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INFECTIVE HEPATITIS AND ARSENOTHERAPY HEPATITIS AS IT OCCURRED AMONGST NAVAL PERSONNEL IN PORTSMOUTH DURING THE 1939–45 WAR

BY F. P. ELLIS, O.B.E., M.D., M.R.C.P. *Surgeon Commander, Royal Navy*

The Medical Research Council's Royal Naval Tropical Research Unit, University of Malaya, Singapore

(With 1 Figure in the Text)

A steady increase in the numbers of patients admitted to the Royal Naval Hospital at Haslar with acute hepatitis during the first three years of the 1939–45 War led to an investigation during 1943 to determine the factors which were responsible, and to identify the similarities or differences between acute hepatitis acquired during the course of arsenotherapy and hepatitis which occurred independently of this form of treatment. Officers and ratings of the Women's Royal Naval Service were not included in the study. The examination of the data obtained was only completed recently. This reveals features of practical importance which deserve more consideration than they have received hitherto.

CASE DISTRIBUTION

Annual and seasonal incidence. The average naval population of the Portsmouth area rose from 23,000 during the last quarter of 1939 to 73,000 in the last quarter of 1943. When the apparent increase in the hospital admission rate is corrected to allow for this (Fig. 1), the increase in the average monthly incidence of infective hepatitis was not so dramatic as the bare numbers of admissions had at first indicated, and only exceeded 2/10,000 of the naval population during 1943. During this year, by Fleet Order, all cases of 'non-surgical' jaundice in the Navy were reported to the Admiralty. The average monthly rates for the total Naval Force for the last 6 months for men with infective and arsenotherapy hepatitis were 2/10,000 and 0·8/10,000 respectively, which correspond closely to the Haslar admission rates of 1·7/10,000 and 0·9/10,000 for the same period. But by no means all cases of arsenotherapy hepatitis were sent to hospital, and the incidence of this condition in Portsmouth therefore almost certainly exceeded the incidence for the total Naval Force, as this was one of the main naval centres for the treatment of syphilis. On the other hand, the majority of cases of infective hepatitis were sent to this hospital, and the hospital admission rates, although by no means comprehensive, resemble the total naval experience closely. The trend in Fig. 1 is also similar to that for the Royal Air Force Home Command during the years 1940–3 reported by McClurkin (McFarlan, 1951), except that the decline in the monthly incidence observed in the Air Force during the summer months of 1941 and 1942 is replaced by an increase.

In 1942 arsenotherapy hepatitis admissions exceeded those for infective hepatitis. This situation was reversed during 1943 after the possibilities of syringe

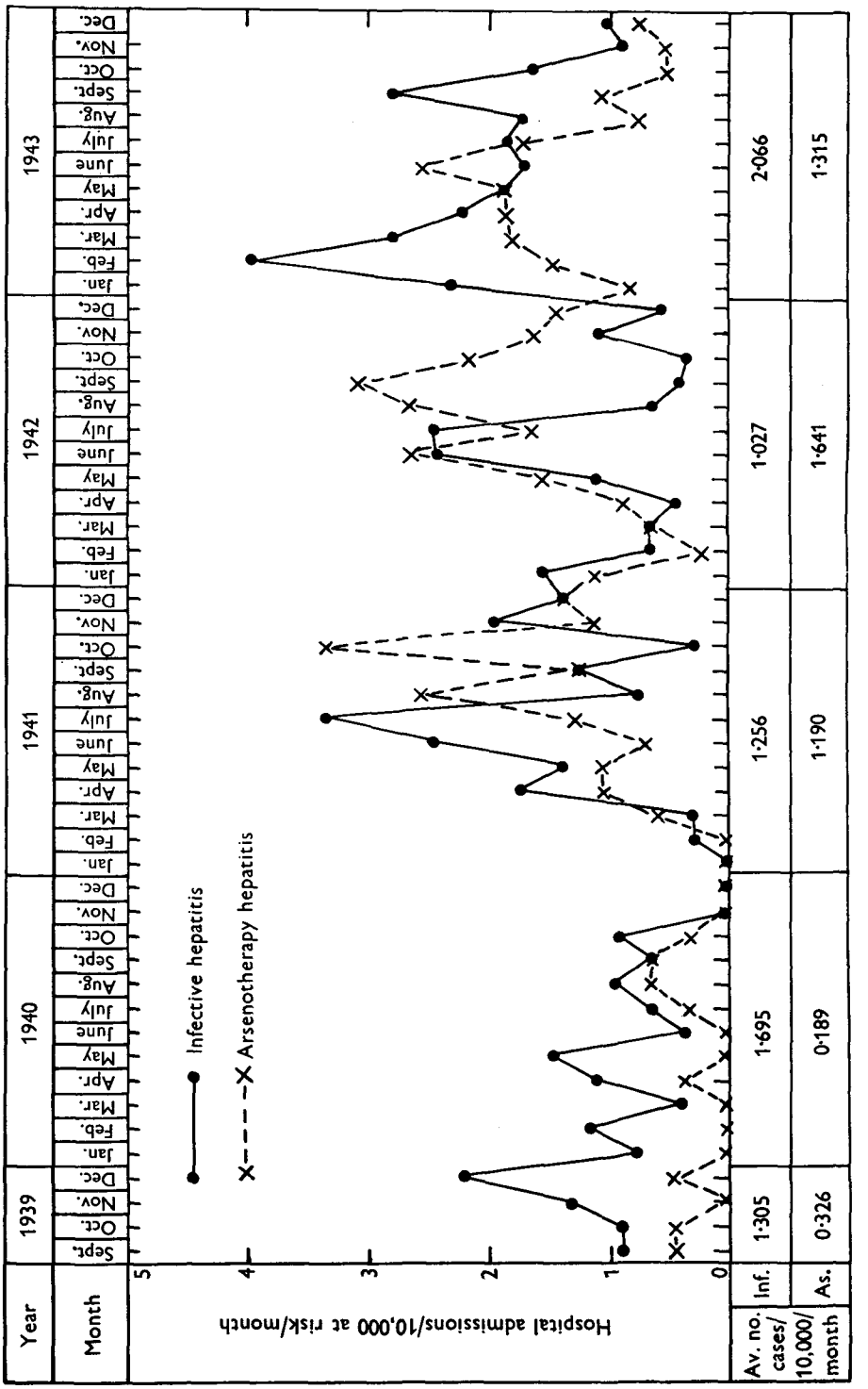

Figure 1. Naval hospital case incidence in the Portsmouth area for infective hepatitis and arsenotherapy hepatitis. 1939–1943

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transmission were raised by Bigger (1943) and MacCallum (1943) and demonstrated convincingly by Salaman, King, Williams & Nicol (1944) at the Royal Victoria Hospital, Netley. The substitution of arsenoxide (Mapharside) for neoarsphenamine as the arsenical preparation of choice for use in the Navy may have assisted the decline to some extent (Dudley, 1943; Anwyl Davies, 1943).

Although the picture given by the hospital experience is incomplete there does appear to be some relation between the seasonal incidence of infective and arsenotherapy hepatitis in 1941, 1942 and 1943, the peak incidence of the latter following two or three months after the peak incidence of the former. When allowance is made for the difference in the incubation periods of syringe-transmitted hepatitis and infective hepatitis which is not syringe-transmitted the picture is not inconsistent with the hypothesis that both types of hepatitis were caused by the same icterogenic agent.

The year 1943 probably saw the peak incidence of hepatitis in England for the war years. This was reflected in the annual admission rates for infective hepatitis at Haslar which fell from 2 % in 1943 to 0·6 and 1 % in 1944 and 1945 respectively, whilst arsenotherapy hepatitis became almost a rarity, the corresponding rates being 0·3 and 0·1 %.

Geographical distribution. The great majority of patients with jaundice came from shore establishments, although the population living afloat was considerable at times. Epidemics were suggested only by the figures from the Royal Naval Barracks and perhaps the Gunnery School which were handling large changing populations throughout these years. Large numbers of isolated single cases occurred in crowded naval establishments. This was not the finding to be expected if the spread of infection was usually by air-borne droplets or particles, unless the great majority of those who were exposed were protected by natural immunity or the virulence of the infective agent was so low that recognizable illness occurred only in persons who were specially susceptible. The occurrence of infective hepatitis was frequently associated with arsenotherapy hepatitis in the same establishments, suggestive of the possibility that both conditions were caused by the same infective agent.

'Officer and rating' incidence. The high incidence of infective hepatitis in the army 'officer' as opposed to the 'other-ranks' populations which has been reported by Spooner (1943), Witts (1944) and McFarlan (1945) was not observed at this hospital. About 10 % of the total force were officers, and the relative incidence was approximately that which might be expected if the risk of infection was equal between the two groups. Officers contracted arsenotherapy hepatitis very rarely.

Incidence in different age groups. The average age of the infective hepatitis patients between 1939 and 1943 was 25 and for arsenotherapy hepatitis it was 27. 75 % of men admitted with infective hepatitis during 1943 were under 25 years of age.

The observed incidence of acute hepatitis in 5-year age groups was compared with the incidence to be expected if proneness to acquire this infection were unassociated with age (Table 1). This was calculated from the numbers in each age group in the naval returns to the Ministry of Labour and National Service for the

years 1940–3 on the assumption that in the Portsmouth area, which usually accommodated about one-tenth of the Navy, the age-group distribution was the same. According to this approximation infective hepatitis was more common amongst those hospital admissions between the ages of 20 and 25 than would be expected if the incidence of infection were unrelated to age; the incidence did not differ significantly from expectation between the ages of 25 and 40, but over the age of 40 there were significantly fewer cases than expected. The close agreement between the observed and expected figures for the '15–19' group, in which according to some contemporary accounts a high relative incidence is to be anticipated, may be partly because the proportion of men of these ages in the numerous training camps in the area was larger than in the total naval force which would put the 'expected' value of 86 at too low a level.

Table 1. *The 'observed' incidence in different age groups of infective and arsenotherapy hepatitis hospital admissions in the Portsmouth area, and the 'expected' incidence, calculated from the age-group distribution for the whole Navy on the assumption that there is no association with age.* 1940–3

	Age groups	15–19	20–24	25–29	30–35	35–35	40–	Total
Infective hepatitis:	Observed	82	106*	45	32	14	13**	292
	Expected	86	83	42	31	21	29	292
Arsenotherapy:	Observed	14**	102*	70**	31	18	18	253
	Expected	74	72	37	27	18	25	253

* Differences are significant ($P < 0{\cdot}05$).
** Differences are highly significant ($P < 0{\cdot}01$).

The incidence of arsenotherapy hepatitis, on the other hand, was markedly lower below the age of 20 than it would have been if there was no association with age, considerably higher between the ages of 20 and 30, and was not significantly different from the expected incidence over the age of 30.

AETIOLOGY

Arsenotherapy

It is certain now that syringe transmission of an icterogenic agent played a part in the transmission of jaundice amongst patients under treatment for syphilis during the early years of the war. The arsenical compounds used in the routine treatment of syphilis in the Navy were also hepatotoxic, although the usually mild and transient nature of the disturbances associated with jaundice in the early phases of arsenotherapy suggest a rather less profound pathology than that which is recognized to occur in infective hepatitis. Hepatitis may also occur in patients with untreated syphilitic infections. Jaundice was thus a well-known feature of syphilitic illnesses, and patients who were affected to only a mild degree and were without constitutional complaints often remained ambulant; whilst 'early' cases of jaundice were not referred to Haslar as the treatment of the syphilitic infection was considered to be of greater importance than the treatment of 'hepatitis' in many cases. Lloyd Jones & Maitland (1943) remark, when discussing the results

of intensive arsenotherapy in the Navy, that only 4 out of 11 cases of jaundice which occurred in 100 persons under treatment required hospital treatment. I am indebted to the late Surgeon-Captain T. R. Lloyd Jones, Royal Navy, for data in Table 2, which show the yearly incidence of hepatitis amongst patients under treatment in Portsmouth at this time.

Table 2. *Jaundice affecting persons receiving arsenotherapy at the Royal Naval Clinic at Cosham*

(*a*) *Patients treated with 'continuous' arsenotherapy*

Years	1940	1941	1942	1943
Cases of jaundice/cases treated (%)	4·8	9·8	7·6	3·4
Cases of jaundice/injections given (%)	0·7	1·5	1·0	0·9
No. of cases treated	392	450	897	798
No. of injections	2696	2874	6606	4498

(*b*) *Patients receiving 'intensive' arsenotherapy in* 1943

Months	Jan.–Mar.	April–June	July–Sept.	Oct.–Dec.
Cases of jaundice/cases treated (%)	22·2	15·6	6·5	0
No. of cases treated	18	45	62	43

The annual incidence of jaundice amongst persons under continuous treatment for syphilis in his clinic varied between 3 and 10 % between 1940 and 1943 (Table 2*a*). The consecutive annual incidence of infective hepatitis in the rest of the naval male population, based only on the cases admitted to hospital, during the same years, was 0·08, 0·15, 0·112 and 0·24 %. According to these figures in 1940, 1941 and 1942, before the risks of syringe transmission were appreciated, men receiving arsenotherapy were 60–70 times as prone to develop acute hepatitis as those who were not; but in 1943 the relative risk for these men was reduced by 75 %. As these arsenotherapy figures are more comprehensive than the infective hepatitis hospital admission rates this is not inconsistent with Marshall's (1943) view that the syphilitic under treatment was at that time 'possibly 20 to 40 times more liable to jaundice than the otherwise healthy person'. When intensive therapy was instituted in 1943 there was at first a marked increase in jaundice (Table 2*b*), but towards the end of the year a more careful syringe sterilization routine was adopted, and individual syringes were used for patients in this group whom it was suspected might be developing jaundice. The marked reduction in cases which was then observed—no patients receiving intensive therapy developed jaundice between September 1943 and March 1944—added further support for the conclusions of the Netley experiment (Salaman *et al.* 1944).

The incidence of jaundice in relation to the number of injections given to men under 'continuous' treatment was remarkably constant and varied around the 1 % mark during the 4-year period.

The cases admitted to Haslar during 1943 represent only a sample, but a large sample, of the men receiving arsenotherapy in the neighbourhood who became jaundiced. When those with relapsed arsenotherapy hepatitis are omitted, the average interval between the first injection of arsenic and the clinical onset of

hepatitis for the forty-six men remaining was 158 (± 99) days. This is a considerable increase on Marshall's (1944) estimate that the greatest incidence of 'delayed' hepatitis occurred about 100 days after the start of treatment, and is much nearer to the average figure of 168 days quoted by McKinlay & Truelove (1947) for the Army in Italy. The shortest interval after the commencement of treatment was 49 and the longest 445 days. These naval figures do not support Wilson's (1951) opinion that the interval between the start of arsenical treatment and the appearance of jaundice is comparable with the incubation period of homologous serum hepatitis. 90% of these men developed hepatitis less than 35 days after their last intravenous injection. If it were possible to assume that this last injection carried the infecting dose, the incubation period would resemble that for infective hepatitis more closely than that for homologous serum jaundice, but this assumption cannot be made. The opportunities for parenteral infection were so numerous in each case that any guess at an incubation period under these circumstances is out of the question.

Inoculation and vaccination procedures

Practically all men and women in the three services in wartime were at one time or another inoculated or vaccinated against either the typhoid group of diseases, tetanus, smallpox, yellow fever, cholera or plague. Those who served abroad were usually immunized on repeated occasions. In view of the incrimination of syringes and needles as paths of infection in arsenotherapy hepatitis it was important to establish whether they might also transmit hepatitis during these immunization procedures.

Table 3. *Numbers of infective (I) and arsenotherapy (A) hepatitis cases who were vaccinated or inoculated prior to developing acute hepatitis in* 1943 *and the numbers 'expected' on the assumption that equal numbers in the Portsmouth area were immunized each month and the hypothesis that hepatitis incidence was not influenced by these immunization procedures*

Vaccinated or inoculated against	I or A	Period between immunization and onset of symptoms: 0–2 months Ob.	0–2 months Ex.	2–3 months Ob.	2–3 months Ex.	3–6 months Ob.	3–6 months Ex.	6–12 months Ob.	6–12 months Ex.	0–12 months	Not within previous 12 months	Total replies
Yellow fever	I	0	2·0	0	1·0	6	3·0	6	6·0	12	127	139
	A	0	1·8	0	0·9	3	2·8	8	5·5	11	83	94
Typhoid, paraty-phoid and tetanus	I	30**	13·5	2	6·8	18	20·3	31	40·5	81	57	138
	A	4	5·8	3	2·9	10	8·8	18	17·5	35	57	92
Smallpox	I	11	8·5	3	4·2	9	12·8	28	25·5	51	85	136
	A	1	3·8	2	1·9	6	5·8	14	11·5	23	69	92

** Significant at $P = 0{\cdot}001$.

If the assumption is made that equal numbers in the Portsmouth area were immunized each month, and the 'expected' numbers of cases are calculated on the hypothesis that the onset of illness was independent of the time after immunization (Table 3), it can be shown by means of a χ^2 test that there is no significant deviation

from this hypothesis for either infective or arsenotherapy hepatitis after immunization against yellow fever or smallpox or arsenical hepatitis after immunization against the typhoid group. But for infective hepatitis after immunization against the typhoid group there is a highly significant ($P = 0{\cdot}001$) deviation from this hypothesis; in other words, the occurrence of infective hepatitis was not independent of the time between inoculation and the onset of illness. The observed number of cases (30) who had been inoculated within the 2-month period preceding the onset of symptoms is significantly ($P = 0{\cdot}001$) higher than the expected number (13·5), but when the delay between the inoculation and the illness exceeded 2 months the observed numbers of cases do not differ significantly from expectation.

The observation that such a large proportion (30/81 or 37 %) of men admitted with infective hepatitis during 1943 who had been inoculated with T.A.B.T. vaccine developed hepatitis afterwards within the probable incubation period of 2 months suggests that inadequately sterilized syringes or needles, contaminated previously during venepuncture as suggested by Sheehan (1944) or during subcutaneous inoculations, as Hughes (1946*a*, *b*) and Evans & Spooner (1950) have demonstrated may occur, provided the path of infection for at least some of these cases. If some factor or factors unassociated with the method of immunization is to account for this finding it would be reasonable to expect a similar increase of the 'observed' over 'expected' numbers of cases for men who had been vaccinated against smallpox. The small apparent increase here was not, however, significant.

Even stock bottles of vaccine may be under suspicion. A time-saving, though perhaps unwise, practice which was adopted occasionally when large numbers of men had to be inoculated in a hurry was to leave a wide-bore needle inserted through the rubber cap of the vaccine bottle and to introduce air into the bottle with a syringe large enough to hold several doses so as to create a positive pressure within the bottle to facilitate rapid filling of the syringe. Separate sterilized fine-bore needles were then employed for each individual injection. If the syringe or wide-bore needle had been contaminated with the icterogenic agent previously, during the aspiration of blood or intravenous therapy or even during the inoculation process itself, and had not been sterilized adequately, the stock bottle might become infected in this way. Finally, the possibility remains that in some cases reactions to T.A.B.T. inoculation may have precipitated clinically recognizable illness in men with infections which might otherwise have passed unrecognized, but this seems a less likely explanation than that the inoculum actually transmitted the infection.

This analysis shows that in Portsmouth at this time hepatitis was less likely to be transmitted by skin scarification during vaccination than by injections made with syringes. Transmission by scarification was, however, probable in the case of one rating who developed the symptoms of hepatitis approximately two months after he had been tattooed with another man who was undergoing a course of arsenotherapy. The artist tattooed his friend first and then used the same instruments to tattoo the rating without resterilizing them. The friend developed jaundice next day and he did not see him again. Since this time Smith (1950) and others

have provided convincing evidence that hepatitis may be acquired during tattooing if reasonable sterilization precautions are neglected.

Previous contacts. A history of previous contact with a person or persons suffering with jaundice was obtained in only about 25% of infective (37/143) and arsenotherapy hepatitis (24/94) cases admitted during 1943. 14% (20/143) of those with infective hepatitis and 10·6% (10/94) with arsenotherapy hepatitis reported that they had been in contact with a jaundiced person during the 4 weeks preceding the onset of symptoms, and about 5% of each group (8/143 and 5/94) recalled a contact within the previous 5–8 week period.

Second attack. 20% (12/61) of arsenotherapy and 8% (7/86) of infective hepatitis cases were experiencing a second attack of hepatitis.

Alcohol. Nearly half (29/61) of the men receiving arsenical injections were moderate or heavy consumers of alcohol; but only a small proportion (13/86) of those who acquired infective hepatitis.

Previous venereal diseases. One-third of the men (21/61) with arsenotherapy hepatitis had suffered previously with venereal disease as opposed to 2% (2/86) of the 'infective' group.

Diet. About one-fifth of both groups had served in circumstances during the war where their diet had been inadequate.

Other factors. A recent history of infection with malaria, dysentery or typhoid, severe burns, choloroform anaesthesia or of working with cordite was sought in each case. These factors were of negligible importance. None of the patients in either group had received blood transfusions or serum injections during the previous year.

CLINICAL IDENTITY OF INFECTIVE AND ARSENOTHERAPY HEPATITIS

The clinical, biochemical and haematological data will be recorded elsewhere, but the picture differed in no important essential from that described by contemporary observers, and supports the view that these two types of hepatitis cannot be distinguished from each other by clinical criteria (Ellis, 1953).

It was fortunate that episodes of homologous serum hepatitis did not complicate the picture. On the epidemiological and clinical evidence available, it appeared reasonable to conclude that these cases of arsenotherapy hepatitis and infective hepatitis were most likely to be due to the same infective agent. Criticism of this hypothesis, arising from MacCallum's (1951) failure to transmit arsenotherapy hepatitis to human volunteers with faeces, might be answerable on the grounds that if an icterogenic agent is injected directly into the blood stream and reaches the liver in this way it does not necessarily follow that contamination or infection of the bowel lumen need occur, in which case the stools would remain innocuous. The different path to be traversed by the infecting agent in the body before it reaches the liver and attenuation of the infecting dose in the blood stream might account for any differences in incubation period observed with oral and parenteral infections, whilst as MacCallum and more recently Sir John McNee (1952) point out, it is hard to believe, if a separate naturally occurring virus were the cause of

arsenotherapy hepatitis, that it would be expected by nature to rely for its survival only on the accident of syringe transmission.

VITAMIN A DEFICIENCY

The liver is the main storage depot for vitamin A, the precursor of the visual purple of the red cells of the retina which are responsible for vision in dim light or at night. Disorders of the liver may interfere with the conversion of carotene to vitamin A and also with the storage or release of the vitamin after conversion. Haig, Hecht & Patek (1938) noted disturbances in the dark adaptation of thirteen out of fourteen persons with 'alcoholic' cirrhosis of the liver. The widespread disorganization of liver structure demonstrated by liver biopsy in cases of hepatitis (Dible, McMichael & Sherlock, 1943) suggested the possibility that impairment of night vision might be a sequel to this condition also. In view of the importance of good night vision to naval look-outs and watchkeepers, arrangements were made with Surgeon Lieutenant-Commander C. L. G. Pratt, R.N.V.R., for men with moderate or severe hepatitis to be tested at the night-vision laboratory of a submarine base near to the hospital. The patients were transported by stretcher and ambulance and were examined as soon as they were considered fit to make the short journey and to stand the test.

I am indebted for the following results to Surgeon Lieutenant D. C. Jackson, R.N.V.R., who supervised the tests, which were made with the Admiralty Pattern Adaptometer. According to naval standards, based on the testing of large numbers of recruits for the submarine service, five out of fourteen men with infective hepatitis and eight out of twenty-one with arsenotherapy hepatitis had abnormally poor night vision during the acute phase of this illness. The average ability of eight of these men whose night vision was abnormally poor to synthesize hippuric acid after oral ingestion of sodium benzoate was 52 % of normal before the night vision test, whilst for eighteen whose night vision was within the normal range it was 69 %. Two out of four men with poor night vision, who were retested 2 or 3 months later, had recovered sufficiently to be classified as normal. The other two were still abnormal. The mean hippuric acid synthesis for these four men before their first night vision test was only 48 % normal (47, 59, 45, 38 % respectively), but when they were retested after intervals of 3–8 weeks it was 114 % (127, 94, 123, 114 % respectively). This suggests that recovery of dark adaptation may be delayed after apparent clinical and 'biochemical' recovery. Three out of eight men with arsenotherapy hepatitis whose night vision was abnormal were cases of relapsed hepatitis.

The defects in night vision were recognized by the patients themselves, and several remarked when they were interviewed after convalescence that they had trouble in the dark, whilst one man who had been severely ill with infective hepatitis said he was 'practically useless' at night.

The early results of these tests were discussed with the late Dr K. J. W. Craik during a visit to the Medical Research Council's Jaundice Research Team at Cambridge. He subsequently tested some of their cases with the Craik Adaptometer and found that the mean final rod threshold for thirty-seven men tested

within 1 week of admission was impaired significantly in comparison with that of twenty normal adults of comparable age; and also that the mean final rod threshold was improved significantly in fourteen men who were retested after an interval of 1 month or more. A diagnostic impairment of night vision in individual patients was not demonstrated with this adaptometer, and statistical analysis was necessary to show the effect (Craik, Macpherson & Harris 1947). Chemical estimations of the plasma vitamin A arranged after these tests revealed abnormally low values in most patients with hepatitis (Harris & Moore, 1947).

The main naval implication is that until more is known about this effect on night vision, men whose duties involve work on the upper deck at night, particularly as look-outs or watchkeepers, but also in other capacities, should whenever possible have their night vision tested on recovery from a severe attack of infective hepatitis or arsenotherapy hepatitis before they are allowed to return to full duty.

In civilian life facilities for night-vision testing are not always available, and the administration of these tests and their interpretation is an expert and controversial procedure. A patient who feels well enough and wishes to return to work may not disclose misgivings he may have about seeing in the dark, or he may not be aware that his night vision is not so good as it was. Yet the disasters which may occur if drivers of motor vehicles or trains resume night work before their powers of night vision have recuperated may be very serious. The data reported here do not permit an estimate of how frequently a serious defect will persist when clinical recovery is otherwise complete. This may not occur very frequently, but information one way or the other should clearly be obtained during a future epidemic of hepatitis in an area where the facilities for expert night-vision testing are available. In the meantime, as a precautionary measure, clinicians should inquire whether patients recovering from a severe attack of acute hepatitis can see as well in the dark as they could before, and, in doubtful cases, warn them against driving at night.

This is only one aspect of vitamin deficiency arising from acute disorganization of the liver by hepatitis. There may be other less easily detectable constitutional effects which persist after the obvious features of acute hepatitis have subsided.

CONCLUSIONS

The increase in the numbers of men admitted to the Royal Naval Hospital at Haslar with acute hepatitis during the first 3 years of the 1939–45 War was due to the increase in the naval population of the area, to syringe transmission of an icterogenic agent amongst those members of the naval community who were under treatment for syphilis with arsenotherapy, and probably to syringe transmission of an icterogenic agent during routine inoculation against the typhoid group of diseases. Except in those cases where transmission of the infective agent by syringes or needles was possible, there was no evidence to indicate the path of infection. The frequent occurrence of isolated single cases in crowded ships or shore establishments is not consistent with the hypothesis that spread of infection was usually due to air-borne droplets or particles, unless the majority of persons exposed to the infection were naturally immune and those who became ill were specially susceptible.

It was not possible to distinguish between arsenotherapy hepatitis and infective

hepatitis by epidemiological criteria, clinical investigations or laboratory tests; although, on the average, the group with arsenotherapy hepatitis were ill for a longer period and showed signs of more serious liver dysfunction. The recent syphilitic infection, the hepatotoxic effect of arsenic, the tendency not to send mild cases of arsenotherapy hepatitis to hospital and the greater incidence of relapsed hepatitis and alcoholism in this group probably explain why arsenotherapy hepatitis presented a more severe clinical picture than infective hepatitis at this hospital.

During 1943, 37 % of patients admitted with infective hepatitis who had been inoculated with T.A.B.T. vaccine had received their inoculations within the 2-month period preceding the onset of symptoms. It is suggested that this method of immunization may have led to a hitherto neglected, but not uncommon, type of syringe-transmitted jaundice in the Services during the war.

The disruption of vitamin A metabolism in the liver in severe acute hepatitis may lead to defective night vision which may persist as a source of danger or inconvenience to those who have to work in the dark after the more obvious symptoms have subsided and the patient has returned to work. In view of the importance of this to the Services, and to such civilian workers as drivers of motor vehicles or railway engines, it is considered that this aspect of rehabilitation after acute liver disorders should be accorded further attention than it has received up to the present.

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