

## RESULTS

The results of applying the classifications of Waterlow and Rutishauser and of McLaren and Read to these three groups of children are shown in tables III, IV, and V.

These results show that there are considerable differences between the two methods of classification, particularly for the severely malnourished cases.

## DISCUSSION

Table III shows that although the results with the two systems agree fairly closely in children who are almost normal, they differ increasingly with increasing malnutrition. The results from the two groups of acutely malnourished children suggest that Waterlow and Rutishauser's system underestimates the problem. Application of the schemes to these extreme cases may be objected to on the grounds that they are not meant primarily to apply in such situations. Since, however, such cases are drawn from the populations for which such schemes are devised, the systems should be capable of classifying them correctly. The results show that Waterlow and Rutishauser's system would apply the "priority" grading to less than half of the severely affected cases, and would even regard 6.8% as needing "no action". Our system would grade over 95% as severely affected. The classification "action" rather than "priority" in such a large percentage of these cases (42% and 23%, respectively) is due to their having relatively little height deficit. We feel that height deficit is not a reliable indication of the present state of malnutrition, and moreover cannot be used as a factor in its classification. A given height deficit may result either from a brief period of retarded growth in early childhood or from a longer retardation of growth at an older age. The age at which the measurement of height is compared with the standard will also affect the result.<sup>11</sup>

Another factor in what we believe is the incorrect classification of many of these seriously and acutely ill and malnourished children is disregard for the effect of age on the expected weight for length in children. This is particularly important in the first twelve months of life, and most of those incorrectly classified were less than one year old. The indices of Dugdale and Ehrenberg which Waterlow and Rutishauser quote in support of age independence of weight as percentage of expected weight/length do not hold true below the age of about one year.<sup>11,12</sup> The practical importance of this point becomes even more evident in the light of the increasing prevalence of worldwide infantile marasmus.<sup>13</sup>

Requests for reprints should be addressed to D. S. McL. from whom copies of the chart may also be had.

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## Public Health

## AN OUTBREAK OF HEPATITIS ASSOCIATED WITH INTRAVENOUS INJECTION OF FACTOR-VIII CONCENTRATE

J. CRASKE

Public Health Laboratory, Poole General Hospital, Dorset

NANCY DILLING \*      DAVID STERN  
Hæmophilia Centre, Royal Victoria Hospital,  
Boscombe, Bournemouth

**Summary** An outbreak of jaundice associated with three out of four batches of a commercial brand of freeze-dried factor-VIII concentrate occurred at the Bournemouth hæmophilia centre between April and June, 1974. Seven cases of non-B hepatitis and four of hepatitis B occurred within 6 months of the first use of this product. Two patients contracted both types of hepatitis; thus nine patients became ill out of a total of twenty regularly seen at the centre, eighteen of whom received commercial factor-VIII concentrate.

## INTRODUCTION

UNTIL lately hæmophilia has generally been treated by cryoprecipitate.<sup>1</sup> The introduction of freeze-dried factor-VIII concentrates<sup>2</sup> has brought considerable advantages. Factor-VIII activity is much greater in freeze-dried concentrates, which can be given by a syringe and needle instead of an intravenous drip, are stable, and have a much more predictable action than cryoprecipitate. They do not produce pyrexia and urticaria which occasionally occur with cryoprecipitate. They have made home treatment more practicable, and major operations on hæmophiliac patients much easier.

Treatment with factor-VIII concentrates exposes the patient to a higher risk of contracting transfusion hepatitis. Cryoprecipitate, in which each bag is made from one or two donations, carries a relatively low risk of hepatitis. Commercial factor-VIII concentrates, which are prepared from pools of 2 to 6000 litres of plasma obtained by plasmapheresis from paid donors, would be expected to carry a much higher risk of transfusion hepatitis.<sup>3</sup>

We report an outbreak of both short-incubation hepatitis (non-B) and hepatitis B associated with the use of 3 out of 4 batches of a commercial factor-VIII concentrate. Seven cases of non-B hepatitis and four of hepatitis B occurred within 6 months of the first use

\* Nancy Dilling died in June, 1975.

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TRANSFUSION HISTORY OF PATIENTS WHO RECEIVED BATCH-S FACTOR-VIII CONCENTRATE BETWEEN NOVEMBER, 1973, AND MAY, 1974

	No. of bottles transfused (all brands of factor-VIII concentrate and cryoprecipitate)					Total
	< 25	25-49	50-74	75-99	100+	
With jaundice ..	4	0	0	0	0	4
Without jaundice	2	0	1	2	2	7
Total .. ..	6	0	1	2	2	11

of this product. Two patients contracted both types of hepatitis, so nine patients became ill out of a total of twenty regularly seen at the centre, eighteen of whom received this product.

#### DESCRIPTION OF OUTBREAK

##### Non-HB<sub>s</sub>Ag-associated Hepatitis

A commercial brand of factor-VIII concentrate was introduced for routine use at the Bournemouth hæmophilia centre at the beginning of November, 1973. In the 6 months following, four batches (P, Q, R, and S) were used. One batch, S, was the only one available at the centre from mid-February, 1974, onwards.

All patients in this outbreak made uneventful recoveries except for one who had a prolonged attack of jaundice lasting 6 weeks and then suddenly improved. One of the seven cases was anicteric. There were no secondary cases.

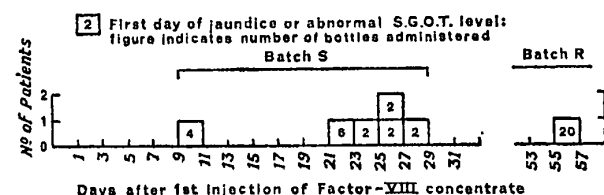
The only common factor in six out of seven cases of non-B hepatitis was an intravenous infusion of one or more bottles of batch S. Thirteen patients were transfused with this batch. Of these, two had received only batch S in the previous 6 months and both contracted hepatitis.

**Incubation period.**—This was taken as the number of days from the first transfusion of the suspect batch to the first day of jaundice or raised transaminases in the case of anicteric hepatitis (see accompanying figure). Apart from one case associated with batch R, in which the incubation period was 56 days, all the cases associated with batch S had incubation periods of between 10 and 29 days. This is characteristic of a point-source outbreak of hepatitis, which in this case was a transfusion of one or more bottles of batch-S factor-VIII concentrate.

**Tests for hepatitis-B-surface antigen (HB<sub>s</sub>Ag) and antibody (Ab).**—All the patients were screened at approximately 6-monthly intervals by electrophoresis<sup>4</sup> and hæmagglutination (Organon Laboratories Ltd.) (H.A.).<sup>5</sup> Four were tested when jaundice developed. All were negative for HB<sub>s</sub>Ag and HB<sub>s</sub>Ab by electrophoresis and for HB<sub>s</sub>Ag by H.A. Samples of batches P, Q, R, and S were found to be negative for HB<sub>s</sub>Ag by the 'Ausria I' radioimmunoassay technique.

**Liver-function tests and clinical signs.**—Hepatitis was diagnosed when serum-glutamic-oxaloacetic-transaminase (S.G.O.T.) was 80 international units per litre or more and the history and clinical signs were compatible with a diagnosis of acute hepatitis.

All patients thought to have acute hepatitis were seen



Outbreak of non-B hepatitis after administration of factor-VIII concentrate.

in the first instance by their general practitioner or an independent physician and were diagnosed by them as having infectious hepatitis in the absence of any knowledge of this outbreak. The results of liver-function tests were available on all patients who became jaundiced.

**Tests for viral antibodies.**—Paired sera from five jaundiced patients and five sera from non-jaundiced patients who received transfusions of batch S were tested for complement-fixing antibodies to cytomegalovirus and heterophil antibodies to sheep red blood-cells (Paul Bunnell test). All were negative by both tests except one of the normal recipients who had a titre of 1/40 in the cytomegalovirus complement-fixation tests. Cytomegalovirus or Epstein-Barr (E.B.) virus was not implicated in this outbreak. E.B. virus was implicated in some cases of asymptomatic infection after transfusion.<sup>6</sup>

**Age of patients.**—The ages of the affected patients were compared with those who received batch S and did not contract hepatitis. There was no significant difference in age between the two groups.

**Evidence for other sources of the outbreak.**—There was no clinical evidence of recent hepatitis-A infection in the medical, technical, or nursing staff of the hæmophilia centre.

**Transfusion history.**—The transfusion histories over the previous 6 months of the jaundiced and non-jaundiced recipients of batch S were compared to see if there was an association between the frequency of past transfusion and susceptibility to hepatitis. The results are shown in the accompanying table. This shows that the patients in whom jaundice developed had received less than twenty-five bottles of all products containing factor VIII over the preceding 6 months compared with up to more than fifty bottles given to other patients who did not become jaundiced. This result is statistically significant at the 5% level ( $p=0.045$ ). Hæmophiliacs visiting Bournemouth in whom hepatitis subsequently developed were excluded from this analysis.

##### Hepatitis-B Outbreak

Four cases of hepatitis B were found in a subsequent survey of all patients treated at the centre. Cases 1 and 2 were associated with batch R and case 3 with either batch R or Q. Two cases were anicteric. Case 1 had received only 20 bottles of batch R and previously had contracted non-B hepatitis. Anicteric hepatitis B developed 170 days after his transfusion. He is still HB<sub>s</sub>Ag positive 8 months afterwards, with evidence of persistent hepatitis. The other three cases recovered and are now HB<sub>s</sub>Ag negative. Case 4 was associated with batch S and this patient had previously contracted non-B hepatitis. Two of these four cases also had transfusions of cryoprecipitate, all the donors of which were traced in one case and were negative for HB<sub>s</sub>Ag when tested later.

#### DISCUSSION

The measures now used by the National Blood Transfusion Service to reduce the incidence of transfusion hepatitis, such as the use of single donations and small pools of plasma, make the occurrence of more than one case of transfusion hepatitis as the result of contamination of a plasma pool by a single donor most unlikely. The risk is greatly increased with factor-VIII concentrates prepared from pools of more than a thousand donations. When blood for transfusion is prepared from commercial donations this increases the frequency of jaundice three to ninefold<sup>8</sup> for single transfusions. The pool size, however, may be critical in factor-VIII concentrates, since transfusion hepatitis is a known hazard with large-pool products prepared from volunteer donors in the U.K.<sup>7</sup>

The overall attack-rate in the Bournemouth outbreak was 50% for all types of hepatitis.

In a study of 37 hæmophilia centres<sup>8</sup> the frequency of jaundice between 1969 and 1971 inclusive was about 1.8%. The highest was observed in the Oxford centre in the year 1971, when nine episodes of jaundice were observed among two hundred and two patients (4.4%). When this is compared with the Bournemouth experience during the first 42 weeks of 1974—i.e., six episodes among twenty patients excluding visitors—there is a clear statistically significant difference ( $\chi^2=15.0$ ;  $P<0.001$ ).

In hospital patients, the chance of contracting transfusion hepatitis varies directly with the number of bottles of blood a patient receives.<sup>3</sup> Patients with severe hæmophilia receive so many transfusions that they might be expected to have a high chance of exposure to both known types of hepatitis virus, and hence a large proportion of them would be immune to hepatitis A and B. Patients with mild hæmophilia receive fewer transfusions and, therefore, a larger proportion of them would be susceptible to transfusion hepatitis.

There was evidence that susceptibility to non-B hepatitis and frequency of transfusion in the patients transfused with batch S were related. We were unable to demonstrate a similar relation in the hepatitis-B outbreak, but the numbers of patients were small. Biggs<sup>8</sup> found a similar relation among hæmophiliacs for hepatitis B.

There seems to be a pronounced increase in the risk of post-transfusion hepatitis when some batches of commercial freeze-dried factor-VIII concentrates are used. This must be balanced against the undoubted advantage that the freeze-dried product has over cryoprecipitate.

Testing the pooled plasma or the factor-VIII concentrate by the current radioimmunoassay techniques is not a reliable method of excluding hepatitis-B virus. Individual donations should be screened by R.I.A. before being pooled.

What is required is a freeze-dried factor-VIII concentrate prepared from volunteer donors in the U.K. prepared according to an approved protocol of testing. A small quantity is available, but it is likely that some reliance will have to be placed on commercial sources for some time to come.

In the meantime, some or all of the following measures might help to lessen the frequency of jaundice.

(1) Commercial factor VIII concentrates should be reserved for the treatment of life-threatening bleeds in all hæmophiliacs and for covering major operations.

(2) If used for treatment, commercial concentrates should be reserved for severely affected hæmophiliacs, since they are more likely to be immune to hepatitis A and B. Treatment should be carried out by experienced staff who are aware of the risks of using large-pool concentrates.

(3) A trial of the administration of human immunoglobulin prepared from HBsAb-positive donors when it is necessary to use a batch likely to contain hepatitis A or B virus might be considered. This should be administered at the same time as the concentrate is given. Ideally an immunoglobulin preparation which can be given intravenously should be used.

A more general study is now in progress to determine the true frequency of jaundice in hæmophiliacs in British hæmophilia centres associated with the use of commercial factor-VIII and U.K. manufactured concentrates, and to find additional cases associated with the batches implicated in this outbreak.

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## OUTBREAK OF FOOD-BORNE TYPE-A HEPATITIS IN GREATER GLASGOW

A. K. R. CHAUDHURI

*Department of Infectious Diseases, Belvidere Hospital, Glasgow G31 4PG*

G. CASSIE

M. SILVER

*Greater Glasgow Health Board*

**Summary** In a fourteen-day period between December, 1974, and January, 1975, 12 out of 118 members of a Glasgow golf club, who had attended their annual dinner/dance at a popular hotel in Glasgow six weeks previously, developed acute icteric hepatitis. Epidemiological investigations suggest that the infection was due to contamination of the cream used in fruit salad and sherry trifle prepared by a pastry-cook at a time when he was incubating type-A hepatitis.

#### INTRODUCTION

OUTBREAKS of food-borne type-A hepatitis are rare. Because of the long incubation period, food as a vehicle of transmission of hepatitis is difficult to establish. Occasionally outbreaks of hepatitis follow events such as banquets, picnics, or annual dinners where a single meal has been responsible, and this may be helpful in finding the offending food or food handler. Such an outbreak of food-borne type-A hepatitis following a dinner/dance in Greater Glasgow is described here.

#### THE OUTBREAK

On Nov. 9, 1974, 118 members of a Glasgow golf club attended their annual dinner/dance at a popular hotel in Glasgow specialising in such functions. Six weeks later, over a period of fourteen days between Dec. 14 and 27, 12 members developed symptoms and