Infectious Hepatitis in Leicester 1963-6

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During the latter part of 1962 the Leicester City Health Department became aware of an increasing incidence of infectious hepatitis among schoolchildren, and on 1 July 1963 the disease was made notifiable in Leicester by an order under Section 147 of the Public Health Act, 1936. This order was to run initially for a three-year period, ending on 30 June 1966, but has been extended for a further three years.

A marginal punch card was devised in conjunction with Kalamazoo Limited to record details of cases, and full information regarding each notified case was obtained at special home visits carried out by health visitors or clinic nurses. During the three-year period 961 cases were notified, and this paper presents an analysis of the epidemiological features of the out-

Monthly incidence of infectious hepatitis in Leicester, July 1963 to June 1966.

break. A preliminary analysis of information collected during the first 16 months has already been published (Burns, 1965).

Epidemic Pattern

General Course of Outbreak

The accompanying Chart shows the monthly incidence of the disease over the three years from 1 July 1963, and indicates that notifications continued at a high level throughout 1964 and during the first half of 1965, but began to fall in the second half of 1965 and remained low throughout the remainder of the period.

Long-term variations in the incidence of the disease with epidemic periods similar to that in Leicester, separated by intervals of several years of low incidence, have been reported from many areas, notably by Mosley *et al.* (1963) in Des Moines, Iowa, and on a national scale by the U.S. Department of Health, Education and Welfare (1964a, 1964b, 1964c). The Chief Medical Officer to the Ministry of Health (1965) showed a similar pattern for the Eastern Region of England and Wales, where the disease has been notifiable since 1943.

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Seasonal Variation

A seasonal variation in incidence was, as the Chart shows, well marked in both 1964 and 1965, with maximum notifications in late winter and high incidence continuing into the spring. A seasonal trend has often been remarked on in this disease (Mosley *et al.*, 1963; Bothwell *et al.*, 1963).

Age and Sex Variations

In this as in other outbreaks (Bothwell *et al.*, 1963; Ward and Krugman, 1962) the disease affected the sexes more or less equally. There was a marked preponderance of cases in the 5-14 age groups, 73.2% of the cases being children in this group. This also is in line with many previous reports (Bothwell *et al.*, 1963; U.S. Department of Health Education and Welfare, 1963), though a predominance of cases in adults has been reported in outbreaks occurring in Denmark (W.H.O. Secretariat, 1964) and in Canada (Bothwell *et al.*, 1963).

Table I shows that the proportion of cases in children under the age of 15 years fell markedly during the final 12 months of the three-year period, coincident with a substantial fall in the number of notified cases as compared with the two previous years. A similar trend has been noted by other observers (U.S. Department of Health Education and Welfare, 1963; W.H.O. Secretariat, 1964). It would appear that this pattern is related to the fact that, in epidemic periods, children under the age of 15 number about three-quarters of the cases, and when a sufficient proportion of them have been infected either clinically or subclinically, and presumably acquired immunity, the incidence of the disease falls to non-epidemic levels, to rise once more when a new generation of susceptibles appears.

Geographical Distribution

During the three-year period cases occurred in all parts of the city. At various stages of the epidemic sizable local aggregations of cases were apparent in particular areas. These formed fairly well defined localized outbreaks, extending over periods of perhaps six to nine months. These local outbreaks tended to involve densely populated parts of the city, of relatively low socio-economic status. The south-eastern quarter

TABLE I.—Percentage of Patients Aged Less Than 15 Years Related to Total Notifications

Period	Total Cases	No Aged Under 15 Years	Percentage Aged Under 15 Years
1/7/63-30/6/64 ..	414	325	78.5
1/7/64-30/6/65 ..	390	324	83.1
1/7/65-30/6/66 ..	157	105	66.9
Total ..	961	754	78.5

of the city, which comprises the more favoured residential suburbs, was almost completely spared. Table II shows the 961 cases notified, broken down into quarterly notifications in each of the city's electoral wards, together with certain additional information derived from the 1961 census report, regarding the ward population and the density of occupation of living accommodation.

Correlation coefficients were calculated between the attack rates per thousand based on the 1961 population figures and the two indices of population density derived from the same source, and gave figures of 0.784 between the attack rate per thousand and the percentage of persons living at more than 1.5 per room and 0.778 between the attack rate per thousand and the average number of persons per room. Both these coefficients are highly significant.

This procedure is, of course, imperfect and open to the dual criticism that neither the population figures from which the attack rates are calculated nor the indices of density of occupation are precisely contemporaneous with the occurrence of the cases. Examination of the annual records of numbers of electors registered in the 16 wards shows, however, that, allowing for alterations in ward boundaries, changes during the period concerned are small in relation to the correlation coefficients, and it is safe to draw the conclusion that the incidence of the disease is closely related to household congestion. Mosley *et al.* (1963) made similar observations on the association of high incidence of the disease with large congested households of low socio-economic status, and it is significant that in Leicester the largest number of cases and the highest attack rate occurred in Ward 16, which at the 1961 Census had the highest occupation densities. This ward consists almost entirely of a single large council estate, populated in the main by large families of low socio-economic status.

A further possible criticism is that as almost three-quarters of the cases occurred in the age group 5–14 years the apparent correlation between attack rates and domestic congestion may merely be a reflection of the possibility that the wards with the highest indices of overcrowding were also those with the highest proportions of children in their populations. Attack rates for the age group 5–14 years were therefore calculated for each of the 16 wards from data from the 1961 census, and the correlations between these rates and the congestion indices are respectively: (a) with the percentage of the population living at greater density than 1.5 per room, 0.877; (b) with the average number of persons per room, 0.524. Both these correlations remain significant, and in particular the high correlation between attack rates in the 5–14 age group and the percentage of the population living at more than 1.5 per room reinforces the conclusion that infectious hepatitis is a disease associated with overcrowding and underprivilege.

Mode of Transmission

The epidemiological pattern indicated direct person-to-person transmission as the mode of infection. This is the mode of spread in the majority of epidemics—for example, in Bristol (Bothwell *et al.*, 1963) and Des Moines, Iowa (Mosley *et al.*, 1963). Outbreaks have, however, been described in which both food and water have been the apparent vehicle of spread (Lancet, 1962, 1964; *Brit. med. J.*, 1964). In the U.S.A. clams and oysters have been incriminated in a number of outbreaks (U.S. Department of Health, Education and Welfare, 1964a, 1964b).

While no general attempt was made, except as regards food-handlers who were family contacts of known cases, to detect anicteric or subclinical cases, it was evident that such cases were a frequent source of infection to others. MacCallum (1961) quotes estimates of the ratio of anicteric to icteric cases of up to 10:1. In the Leicester outbreak the part played by subclinical cases in transmitting the disease manifested itself when, as happened occasionally, one or more cases occurred in a family where the only history of contact with a previous known case of the disease was in another member of the family who did not suffer an overt attack. Another index of the important part played by asymptomatic and unrecognized cases in the spread of the disease was the fact that of the 961 cases 638 (66.4%) were unable to recall any contact with a known case of the disease.

Spread within the Family

The 961 cases occurred in 742 households. In the affected households 36.2% of the children and 9.6% of the adults contracted clinical attacks of the disease. These figures compare very closely with those of Bothwell *et al.* (1963), who found in the Bristol outbreak that 39% of children and 10.3% of adults in affected households fell ill.

The secondary attack rate among child family contacts was 11.8% and among adults 1.9%. Mosley *et al.* (1963) reported a secondary attack rate of 10% among family contacts not protected with gammaglobulin.

School Spread

There are 185 schools in the city and cases occurred in 115 of them. In 62 schools there were fewer than five cases, 25 had more than 10 cases, and nine had more than 20 cases. These nine schools between them produced 267 cases—that is, more than a quarter of the total number of cases in the city and more than one-third of the cases among schoolchildren.

TABLE II.—Distribution of Cases by Electoral Wards

Period	No. of Cases in Ward:																Whole City
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
1/7/63–30/9/63 ..	2	—	—	—	—	—	2	4	2	2	10	31	—	—	—	—	53
1/10/63–31/12/63 ..	4	—	1	—	4	—	1	3	2	1	36	9	2	6	5	2	76
1/1/64–31/3/64 ..	3	6	17	3	6	3	1	7	5	3	58	2	4	11	5	2	134
1/4/64–30/6/64 ..	2	4	5	9	13	2	2	19	5	4	14	8	2	49	11	2	151
1/7/64–30/9/64 ..	3	2	6	6	4	7	—	10	2	2	3	4	3	12	4	3	71
1/10/64–31/12/64 ..	1	1	—	6	3	1	1	7	8	8	5	4	9	10	8	28	100
1/1/65–31/3/65 ..	1	2	1	2	3	2	6	5	12	2	—	3	5	9	11	53	117
1/4/65–30/6/65 ..	—	—	8	2	—	1	1	6	14	3	—	—	4	10	13	40	102
1/7/65–30/9/65 ..	—	9	9	—	3	—	2	2	2	1	—	2	2	6	5	6	49
1/10/65–31/12/65 ..	—	4	5	—	3	3	4	9	—	—	—	1	—	4	3	5	40
1/1/66–31/3/66 ..	—	—	2	1	2	—	1	9	2	—	1	—	—	1	4	—	22
1/4/66–30/6/66 ..	—	—	2	1	—	—	—	35	—	—	1	1	—	2	2	2	46
Total ..	16	28	56	29	40	19	21	116	52	26	128	65	31	120	71	143	961
Population (1961 census)	9,858	13,194	13,035	14,557	12,181	9,355	17,639	25,774	23,699	17,605	20,827	19,385	18,162	18,559	21,969	17,671	273,470
% of persons at more than 1.5 per room (1961 census) ..	1.7	2.3	3.7	4.4	8.3	4.2	1.9	4.9	2.4	2.1	5.3	1.6	0.7	6.6	2.3	11.6	4.0
Average No. of persons/room (1961 census) ..	0.56	0.55	0.57	0.55	0.60	0.56	0.53	0.73	0.66	0.59	0.68	0.63	0.52	0.65	0.65	0.74	0.62
Attack rate/1,000 (based on 1961 population figures) ..	1.62	2.12	4.30	1.99	3.28	2.03	1.19	4.50	2.19	1.48	6.15	3.35	1.71	6.47	3.23	8.09	3.51

The fact that more than half of the affected schools produced fewer than five cases each and 17 (14.8%) of them produced only one case is in striking contrast to the high incidence in the relatively small number of schools in which substantial outbreaks occurred. The reason for the great differences in the epidemiological pattern of the disease observed in different schools is obscure, but it does not appear to be related to factors within the school, such as adequacy of sanitary or washing facilities. The wide variation in the natural history of school outbreaks makes the evaluation of preventive measures, such as mass gammaglobulin administration or the institution of stringent hygienic measures as described by Schofield (1964), extremely difficult, and underlines the need for carefully controlled trials before conclusions are drawn regarding the efficacy of such measures and the circumstances in which they should be applied.

As already stated, the great majority of cases were children of school age. Within this group, however, there was a marked difference between the primary and secondary age groups. All nine schools with sizable outbreaks were primary schools, and when cases occurred in primary schools a substantially larger proportion of the children tended to fall ill than in a secondary school. At schools where cases occurred the overall attack rates were: primary 2.8%, secondary modern 1.2%, and grammar 0.5%. The difference between secondary modern and grammar school attack rates is striking, and a number of factors, including smaller classes in grammar schools, the presence in them of a proportion of young people aged 16 years and over with a less tendency to the disease, and, of course, differences in socio-economic background, may have contributed to this.

Outbreaks of infectious hepatitis have often been associated with schools and have characteristically smouldered on for several months, with shorter periods of explosive incidence within the outbreak. Tilley (1960), Flanagan and Lister (1962), Schofield (1964), and Yarrow (1964) have described such outbreaks in recent years, while Pickles (1939) stressed the role of school contact in the occurrence of outbreaks. On the other hand, Mosley *et al.* (1963) stated that in the outbreak in Des Moines, Iowa, examination of the role of the school indicated that the school, particularly the classroom, was not the primary source of infection, and that closer social and personal contact was necessary for transmission of infection to occur than was afforded by casual classroom association.

In the Leicester outbreak a close examination was made of 43 cases occurring at an infant school of 508 pupils, giving an attack rate of 8.44%. In these 43 cases the apparent source of infection was: known classroom contact, 34.9%; family/household contact, 22.1%; probable subclinical class contact, 10.5%; unidentified, 32.5%. In addition, all cases occurring in the families of these 43 children were examined, and of the 61 cases involved the apparent source of infection was: known classroom contact, 27.9%; family/household contact, 31.2%; probable subclinical class contact, 6.6%; unidentified, 34.3%.

The small numbers and the high proportion of cases of unidentified origin do not permit the drawing of conclusions on the relative importance of classroom as opposed to family contact in the transmission of the disease, but it does seem clear, in contrast with the findings of Mosley *et al.*, that contact in the classroom was a factor of considerable importance.

School Meals

The possibility of school meals being implicated in the spread of the disease was thoroughly investigated and there was no evidence that they were a factor. Of the 776 cases occurring among schoolchildren 336 (43.3%) took school meals, while of the total of 37,941 pupils in the schools where cases occurred 19,966 (52.6%) took school meals. Of the 19,966 children taking meals 336 (1.7%) suffered attacks, while of the 17,975 not taking meals 440 (2.5%) suffered attacks.

Clinical Features and Prognosis

Jaundice occurred in 91% of notified cases. Reference has already been made to the substantial numbers of anicteric cases and symptomless excretors of virus which are believed to occur during any outbreak, the present one being no exception. It was obvious that many anicteric cases were occurring among both school and family contacts, but no general attempt was made to search for them. The absence of any specific serological or virological test for the presence of infection is a most serious handicap in detecting such cases. The use of tests for the presence of bilirubin in the urine has been suggested (*Brit. med. J.*, 1963b) as a means of detection, and a number of such tests were carried out in the current investigation in family or school contacts who displayed symptoms but no clinical jaundice. The results were all negative: 44 (4.6%) of the cases required admission to hospital and 31 (70.5%) of these were between the ages of 5 and 14 years, while 9 (20.5%) were aged over 20 years. Three of the cases were fatal. An Indian immigrant woman aged 32 died in hepatic coma after a three-weeks illness; a schoolboy aged 5 years died of subacute liver failure after a six-weeks illness; and a 9-year-old boy died in hepatic coma after eight days. These three deaths represent a mortality rate of 3.1 per thousand.

Sherlock (1963) stated that the mortality in large outbreaks of infectious hepatitis has been generally quoted as one to two per thousand. In the Bristol outbreak (Bothwell *et al.*, 1963) there were three deaths in 2,107 cases. Occasionally, however, outbreaks have been reported with higher mortality. The *Lancet* (1962) referred to an outbreak in New Jersey in 1961 where there were 2,095 cases with 34 deaths.

There is some evidence (*Brit. med. J.*, 1963a) that cirrhosis may occasionally follow infectious hepatitis, but Sherlock (1963), reviewing the question of long-term sequelae, concluded that rapid and complete recovery is the rule, and while transition to cirrhosis does occur it is infrequent. Bothwell *et al.* (1963) reported that early follow-up studies of their cases appeared to confirm the rarity of prolonged ill-health or cirrhosis.

Discussion

Infectious hepatitis has been described as one of the biggest unsolved problems in medical virology (*Brit. med. J.*, 1964). The epidemiological features of the disease have been studied extensively in the United States, where the Department of Health, Education and Welfare has published a series of surveillance reports since April 1960, and in a number of European countries. In 1964 a symposium on viral hepatitis sponsored by the W.H.O. Regional Office for Europe was held in Prague. Seventeen countries including the U.K. were represented at this symposium, at which the clinical, laboratory, epidemiological, and control problems presented by the disease were reviewed and the setting up of detailed surveillance programmes in the different European countries was recommended.

So far as the United Kingdom is concerned, the disease is not generally notifiable, so that the magnitude of the problem it presents is unknown, and no information regarding its epidemiological pattern on a national scale is available. Local studies, including that carried out in East Anglia under the Jaundice Regulations, 1943 (MacCallum *et al.*, 1951), the reports by Bothwell *et al.* (1963) on 2,101 cases which occurred in Bristol in 1961–2, and by Clayton (1967) on his survey at Coventry, together with numerous reports of local outbreaks in schools or other communities (Tilley, 1960; Flanagan and Lister, 1962; Schofield, 1964; Yarrow, 1964; Pollock, 1964), and, of course, the classical studies of Pickles (1939), clearly indicate that in this country a considerable amount of ill-health is being caused by this infection, more especially among schoolchildren, and that an unknown though

probably small amount of permanent liver damage also results from it.

The control of the disease presents peculiarly difficult problems. Not only do large numbers of anicteric or subclinical cases occur which, though remaining undiagnosed, are nevertheless infectious, there is evidence (MacCallum *et al.*, 1951; Ward and Krugman, 1962) that patients are infectious during the incubation period, about 20 days before the onset of jaundice. The incubation period itself is long and variable—up to six or eight weeks, and cases may follow each other in a family, separated by this interval. Furthermore, there is evidence that some patients continue to excrete virus for long periods after clinical recovery. Ward and Krugman (1962) quoted evidence of the finding of virus in the stools up to 15 months after the onset of illness. Despite the work of Rightsel *et al.* (1961) there is no simple laboratory method of detecting the presence of virus and no specific test for the carrier state. In food- or water-borne outbreaks, if the source can be traced and appropriate measures taken, good results may be obtained. In contact-spread outbreaks, on the other hand, it is doubtful whether at the present time effective control measures are possible.

The epidemiological features already referred to, together with the absence of any specific laboratory test for the carrier state, clearly render quarantine of contacts of no practical value, and this is confirmed by the work of Kostrzewski and Szmunes (1964). It seems reasonable to keep contacts who are food-handlers under surveillance for a period, and in Leicester such surveillance is maintained until six weeks has elapsed after the onset of illness in the last case in the family. Bothwell *et al.* (1963) excluded food-handlers in the school meals service for a period of one month if they were well; but this seems arbitrary and difficult to justify in view of the facts stated above. In Leicester these persons are kept under surveillance, their urine is tested weekly with the Ictotest tablet, and blood is taken for serum alanine aminotransferase estimation.

Schofield (1964) described an outbreak affecting two primary schools which was apparently abated by the introduction of stringent measures of hygiene, including special supervision of the children's handwashing, and disinfection thrice daily of all W.C. seats, flush-handles, washbasin taps, and door-handles. Similar measures were used at schools in Leicester where outbreaks occurred, but without noticeable effect.

Evidence is available (Ward and Krugman, 1962; Mosley *et al.*, 1963) of the efficacy of gammaglobulin in the U.S.A. in providing passive protection against a clinical attack of infectious hepatitis and similar claims have been made in respect of British gammaglobulin. However, properly controlled trials have hitherto been lacking in this country, and the need for caution in drawing conclusions from uncontrolled trials in view of the wide variations in the natural history of school and other institutional outbreaks has already been referred to. A controlled trial at present being carried out by the Epidemiological Research Laboratory, Colindale, will, it is hoped, clarify this question.

Future progress in the control of this disease would appear to lie in two directions. Firstly, the introduction of a simple and reliable test for the presence of the virus, and, secondly, the production of an effective vaccine. In the meantime there is a good case for general notifiability, at least for a period, in order to extend knowledge of the incidence and epidemiological pattern of the disease in this country, and so to provide the facts on which the use of improved control measures can be based when they become available. The whole problem may acquire much greater urgency if the suggestion made by Stoller and Collmann (1965) of an association between infectious hepatitis and Down's syndrome should be substantiated.

Summary

During the three years 1 July 1963 to 30 June 1966 961 cases of infectious hepatitis were notified to the Leicester City

Health Department. The peak of the epidemic occurred during the first two years of that period. A well-marked seasonal trend, with maximum incidence in late winter and spring, was observed. Over the whole period more than three-quarters of the patients were aged under 15 years, children in primary schools being the most heavily affected group. As the intensity of the epidemic waned the proportion of child cases tended to fall. There was a significant association between high incidence of the disease and domestic overcrowding and poor living standards. There was evidence that anicteric and subclinical cases played a large part in the spread of the disease. The overall secondary attack rate among family contacts was 5.44%. Among children the rate was 11.8% and among adults 1.9%.

Cases occurred in 115 of the 185 schools in the city, but in the great majority of schools no extensive outbreak developed. The natural history of the disease as it affected schools showed wide variations, and there was no means of distinguishing in advance the small minority of schools in which the initial cases were followed by a sizable outbreak from those where only a small number of cases occurred. This makes the evaluation of both the efficacy of preventive measures, such as the administration of gammaglobulin, and the circumstances in which they should be used very difficult. Both family and school contact were important in transmitting the disease; there was no evidence, however, that school meals were a factor. Most of the cases had illnesses of mild or moderate severity, but three (3.1%) died.

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REFERENCES

- Bothwell, P. W., Martin, D., Macara, A. W., Skone, J. F., and Wofinden, R. C. (1963). *Brit. med. J.*, 2, 1613.
 — 1963a, 1, 5.
 — 1963b, 2, 1602.
 — 1964, 2, 69.
 Burns, C. (1965). *Roy. Soc. Hlth J.*, 85, 144.
 Chief Medical Officer, Ministry of Health. (1966). *Annual Report 1965*, p. 45. H.M.S.O., London.
 Clayton, T. M. (1967). *Med. Offr.*, 117, 195.
 Flanagan, K. T., and Lister, J. (1962). *Brit. med. J.*, 2, 376.
 Kostrzewski, J., and Szmunes, W. (1964). *W.H.O. Report on European Symposium on Viral Hepatitis*, p. 75.
Lancet, 1962, 2, 491.
 — 1964, 1, 422.
 MacCallum, F. O. (1961). In *Virus and Rickettsial Diseases of Man*, 3rd ed., edited by S. P. Bedson, A. W. Downie, F. O. MacCallum, and C. H. Stuart-Harris, p. 221. London.
 — McFarlan, A. M., Miles, J. A. R., Pollock, M. R., and Wilson, C. (1951). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 273.
 Mosley, W. H., Speers, J. F., and Chin, T. D. Y. (1963). *Amer. J. publ. Hlth*, 53, 1603.
 Pickles, W. N. (1939). *Epidemiology in Country Practice*. Bristol.
 Pollock, G. T. (1964). *Med. Offr.*, 111, 301.
 Rightsel, W. A., Keltch, R. A., Taylor, A. R., Boggs, J. D., and McLean, I. W. (1961). *J. Amer. med. Ass.*, 177, 671.
 Schofield, R. (1964). *Med. Offr.*, 111, 299.
 Sherlock, S. (1963). *Diseases of Liver and Biliary System*, 3rd ed. Oxford.
 Stoller, A., and Collmann, R. D. (1965). *Lancet*, 2, 1221.
 Tilley, J. H. MacD. (1960). *Brit. med. J.*, 2, 1354.
 U.S. Department of Health, Education and Welfare (1963). *Hepatitis Surveillance Report*, No. 17.
 — (1964a). *Ibid.*, No. 18.
 — (1964b). *Ibid.*, No. 19.
 — (1964c). *Ibid.*, No. 20.
 Ward, R., and Krugman, S. (1962). *Progr. med. Virol.*, 4, 87.
 World Health Organization Secretariat (1964). *Report of Symposium on Viral Hepatitis in Europe*. Annex 11, p. 19.
 Yarrow, A. (1964). *Lancet*, 1, 485.