

EPIDEMIOLOGY OF ACUTE HEPATITIS IN THE ROYAL AIR FORCE*

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Acute hepatitis has been recognized as an outstanding military disease for many years. Compulsory notification of acute hepatitis and jaundice in the Royal Air Force in recent years revealed many cases amongst Servicemen stationed at home and abroad. The number of cases together with the long duration of illness and the occurrence of three deaths attributed directly to acute hepatitis became matters of some concern. An investigation was, therefore, undertaken to study the epidemiology of acute hepatitis in the Royal Air Force and to determine the role, if any, of syringe transmission in a population which is constantly receiving many prophylactic inoculations for which a variety of methods and widely differing sterilization techniques are used. In addition, the clinical and laboratory features and complications of acute hepatitis were studied in some detail.

MATERIALS AND METHODS

Acute hepatitis is a notifiable disease in the Royal Air Force. All cases of jaundice occurring in Servicemen and their dependants are also notified both to the Principal Medical Officers and to the Air Ministry. During the period January, 1957, to July, 1962, 401 cases of acute icteric hepatitis were notified in Servicemen stationed in the United Kingdom and 494 cases in men overseas. Servicewomen and dependants suffering from acute hepatitis were excluded from this survey.

The investigation was divided into two main parts: an investigation of all new cases of jaundice in the

Royal Air Force from March, 1961, until July, 1962, and a retrospective study of all patients with jaundice, hepatitis, cirrhosis, inoculation, injection, and transfusion reactions in the Royal Air Force from January, 1957, until March, 1961.

(1) INVESTIGATION OF NEW CASES OF JAUNDICE OCCURRING IN THE BRITISH ISLES

As soon as the diagnosis was made cases were notified by letter to the Air Ministry and by telephone to the Laboratory. Whenever possible the Stations were visited personally and the patient examined, and at the same time a number of controls were interviewed. The controls consisted of airmen of about the same age and the same length of completed service as the patient, chosen strictly at random from a complete list of the Station's personnel, but were otherwise unselected. A standard questionnaire was completed for both patients and controls. The information obtained verbally was then checked against the personal documents and against the records held at Sick Quarters. During the same visit information was sought on the method of sterilizing instruments, syringes, and needles, and the method of administering injections and inoculations. Attendance at an "inoculation session" was usually possible. The Medical and Dental Officers of Stations which could not immediately be visited were requested to provide the same information by letter; a general discussion was then held over the telephone and, if possible, the unit was visited at a later date. Four RAF hospitals and 25 RAF Stations were visited between March, 1961, and July, 1962. The Stations were spread over a wide geographical area and were representative of most types of RAF units. In the course of these visits 96 patients

* This work has been approved by the University of London for submission of a thesis for the degree of M.D.

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suffering from acute hepatitis were examined and investigated and 245 controls were interviewed.

(2) CASES OF JAUNDICE OCCURRING OVERSEAS

It proved impracticable to obtain information in the same manner from Overseas units. However, the Medical Officers were requested to provide a full history of injection and of any other skin penetration within the 6 months preceding the onset of illness at the time of notification. Further information was sought, where necessary, by letter. The detailed clinical history was subsequently obtained from the Air Ministry Medical Records Office.

The complete medical and dental history of all the patients investigated was examined at a later date at the Medical Records Office, to obtain the full clinical and laboratory details as well as for follow-up.

(3) RETROSPECTIVE INVESTIGATION, 1957-61

Patients suffering from jaundice, hepatitis, cirrhosis, and any local or generalized reactions to injections, inoculations, or transfusions are coded by the International method at the Air Ministry and are recorded by the Medical Statistics Division. The complete personal, medical, and dental clinical history is stored at the Air Ministry. The medical and dental records of all these patients for the years 1957-61 were taken out and studied individually. No control group was available for patients included in this part of the investigation.

2,869 medical histories were thus available for examination. Patients suffering from liver disease other than infectious hepatitis, serum hepatitis, and cirrhosis were excluded, thus leaving 939 cases for study of whom twenty were patients with long-standing alcoholic cirrhosis.

The inoculation and injection history is recorded on the patient's medical envelope (F.Med.4), and is stored separately from the other medical records except in Station Sick Quarters. This envelope is kept at the unit if the patient is on active service, at the Air Ministry Records Office at Gloucester if the patient has completed his service, or at the Ministry of Pensions and National Insurance if the patient has been invalided. These documents were also made available for study through the courtesy of the Air Ministry and the Ministry of Pensions and National Insurance. There remained, however, one further small group of patients for whom the injection history was not fully documented or for whom it was impossible to trace the individual records through inaccuracy in name or service number. A postal inquiry was then made to the patient's medical practitioner or directly to the patient whenever

possible. Nevertheless, the injection history could not be obtained for ten patients.

In this way two standard forms, a detailed epidemiological record and a clinical and laboratory record, were completed for each patient.

FINDINGS

METHODS OF STERILIZATION AND INOCULATION

Autoclaving was the only method of sterilizing syringes, needles, and dressings in the four hospitals visited. In one large transit unit, all syringes and needles were sterilized in an oven by dry heat at 180°C. for one hour before use. Some stations used the local hospital central sterile supply service for their syringes only. In the remaining Stations syringes and needles were sterilized at Station Sick Quarters by boiling in water, but in most of them for times varying from only a few seconds to a few minutes.

The methods of inoculation at all units visited were uniform.

Vaccinations against smallpox were carried out with Hagedorn needles which were flamed before and after use.

Multidose vials (ten doses) of Typhoid-Paratyphoid A and B—Tetanus vaccine (TABT), anti-tetanus toxoid (ATT), poliomyelitis, cholera, and influenza vaccines, were used at almost all stations. 10- or 20-ml. syringes were loaded with five to ten doses of the vaccine. After insertion of the needle into the arm, the piston of the syringe was withdrawn to ensure that the needle was not placed in a blood vessel. A fresh needle, but not a fresh syringe, was used for each patient.

The inoculation of yellow fever vaccine was carried out only in hospitals and in selected units. The multidose method of syringe-loading was used, with a change of needle after each insertion.

A separate syringe and needle was used for each patient when therapeutic injections, such as penicillin, were given at both stations and hospitals.

The cartridge-type of syringe was universally used for dental injections. Sterilizing the needle and holder by boiling in water, however, varied considerably from a few seconds to 30 minutes. The sterilization of dental instruments for dental procedures such as the scaling of teeth, which almost invariably resulted in drawing-off some blood from the gums, was to all intents and purposes not carried out.

GENERAL EPIDEMIOLOGY

During the period of this investigation (January, 1957, to July, 1962), there were 401 cases of acute hepatitis with jaundice in RAF personnel stationed in the United Kingdom, and 494 cases overseas; 24

cases of acute hepatitis in the second half of 1962 are also included. These patients were not investigated personally but are included so as to give comparable information for each year. The mean annual strength of the RAF and the calculated rate of acute hepatitis with jaundice per 100,000 men is given in Table I.

TABLE I
MORBIDITY RATE OF ACUTE HEPATITIS PER 100,000 MEN IN THE ROYAL AIR FORCE

Year	Home Units		Overseas Units	
	No. of Men	Rate per 100,000	No. of Men	Rate per 100,000
1957	164,666	54.6	49,672	140.9
1958	137,347	35.0	42,802	212.6
1959	125,865	52.4	39,513	265.7
1960	120,433	83.9	37,792	259.3
1961	113,535	69.6	35,877	231.3
1962	106,823	31.8	34,280	172.1

The incidence of acute hepatitis was much higher abroad than at home, and this is largely accounted for by the very high incidence in the Middle East Air Force Command. The seasonal incidence of acute hepatitis is shown in Fig. 1, the quarterly incidence at home and overseas is very similar with a peak in mid-winter, the lowest number of cases occurring during the summer.

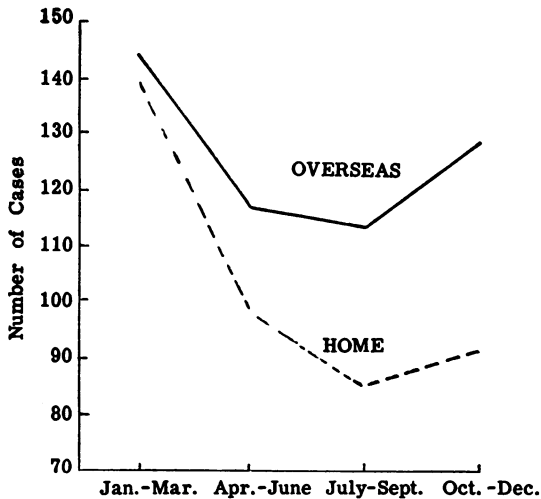


FIG. 1.—Quarterly incidence of hepatitis.

Five age groups were considered. The highest attack rate of acute hepatitis in the Royal Air Force occurred in the 20 to 29-year age group with 98.5 per 100,000, followed by 92 per 100,000 in the 30 to 39-year group. The lowest attack rate was

recorded in the 40 to 49-year group with 52 per 100,000. In the under-20s, the boy-entrants were considered separately from the remainder of this age group who were recruits, because the former entered the Service and were trained and housed under conditions which were more like school-life. The attack rates in these two groups were found to be similar (Table II).

TABLE II
AGE DISTRIBUTION AND MORBIDITY RATE OF ACUTE HEPATITIS PER 100,000, 1957-62

Age Group (yrs)	Boy Entrants 16-18	Under 20	20-29	30-39	40-49	50 and Over
No. of Patients*	29	68	603	148	53	8
Total Man-years	41,359	77,464	612,399	160,832	101,833	14,692
Rate per 100,000	70.1	87.8	98.5	92.0	52.0	54.5

* Including 24 cases occurring from August to December, 1962.

The incidence of hepatitis in relation to rank was 106.7 per 100,000 in officers and 88.7 per 100,000 in airmen; this difference was not significant.

The length of time between the first case and subsequent cases among 492 patients was analysed in the 58 outbreaks which occurred during the whole period of this investigation. Of these outbreaks, 27 consisted of only two related patients (*i.e.* with a serial interval of up to 60 days and therefore assumed to have been contracted from a common source), sixteen consisted of three to five related cases, ten of six to ten cases, and five of more than ten icteric cases. The remaining 403 cases of acute hepatitis were quite unrelated (*i.e.* with a serial interval longer than 60 days), and these were therefore unlikely to have been caused by spread from person to person.

The highest number of cases of acute hepatitis at home units occurred in men serving between 1 and 2 years, and overseas in those serving between 2 and 5 years (Table III).

TABLE III
LENGTH OF SERVICE AND INCIDENCE OF HEPATITIS

Units	Length of Service							Total
	0-6 mths	7-12 mths	13-24 mths	2-5 yrs	5-12 yrs	12-20 yrs	20 yrs	
Home	54	26	95	80	61	57	28	401
Overseas	0	21	87	177	148	35	26	494

A significant number was also noted in men who served for over 12 years. These figures, however, are

those of actual illness, and accurate rates are not known in the absence of information on the breakdown of RAF personnel into groups by length of service completed.

ROLE OF INJECTIONS

The complete history of injection and inoculation, dental injection, and any skin penetration, including tattooing, in the 6 months preceding the onset of symptoms was obtained in 829 (92.6 per cent.) of the 895 patients, of whom 368 were injected and 461 received no injections. Eleven patients were tattooed within 6 months of the onset of illness, three of them on a number of occasions. In 56 patients (6.2 per cent.) the dental injection history was not available, and in another ten (1.2 per cent.) the injection history was not known. The 24 patients with acute hepatitis notified in the second half of 1962, who were not investigated, are excluded.

The number of injections given to 100 patients and controls is shown by the monthly interval between the injection and the onset of illness in Table IV.

TABLE IV
INJECTION RATES PER 100 PATIENTS AND CONTROLS, BY MONTHLY INTERVAL BETWEEN INJECTION AND ONSET OF ILLNESS

Group	Interval (mths)						Total No. of Men*	
	0-1	>1-2	>2-3	>3-4	>4-5	>5-6		
Controls	18.7	11.4	13.1	13.1	8.9	10.6	245	
Patients	Visited	24.2	24.4	15.5	17.9	20.6	16.9	96
	Not Visited	17.7	18.5	18.1	16.1	16.5	10.6	733
All Groups	20.9	21.5	16.8	17.0	18.5	13.7	829	

* 56 patients for whom the dental injection history was not known, and another ten patients for whom no injection history was available have been excluded.

There were differences in the injection rates between patients with jaundice and controls at the time interval 1 to 5 months, but the differences between the patients injected at 2 to 3 and 3 to 4 months and the controls did not attain the 5 per cent. level of statistical significance. However, the differences between the controls and the patients who received injections 1 to 2 and 4 to 5 months before the onset of illness were more marked. There were only small and statistically non-significant differences between the rates in the patients visited personally and in those not visited, and consequently all the patients were grouped together. The controls, although these were strictly applicable only to the patients who were visited, could therefore be reasonably considered in relation to the whole group of

patients. The injection rates were then calculated for patients with sporadic and unrelated illness (i.e. serial interval between cases longer than 60 days) and these were compared with related cases and controls (Table V). A marked difference was again noted in the unrelated patients injected at 1 to 2 months and to a lesser extent in those injected 4 to 5 months before the onset of illness ($P < 0.05$).

TABLE V
INJECTION RATES PER 100 PATIENTS IN UNRELATED AND RELATED CASES, BY MONTHLY INTERVAL BETWEEN INJECTION AND ONSET OF ILLNESS

Group	Interval (mths)						Total No. of Men*
	0-1	>1-2	>2-3	>3-4	>4-5	>5-6	
Unrelated (sporadic, or serial interval more than 60 days)	21.8	30.5	13.8	15.4	24.9	13.0	376
Related (serial interval within 60 days)	20.1	12.4	19.8	18.6	13.2	14.5	453
Controls	18.7	11.4	13.1	13.1	8.9	10.6	245

* 56 patients for whom the dental injection history was not known, and another ten patients for whom no injection history was available, have been excluded.

A study of the injection history and seasonal onset of hepatitis (Fig. 2) shows that the curve for patients injected within 6 months of illness is, on the whole, flatter.

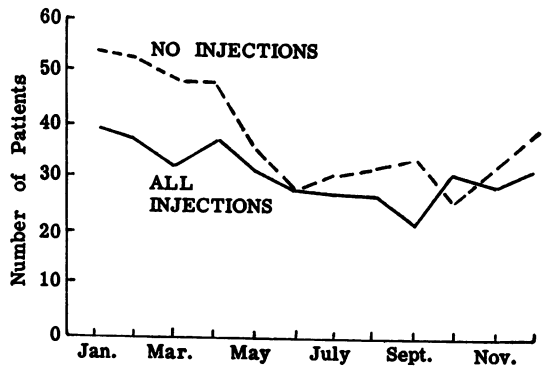


FIG. 2.—Seasonal onset and injection history.

When the patients with unrelated illness who were injected at 1 to 2 and 4 to 5 months were plotted separately, an almost straight line was obtained (Fig. 3, opposite). The time distribution of the administration of the injections was reviewed to exclude differing seasonal injection rates. These were essentially similar in the four quarters of the year, and were unlikely, therefore, to have influenced

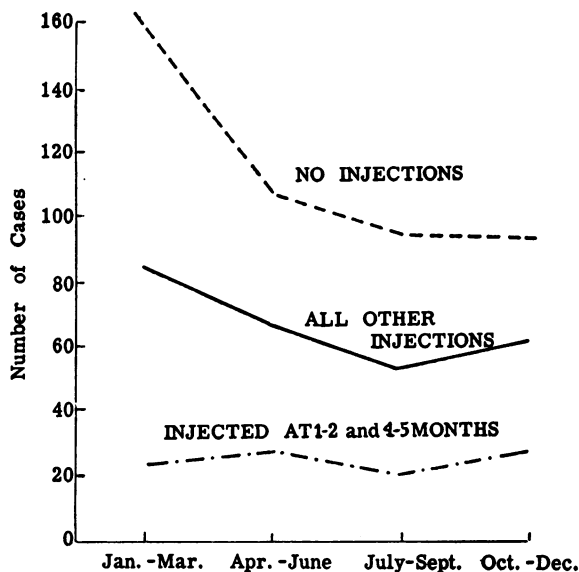


FIG. 3.—Quarterly incidence of hepatitis and injection history.

the seasonal onset of illness. Analysis of the distribution of prophylactic, therapeutic, and dental injections in patients and in controls showed only minor differences between the injections given to patients suffering from hepatitis and those given to controls, at all the monthly intervals considered. Thus no particular type of injection nor the route employed for inoculation could be implicated in the transmission of hepatitis.

DISCUSSION

It has been generally agreed that the incubation period for infectious hepatitis is 15 to 40 days, whether it is transmitted *via* the alimentary canal or parenterally, and that 60 to 160 days is the period for serum hepatitis. However, the incubation period of cases labelled serum hepatitis has varied from less than 40 up to 180 days. While the shorter incubation period is within the range of infectious hepatitis, it is more difficult to account for the long incubation periods in some cases of serum hepatitis. Downie (1963) considered that, in carriers whose infection has lasted for months, the amount of virus in the blood might diminish, the virus might have become attenuated, or the blood in which the virus was transferred might delay multiplication of the virus in the recipient; some support for these notions comes from the observations of Boggs, Capps, Weiss, and McLean (1961), and of Stokes and 13 others (1954). The studies of Francis, Frisch, and Quilligan (1946) and Harden, Barondess, and Parker (1955) also suggest that the incubation period of

virus hepatitis is not wholly dependent on the route of inoculation, but may be related to the virus titre inoculated. They found, in cases of transfusion hepatitis, incubation periods which were unusually short, 11 to 14 days to the onset of illness and 21 to 30 days to the onset of jaundice. Neefe, Stokes, Rheinhold, and Lukens (1944), in experimental transmission of hepatitis, gave 1, 9, 10, and 12 ml. icterogenic plasma intravenously to four volunteers, and jaundice occurred at decreasing intervals of 110, 99, 74, and 73 days respectively. A fifth volunteer who received 100 ml. did not develop jaundice at all. Allen and Sayman (1962), in a careful study of serum hepatitis following blood transfusion, found that 58 (51.3 per cent.) of 113 patients who received all the transfusions within a period of 48 hours developed serum hepatitis between the 30th and 60th day after the transfusion. Another report, from the US Communicable Disease Center, Atlanta (1963), noted that the maximal incubation periods in 54 (50.9 per cent.) of 106 patients with hepatitis following blood transfusion were within 15 to 60 days of the earliest transfusion. Krugman, Ward, and Giles (1962), in experimental transmission of infectious hepatitis to children, found longer incubation periods after inoculation with diluted serum and, although the numbers were small, these observations also suggested a possible relationship between the length of the incubation period and the titre of virus introduced parenterally. It is, therefore, doubtful whether the differentiation between the virus of infectious hepatitis (Virus A) and serum hepatitis (Virus B) is justifiable on the basis of the incubation period.

On the basis of the injection history in the present investigation, significant differences in injection rates were found only for the 100 patients with a sporadic illness who had been injected 1 to 2 and 4 to 5 months before the onset of symptoms. In subsequent analyses, such as seasonal variation in incidence, duration of illness, duration of jaundice and biliuria, and laboratory findings of serum bilirubin levels, serum alkaline phosphatase readings, and activity of serum transaminases (Zuckerman, 1964), significant differences were also apparent between the group of 100 patients injected at 1 to 2 and 4 to 5 months, the 268 patients injected at all other times, and the 461 patients not injected. These findings suggest that many of the 100 patients belonging to the first group suffered from syringe-transmitted hepatitis. It is also conceivable that some cases of syringe-transmitted hepatitis occurred at different time intervals, but many of the patients who received injections at other times probably suffered from infectious hepatitis, and any cases of serum

hepatitis would have, therefore, been diluted. Finally, this hypothesis would also be supported by the results of the study of sterilization and inoculation techniques practised in the Royal Air Force. Even allowing for faulty sterilization technique, the practice of loading a single syringe with ten doses of a vaccine and inoculating a number of patients after changing only the needle would greatly favour the syringe-transmission of hepatitis.

Ellis (1955) found that a significantly greater number of Navy personnel than would be expected developed hepatitis within 11 to 40 days of inoculation with TAB vaccine during the years 1944 to 1947. In 1945, the observed numbers were also significantly greater than expected after 41 to 70 days between inoculation and the onset of illness. Thus the incubation period of 1 to 2 months for syringe-transmitted hepatitis by routine immunization procedures in the Royal Air Force has previously been observed in the Royal Navy. The longer incubation period of 4 to 5 months may be explained on the basis of classical serum hepatitis, or by the existence of several antigenic strains of virus, but probably the more likely explanation of the wide range of incubation periods would rest on the actual dose of virus inoculated.

SUMMARY

895 patients with acute icteric hepatitis which occurred in members of the Royal Air Force between January, 1957, and July, 1962, were investigated. The incidence of acute hepatitis was considerably higher in RAF personnel stationed abroad than in those at home. The seasonal incidence was similar at home and overseas with a peak incidence in mid-winter while the lowest number of cases occurred during summer. The highest attack rate of acute hepatitis was found in men aged 20 to 29 years (98·5 cases per 100,000). The lowest attack rate was recorded in the age group 40 to 49 years (52 per 100,000). There was no significant difference in incidence between officers and airmen. During the whole period of the investigation 58 outbreaks occurred, involving a total of 492 patients. The remaining 403 cases were sporadic.

The complete injection history in the 6 months preceding the onset of symptoms was obtained in 829 (92·6 per cent.) of the 895 patients. The injection rates by the monthly interval between injection and onset of illness, differed significantly only in unrelated patients injected at 1 to 2 months and to a lesser extent at 4 to 5 months from both related

cases and the controls. The differences in the incubation periods of the virus of infectious hepatitis (virus A) and serum hepatitis (virus B) are discussed, and it is suggested that there is a wide range of incubation periods for serum hepatitis which may possibly depend on the dose of virus inoculated.

The methods of sterilization and inoculation techniques practised at most of the 29 units visited were found to be inadequate. The multidose method of syringe-loading and injection, using one syringe with change of needle for each patient, was universally practised.

On the basis of the injection history in patients with a sporadic illness, in related cases, and in controls, and taking into account the epidemiological and other features, it is estimated that approximately 100 of the 895 cases of acute hepatitis were due to syringe transmission.

I am grateful to Dr J. C. McDonald, Director of the Epidemiological Research Laboratory, Colindale, for his advice, and to the Directorate of Hygiene and Research, the Medical Records Office, the Statistical Division and the Gloucester Records Office of the Air Ministry, and the Ministry of Pensions and National Insurance for their kind help and forbearing patience. I am indebted to the many Station Medical and Dental Officers for their help throughout this investigation, to the Director General of the Royal Air Force Medical Services for granting the facilities to undertake this investigation and for permission to publish the results, and to Mrs A. Zuckerman for invaluable secretarial assistance.

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