whole lived in more crowded conditions than the adults. Thirty per cent of the children with hepatitis A came from a home where there was more than one person per room compared with 10 per cent of adults with hepatitis A, 7 per cent of adults with hepatitis B and 9 per cent of adults with non-A, non-B hepatitis.

The Registrar General's report for 1971 covering the 3 boroughs shows that 13.3 per cent of the population in those boroughs lived in a home where there was more than one person per room. The percentage varied from 18.6 per cent in Ealing to 7.4 per cent in Richmond. Unfortunately these figures were not given according to age. Since more than half of the children in the survey lived in Ealing it might be argued that the children, as a group, would be expected to live in more crowded conditions for they merely reflect the social conditions of the community from which they were drawn. However, the annual incidence of

hepatitis among children under the age of 15 years was highest in Ealing and lowest in Richmond and correlated with the density of occupation. Since most of the children had hepatitis A this suggests that relative overcrowding, especially among children, remains a factor in the transmission of this type of hepatitis as reported previously in epidemic conditions.

In contrast, more than half the patients with hepatitis B and non-A, non-B hepatitis, who were mainly adults, lived in small households with one or 2 others. They consequently lived in less crowded conditions. Forty per cent of those with hepatitis B and 37 per cent of those with non-A, non-B hepatitis lived in houses where there was less than 0.5 persons per room. These proportions were also greater than those in the local community. These findings were probably due to the large number of young single men who had hepatitis B and single women who had non-A, non-B hepatitis.

4.6.5 Domestic Facilities

Living standards have risen in England and Wales over the past few decades along with other western countries. In the boroughs under study well over 90 per cent of the population had access to hot water, a bath or shower and a toilet. Between 80 and 90 per cent have exclusive use of these domestic facilities. All the patients studied enjoyed similar facilities and thus such factors appeared to have no bearing on the prevalence of hepatitis in the community. This is in sharp contrast to many other parts of the world where low socio-economic standards have been associated with a higher prevalence of both hepatitis A and hepatitis B.

SUMMARY

Acute and convalescent sera from 368 patients, studied during a three year total population survey of viral hepatitis in West London between 1972 and 1975, were examined for hepatitis B core and hepatitis A virus antibody. The presence of hepatitis B surface antigen had been determined as previously reported.

Two patients had evidence of infection with the Epstein Barr virus and were excluded. Of the remaining 366 patients, 59 per cent had hepatitis A, 28 per cent hepatitis B and 13 per cent were, by exclusion, considered to have had non-A, non-B hepatitis. Five patients had evidence of recent exposure to both hepatitis A and hepatitis B infection.

Hepatitis B was more common in older men. The majority of children had hepatitis A. Close association between members of large families appeared to promote the spread of hepatitis A. Travel abroad during the summer accounted for an increase in the prevalence of hepatitis A in the autumn although the majority of cases occurred in the late winter and early spring. Hepatitis B increased a little in the last 4 months of the year whereas non-A, non-B hepatitis showed a constant pattern throughout the year.

Among adults, hepatitis B was only slightly more severe than hepatitis A but non-A, non-B hepatitis was a much milder disease. The severity of the illness increased with age. This was most marked with hepatitis A ($p < 0.001$).

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