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Spread of Infectious Hepatitis in the Family Group;† a report of biochemical investigations

by

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The epidemiology of infectious hepatitis is poorly understood. Although the gastro-intestinal tract is the principal pathway of infection in this widespread disease, parenteral transmission is known to occur in a variety of ways. The possibility of the respiratory route has been indicated by MacCallum, MacFarlan, Miles, Pollock & Wilson (1951) from their epidemiological studies. There are in addition several reports of epidemics caused by food (Ballance, 1954), water (Roos, 1956) and milk.

An important method of spread appears to be person to person contact. This is facilitated under conditions where people congregate such as in military camps and institutions for mental defectives (Leading Article, 1964). Other factors which favour the spread of this disease has been found to be household congestion, together with poor sanitation and hygiene which are prevalent among the lower economic groups.

In the endemic as well as in the epidemic situations, anicteric and asymptomatic cases of infectious hepatitis may be present widely in the population at risk. The importance of such cases in the epidemiology of the disease is becoming well recognised. Anicteric and asymptomatic cases are not uncommon (Paul, 1957), and the only abnormalities seen are in the liver function tests (Goldberg and Campbell, 1962). The importance of these cases as potent sources of infection is obvious. In Ceylon, as in other countries there is an increasing incidence of infectious hepatitis. Epidemics are uncommon but sporadic cases abound.

With the above in view it was thought worthwhile to investigate the families of patients admitted to hospital with infectious hepatitis, to map out the incidence of infection in the household and to evaluate the common liver function tests under such a situation.

Tests used in the study of patients with liver and biliary tract diseases can be classified according to the specific function of the liver involved. These include abnormalities of pigment metabolism, tests based on the liver's part in carbohydrate metabolism, tests based on changes in plasma protein, tests based on abnormalities of plasma lipids, determination

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TABLE I.

BIOCHEMICAL FINDINGS IN THE THIRTY (30) POSITIVE CASES OF INFECTIOUS HEPATITIS

	Serum Bilirubin		Zinc Sulphate Turbidity			Alkaline Phosphatase			Serum Glutamic Oxal—Acetic Transaminase			Serum Glutamic Pyruvic Transaminase		
Normal Values	0.8 mg %		2.0 — 8.0 units			3 — 13 KA units			23 — 107 units			25 — 110 units		
Range	1.2 — 22.5 mg %		9.0 — 35.0			13.0 — 58.0			130 — 500			120 — 430		
Mean	5.77		24.97			35.0			326.8			333.7		
S D	5.2		7.18			14.32			90.3			14.3		
Values	0.9—3.0	>3.1	9—12	13—16	>17	14—21	22—29	>30	108—158	159—258	>259	111—161	162—261	>262
Percentage of Total	36.7	63.3	6	13	81	13	17	70	6.6	13.3	80.1	6.6	10.0	83.4

of serum enzyme activities and several others. In the present investigation we determined the abnormalities of pigment metabolism (serum bilirubin), changes in plasma proteins (zinc sulphate turbidity) and serum enzyme levels (alkaline phosphatase and the transaminases, serum glutamicpyruvic transaminase, (SGPT) and serum glutamic oxaloacetic transaminase, (SGOT). These tests are carried out as a routine in liver diseases in most of the Institutions in Ceylon.

The samples of blood were drawn from household members of patients with infectious hepatitis, warded at the Government Hospital, Kegalle, which is situated about forty miles from the Medical Research Institute where the biochemical tests were carried out. In view of the transport difficulties encountered and in order to maintain a uniformity, all tests were carried out within four days of collection of samples of blood, unless stated to the contrary. The serum bilirubin (Dyke, 1951), zinc sulphate turbidity (Kunkel, 1947), alkaline phosphatase (King and Jegatheesan, 1959), serum glutamic oxalacatic transaminase and serum glutamic pyruvic transaminase (King, 1958) were estimated in all cases except when the samples were found to be haemolysed.

RESULTS

The normal values for serum bilirubin, zinc sulphate turbidity, alkaline phosphatase and the transaminases are provided in Table I which also shows the biochemical findings in thirty positive cases of infectious hepatitis. For purposes of recording and analysis of the findings the values were arbitrarily divided into various groups viz: Zinc sulphate turbidity 9-12, 13-16 and > 17 units; alkaline phosphatase 14-21, 22-30 and > 30 KA units; SGOT 108-158, 159-258 and > 259 units; SGPT 111-161, 162-261 and > 262 units.

The age and sex distribution of the 140 contacts subjected to the present investigation are provided in Table II. The subjects were found to be equally distributed among the sexes and about 50% were below the age of 19 years.

TABLE II

AGE AND SEX DISTRIBUTION IN FAMILY CONTACTS

Age group	Male	Female	Total
0—4	11	4	15
5—9	18	10	28
10—14	7	8	15
15—19	9	7	16
20—24	4	8	12
25—29	3	5	8
30—34	1	6	7
35—39	3	9	12
40—44	6	8	14
45 above	7	6	13
	69	71	140

TABLE III

SIZE OF FAMILIES

Number of occupants	Families
3	3
4	8
5	7
6	4
7	6
8	0
9 and more	2
	30

Table III shows the size of the families; little less than half of the families having six or more members in their households.

Bilirubin: Of the positive cases of infectious hepatitis investigated all of them had bilirubin values above 1.2 mg% (Table I) and in 63.3% it was above 3.1 mg%. The picture was quite different in the case of the contacts, all had values within the limits of normality.

TABLE IV

BIOCHEMICAL ABNORMALITIES IN RELATION TO FAMILY SIZE.

Family size	3—4 Members	5—6 Members	>7
Numbers of families	11	11	8
Zinc sulphate turbidity	22	48	47
Alkaline phosphatase	11	28	34
SGOT	8	9	9
SGPT	8	10	6

TABLE V

FAMILY DISTRIBUTION OF CONTACTS WITH ABNORMAL BIOCHEMICAL DATA.

Numbers of members affected in each Family.	Zinc sulphate turbidity	Alkaline phosphatase	SGOT	SGPT
1	1	8	7	10
2	5	9	5	5
3	8	4	2	1
4	7	4	1	1
5	5	3	0	0
6 and > 6	2	1	0	0

Zinc sulphate turbidity : Among the positive cases of infectious hepatitis, all of them had values ranging from 9.0 to 35.0 units (Table I) while 83% of the contacts possessed abnormal values viz: 42% between 9-12, 35% between 13-16 and the balance having values > 16 units. Abnormal values were distributed almost equally among the sexes.

In Table IV and V we have also provided the biochemical abnormalities in relation to the family size and family distribution respectively.

The number showing abnormal zinc sulphate turbidity in families with five or more members was more than four times as much as those families who had less than five members. In two families, (Table V) six or more members, had abnormal values.

Alkaline phosphatase: Elevated levels of alkaline phosphatase were observed in all positive cases of infectious hepatitis (Table I) and in 50% of the contacts (Table VI). In 40.8% of the contacts the values were found to lie between 14-21 ; in 32.4% between 22-30 and in the balance > 30 units of activity. The younger age groups showed a considerable increase in the phosphatase activity.

Transaminase: Raised transaminase levels were found in all the positive cases of infectious hepatitis (Table I). The values ranged from a low value of 130 units to a high value of 500 units. But among the contacts the pattern was quite different. Thus 22.3% had raised SGPT activity, 51.9% between 108-158 units; 24.1% between 159-258 units and the same with values over 259 units (Table VII). A higher incidence in this abnormality was once again seen in the younger age groups; the highest values being in the 10-14 year group. The SGPT levels among the contacts also showed a similar pattern. The incidence of the increased SGOT and SGPT activity (Tables IV and V) appear to have no relation to the family size and the greatest number showing abnormal activity were in families with 1-2 members per family. In many cases the SGPT values were found to be raised while the SGOT remained within normal limits. These will be discussed at the end of this paper.

TABLE VI .

CONTACTS WITH ELEVATED ALKALINE PHOSPHATASE IN RELATION TO AGE

Age groups.	Number of contacts with elevated levels of alkaline phosphatase	%
0—4	15	100
5—9	23	79
10—14	15	100
15—19	9	56
20—24	2	17
25—29	0	0
30—34	0	0
35—39	3	23
40—44	3	21
45 and above	1	8

DISCUSSION

Biochemical investigations : The importance of anicteric and asymptomatic cases have been stressed and their detection presents very many difficulties. This is mainly due to the non-availability of a technique to isolate the causal viral agent and to find a susceptible host animal for the infection. This difficulty has been overcome to a great extent by the introduction of serum enzyme studies.

TABLE VII

SGOT ACTIVITY IN RELATION TO OTHER BIOCHEMICAL DATA AND *SGOT* ACTIVITY WITH NORMAL *SGOT* LEVELS.

SGOT units/ml.	SGPT units/ml.	Zinc Sulphate turbidity (units)	Alkaline Phosphatase KA—units
Contacts showing SGOT activity of 259 or more units.			
460	350	9	15
380	320	16	36
320	275	10	37
280	387	11	35
Contacts showing SGOT activity of 158-258 units.			
230	245	23	30
220	150	10	19
200	120	11	6
200	128	13	50
210	120	9	19
180	30	16	28
166	130	15	
Contacts showing SGOT activity of 108-157 units.			
150	135	17	15
150	120	10	15
150	78	13	8
140	49	8	25
140	123	18	11
144	67	12	8
130	75	8	13
124	90	27	26
122	60	19	14
120	185	24	22
120	67	11	50
110	18	19	20
110	52	15	7
110	67	11	33
Contacts showing elevated SGPT activity but normal SGOT			
90	135	11	10
60	230	15	36
86	142	12	16
80	150	9	19
40	120	9	26
100	112	16	19
60	136	12	13

In the present investigation we have observed that in all positive cases of infectious hepatitis the bilirubin values were all raised above the limits of normality while among the contacts none had values above the normal limits. Therefore, the determination of the serum bilirubin would not throw any light when investigating an outbreak of infectious hepatitis.

While the flocculation and turbidity tests employed in liver and biliary diseases depend to a large extent on the alterations in gamma-globulin, other factors are also involved. Kunkel (1947) described a zinc sulphate turbidity test which he claimed gives an index of the amount of gamma-globulin present. Discombe *et al.* (1954) also reported a close correla-

tion with gamma-globulin as measured by electrophoresis. The normal range was found to lie between 2 and 9 units for Ceylon subjects but results of up to 60 units have been obtained in our laboratories (unpublished data, 1968) in cases with liver disease. Kunkel (1947) also observed delayed rise in gamma-globulin in infectious hepatitis with subsequent prolonged high levels and suggested that this might reflect the production of antibodies rather than a disturbance in liver function. He claimed that the zinc sulphate test is the most sensitive for the detection of residual hepatitis. However, the present studies show that among the contacts abnormal values were obtained in 83% of cases. Therefore, the determination of zinc sulphate turbidity might give a better indication of the presence of infectious hepatitis in the early stages of the disease. The present findings are therefore contrary to the observations made by Kunkel (1947). We are not in a position to provide a suitable explanation for such variation. It might be that the Ceylonese are more susceptible to infection than the European subjects. This needs further study.

An analysis of serum enzyme levels among the contacts showed that 50% of them had an elevated serum alkaline phosphatase and a greater percentage of this abnormality was seen in the younger age group. These findings are in close agreement with those of Harris and Beveridge (1967). The latter investigators found that the alkaline phosphatase levels in growing children are on the higher side of normal. This test becomes very valuable when taken in conjunction with zinc sulphate turbidity test.

It has been shown by several workers that among the enzymes the transaminase estimation yields a better index of liver function especially in the detection of subclinical cases. Both the transaminases SGOT and SGPT are found in most tissues but the relative amounts vary. Thus the liver is rich in SGPT while the heart in SGOT (Wroblewski, 1958). In infectious hepatitis the rise in SGOT generally preceded the appearance of other abnormal clinical and laboratory criteria and therefore served as an important and useful criterion in the diagnosis of this illness (Bodansky *et al.*, 1954). In induced hepatitis, in an asymptomatic and anicteric patient Krugman *et al.* (1959) found that the only indication of liver involvement was an increase in the serum transaminase when all other conventional tests were within normal limits. But in the majority of their cases of anicteric hepatitis both the enzymes and the usual biochemical tests were abnormal. According, to them the serum transaminase activity though not specific may be the most sensitive test for hepatitis in a patient who is thought to be incubating the disease.

In an outbreak of infectious hepatitis in West Germany where 70% were anicteric, Schoen and Wust (1961) concluded that the measurement of SGPT was the most sensitive test for diagnosis and epidemiological purposes. Similarly, Goldberg and Campbell (1962) reported that the SGPT is the most reliable index of infectivity in all forms of the disease. The rise of SGOT precedes that of SGPT but the relative rise in the latter is generally greater than that of SGOT though SGPT enzyme is less stable (Bodansky *et al.*, 1954). In our series, contacts who showed a marked or moderate rise in SGOT activity also showed similar rise in SGPT activity (Table VII) but those who had minimum SGOT activity often had normal SGPT activity and vice versa. It is therefore not possible to conclud

from our series as to which is the more sensitive test for the detection of anicteric asymptomatic or subclinical cases. Using the transaminase activity as an index of infectivity approximately 20% of the household members were infected.

Epidemiology: The high infectivity of infectious hepatitis is well known. In the Bristol outbreak, Bothwell *et al.* (1963) found that 10.3% of the adults and 39.6% of the children in the infected households had the illness. Out of a total of 2107 cases in 2 years, 790 (37%) were members of a family with one or more other cases. In Leicester (Burns, 1967) 9.6% of the adults and 36.2% of the children were affected. Case to case infections and multiple cases within a household are frequent.

The high infectivity accounts for the high incidence of anicteric and asymptomatic cases. The high incidence of these cases in the epidemic as well as in the endemic situation is well established. According to Capps *et al.* (1948) the non-icteric forms may represent 90% of the cases in a given epidemic.

Capps *et al.* (1952) in a study of endemic hepatitis in an infant orphanage found that 90% of the patients who had the disease were without jaundice or hyperbilirubinaemia, anicteric hepatitis is twice as common as the icteric in the endemic situation. Krugman *et al.* (1959) and MacCallum (1961) estimate the ratio of anicteric to icteric as 10:1. In an out-break of hepatitis in a bakery in which 41 persons had jaundice one was ill but without jaundice and 5 of the remaining 34 had abnormal liver function tests, the remainder being apparently well (Thorling, 1954). Schneider and Mosley (1959) studied families with hepatitis and control families in two situations; one where infectious hepatitis was epidemic and the other where it occurred as sporadic cases. Two to five measurements of SGOT activity were performed over a period of 1-3 months. In the former situation they found that 46% had abnormal SGOT as compared with only 6% in the controls. In the latter situation 39% of the families had abnormal SGOT activity while only 8% were affected among the controls.

The anicteric and asymptomatic cases are potent sources of infection and present difficulties as to the control of the illness and their detection. Where the disease is endemic there are thus many sources as well as many ways of spread.

Bothwell *et al.* (1963) in the Bristol outbreak has referred to the roles played in the illness by housing type, population density, sanitary provision, standards of hygiene in the social class, play situation, dental decay and shedding of teeth in children. In the Leicester outbreak, Burns (1967) found a significant association between the high incidence of the disease and domestic overcrowding and poor living standards and further the large part played by anicteric cases in the spread of the disease.

Person to person contact is a common mode of spread, contact history according to Bothwell (1963) implies ingestion or inhalation of the virus material on the hands, clothing or bodily contact or exhalation on its recipient. 43% of 4341 patients with infectious hepatitis admitted to the hospital gave a history of contact with infection (Boughton, 1967).

In the endemic situation large families household congestion and social class were some of the factors noted in the increasing incidence in Ceylon (Nagaratnam and Sikkander, 1969). The greater incidence in the wet zones were attributed by them to the increased population density in these areas.

SUMMARY

Thirty Ceylonese families of patients with infectious hepatitis consisting of 140 contacts were investigated. Of these, 80% had raised zinc sulphate turbidity levels, 50% had raised alkaline phosphatase levels and about 20% had raised transaminase levels (SGOT and SGPT). The index of infectivity as determined by these biochemical tests would have been higher, had more frequent estimations been done at regular intervals over a longer period. It was noticed that those who showed a moderate increase in SGOT activity also showed an increased SGPT activity as well. On the other hand, a minimal increase in SGOT activity was more often unaccompanied by a rise in SGPT activity and the converse was also found to be true. We are unable to conclude from this series as to which is the more sensitive test under these conditions.

The epidemiology of this illness has been briefly discussed and the importance of anicteric and asymptomatic cases stressed. The importance of large families with the accompaniment of poverty, overcrowding, unhygienic living conditions and increased avenues for person to person contact has been stressed in regard to the high incidence of the infection in such families.

The prevention of this illness therefore, to a large extent is purely a problem of hygiene and on the individual level where faecal-oral contamination is responsible. Personal cleanliness should be emphasised in the home.

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