HOMOLOGOUS SERUM JAUNDICE

BY

DERMOT LEHANE, M.B., B.Ch.

Regional Blood Transfusion Officer

*CATHERINE M. S. KWANTES

*MARY GALTON UPWARD

AND

*DOROTHY ROSEMARY THOMSON

(From the Regional Blood Transfusion Centre, Liverpool)

In 1938 MacNalty drew attention to the fact that jaundice had followed the subcutaneous injection of convalescent measles serum; of 109 recipients 41 developed jaundice. Despite this and similar reports, little interest was aroused until in 1942 Sawyer *et al.* reported 28,585 cases among United States troops following inoculation against yellow fever with vaccine suspended in human serum. Subsequently there were reports of jaundice following the transfusion of human plasma or serum. In 1943 a memorandum was published (*Lancet*, 1943) by Medical Officers of the Ministry of Health reviewing the literature on homologous serum jaundice and reporting that recipients of plasma transfusions had developed jaundice. Spurling, Shone, and Vaughan (1946), in their survey of 1,054 patients given plasma, found that 7.3% developed jaundice, whereas in 891 patients given whole blood there were no cases of jaundice which could be attributed definitely to transfusion. Brightman and Korn (1947) investigated 649 cases in which plasma had been transfused, and found a 4.5% incidence of jaundice.

From these and other reports it was obvious that certain pools of plasma were definitely icterogenic while others were non-icterogenic. It therefore seemed probable that the icterogenic factor was present in the blood of a small percentage of donors, and that the inclusion of such donors' blood in the pools was responsible for their icterogenicity. It was considered likely that by limiting the number of donors contributing to each pool it should be possible to limit the dissemination of the icterogenic agent, and accordingly small-pool plasma was introduced in June, 1949.

This paper reports the results of a survey carried out during the period October, 1945, to March, 1948, in the region served by the Liverpool Regional Blood Transfusion Centre. The main object of the survey was to obtain comparative figures for the incidence of homologous serum jaundice following the transfusion of different blood products. The transfusion materials investigated were:

Large-Pool Plasma.—This consisted of plasma processed at the Medical Research Council Drying Plant at Cambridge or the Army Blood Supply Depot at Bristol before June, 1945, each pool being derived from not fewer than 300 donors; this plasma was Seitz-filtered before drying. In addition to this a small quantity of similar large-pool dried serum, supplied during the war by the Government of the Dominion of Canada and the Canadian Red Cross Society, was used. It was considered that no useful purpose would be served by recording separately cases receiving large-pool plasma and large-pool serum.

Small-Pool Plasma.—Consisting of unfiltered plasma, collected and processed since June, 1945, each pool being derived from not more than 10 donors.

Whole Blood.—Collected and bottled by the standard technique of the National Blood Transfusion Service.

Method of Follow-up

The survey was carried out on the following lines: (1) Names of patients receiving transfusions were reported to the Regional Transfusion Centre by the hospitals. (2) Permission was obtained from the hospitals to abstract from their records information such as the patient's home address, the condition for which the transfusion was given, and other relevant details. (3) After a period of six months from the date of transfusion had elapsed a letter was sent to the patient's home address. This letter was in the form of a general inquiry regarding the health of the patient following his discharge from hospital. A questionnaire was included with the letter, and the patient was asked to indicate whether he had had various illnesses, including jaundice. On receipt of the completed questionnaire, those patients whose replies indicated that jaundice had occurred were visited.

This "home visit" was essential for the discovery of cases of homologous serum jaundice, because very few were reported by hospitals or private practitioners. Furthermore, it was necessary to ascertain whether jaundice had occurred in other members of the patient's household, as if this had occurred it was doubtful whether the illness of the recipient could be attributed to transfusion. When full details of the course of the illness had been obtained from the patient, further inquiries were made from the physician who had treated the case, so establishing a comprehensive history and accurate diagnosis.

The "home visit" was omitted in the case of death of the recipient, and a careful check of the case papers and the private practitioner's records was carried out to ensure that homologous serum jaundice had not occurred.

A diagnosis of homologous serum jaundice was made only if each of the following conditions was fulfilled: (1) jaundice occurring one to six months after transfusion; (2) absence of history of contact with cases of infective hepatitis; and (3) absence of other pathological causes of jaundice.

TABLE I.—*Particulars of Patients given Blood, Large-Pool Dried Plasma, and/or Small-Pool Dried Plasma*

	Blood Alone	Large-Pool Plasma	Blood and Large-Pool Plasma	Blood and Small-Pool Plasma	Small-Pool Plasma	Totals
Total No. of patients followed up	4,270	893	666	703	584	7,116
No. of patients untraced	704 (16.4%)	133 (14.8%)	173 (25.9%)	83 (11.8%)	50 (8.5%)	1,143 (16.1%)
No. of patients traced	3,566	760	493	620	534	5,973
No. of deaths within 6 months of transfusion (not with jaundice)	770 (21.6%)	307 (40.4%)	126 (25.5%)	202 (32.6%)	138 (25.8%)	1,543 (25.8%)
No. of surviving patients upon whom incidence of jaundice is based	2,796	453	367	418	396	4,430
No. who reported no history of jaundice within 6 months	2,772 (99.1%)	399 (88.1%)	320 (87.2%)	410 (98.1%)	391 (98.8%)	4,292 (96.9%)
No. with unconfirmed history of jaundice or doubtful aetiology	2 (0.1%)	0	1 (0.3%)	1 (0.2%)	0	4 (0.1%)
No. who developed jaundice attributed to transfusion within 6 months after transfusion	22 (0.8%)	54 (11.9%)	46 (12.5%)	7 (1.7%)	5 (1.3%)	134 (3.0%)
No. who died of jaundice	0	3 (0.7%)	3 (0.8%)	1 (0.2%)	0	7 (0.2%)

Overall case mortality rate = 5.22%.

In three of the four cases listed as "doubtful" the history of jaundice was extremely vague, and it was not possible to obtain confirmation of the illness from the patients' private doctors. In the fourth case the patient had been in contact with a case of infective hepatitis.

Of the 1,543 patients who died within six months of transfusion without evidence of jaundice or hepatitis, 1,308 (84.8%) died within one month and 235 (15.2%) within the next five months.

*Working with a grant from the Medical Research Council.

Results of Follow-up

Particulars of the patients followed up are shown in Table I. Letters were sent to 7,116 recipients of transfusion, and 5,973 were traced, of whom 1,543 were reported to have died within six months, leaving 4,430 to be interviewed.

Classifying these according to fluid transfused, 2,796 received whole blood, 453 large-pool plasma, 396 small-pool plasma, 367 blood and large-pool plasma, and 418 blood and small-pool plasma. In all, 134 cases of jaundice were discovered.

The 2,796 recipients of whole blood were given 6,210 bottles, equal to an average of 2.2 bottles per patient. Twenty-two cases of homologous serum jaundice occurred following the use of these 6,210 bottles of blood: if each case of jaundice received only one bottle of icterogenic blood, and assuming that each donor gave only one bottle of blood, then at least 0.35% of the donors were carrying an icterogenic agent in their blood stream with no symptoms indicative of disease. It is unlikely that all recipients were susceptible, so that the rate is possibly higher than this.

Among those who received large-pool plasma and blood and large-pool plasma 100 cases of homologous serum jaundice occurred. The batches of plasma used in six of these cases were also found to be icterogenic when used in other areas. Seventy-one of the cases followed the use of 25 batches—for example, Batch No. C307 was involved in seven cases. Each of the remaining 23 cases was associated with a different batch of plasma.

Similarly, among those receiving small-pool plasma and blood and small-pool plasma the plasma used in six of the 12 cases was drawn from 13 different batches. The remaining six cases each followed the use of a different batch. These batches were not associated with jaundice in any other recipients.

It is impossible to give an attack rate for any particular batch of icterogenic plasma in this series, but it was found, for example, that Batch No. C307 was given to 15 patients without complication, although this batch was followed by jaundice in seven other patients. The total number of recipients of this batch, which was widely distributed in other areas, is not known.

Fatal Cases.—There were seven deaths from homologous serum jaundice in the series—namely, three in the large-pool plasma group, three in the blood and large-pool plasma group, and one in the blood and small-pool plasma group. There were no fatal cases in the groups which received small-pool plasma or whole blood (see Table II).

TABLE II.—*Fatal Cases*

Illness	Age	Sex	Incubation Period	Transfusion Fluid
Incomplete abortion ..	36	F	12 weeks	Blood and small-pool plasma
Post-partum haemorrhage ..	28	F	16 "	Blood and large-pool plasma
Arthrodesis of hip ..	55	M	6 "	" " " "
Ruptured spleen ..	40	M	6 "	" " " "
Multiple injuries and shock ..	73	M	9 "	Large-pool plasma "
Prostatectomy ..	67	M	13 "	" " "
Partial gastrectomy ..	65	M	6 "	" " "

Incubation Period.—The incubation period of the illness varied considerably in the cases investigated, but unless the jaundice occurred between one and six months after transfusion it was not classified as homologous serum jaundice. In fact, no cases of jaundice occurred within one month of the transfusion. In the majority of cases the

jaundice occurred 8 to 16 weeks after transfusion (see Chart).

Nature of the Illness.—Eight of the cases (6%) were very mild, with an illness lasting less than one week, and three of these were indisposed for two to three days only. On the other hand, two cases terminated fatally within three days of the onset of symptoms. Twenty-one cases (15.7%) were severe, with an illness which lasted six weeks or more, while the remaining 98 cases (73.7%) were ill for one month or less and their symptoms were not severe. The average duration of illness was 30.5 days, with extremes of two and 112 days. The incidence of the various symptoms and signs is shown in Table III.

Chart showing incubation period. Ten cases are omitted because the incubation period could not be accurately determined.

TABLE III.—*Symptoms and Signs*

Symptoms and Signs	No. of Cases
Jaundice	134 (100%)
Nausea, vomiting, and anorexia	60 (44.8%)
Lassitude	35 (26.1%)
Joint pains	33 (24.6%)
Skin rash	21 (15.7%)
Epigastric pain	14 (10.4%)

Age Incidence.—The age incidence is set out in Table IV; the upper and lower limits were 73 years and 9 years respectively.

TABLE IV.—*Age Incidence*

Age Group	No. of Patients Transfused		No. of Cases of Jaundice	
	Blood Alone	Plasma and Plasma and Blood	Blood Alone	Plasma and Plasma and Blood
0-10 ..	87	127	—	1 (0.8%)
11-20 ..	136	104	2 (1.4%)	6 (5.7%)
21-30 ..	655	294	6 (0.9%)	20 (6.8%)
31-40 ..	758	339	7 (0.9%)	24 (7.1%)
41-50 ..	480	254	2 (0.4%)	23 (9.1%)
51-60 ..	294	204	2 (0.6%)	19 (9.3%)
61-70 ..	267	211	2 (0.7%)	17 (8.1%)
71-80 ..	112	88	1 (0.8%)	2 (2.2%)
81-90 ..	7	13	—	—
Totals ..	2,796	1,634	22 (0.8%)	112 (6.1%)

The illness which necessitated transfusion therapy was taken into account in all cases, but nothing significant was noted. Similarly, the cases were more or less equally distributed between the sexes, 71 (53%) being female and 63 (47%) male.

Discussion

In the present investigation the incidence of homologous serum jaundice (11.9%) found among the recipients of large-pool plasma is considerably higher than that reported by other workers. Of the 54 cases, three were fatal, whereas Spurling and others reported 77 cases, none of which was fatal.

In those patients who received small-pool plasma, on the other hand, the incidence of homologous serum jaundice was significantly lower, amounting to only 1.3%. The considerable reduction in the incidence of this complication of plasma transfusion seems to justify the decision made in 1945 to produce only small-pool plasma.

Of the recipients of whole blood 22 developed jaundice—i.e., 0.8% of the cases—whereas among 891 recipients investigated by Spurling and others six cases of jaundice (0.7%) were reported, but these were listed as "doubtful if due to transfusion."

Inquiry failed to reveal any increase in the incidence of infective hepatitis during the period under review in the North-West Region, the population of which is 3,250,000. In another part of England the attack rate per 1,000 per annum was 0.06 in 1945, 0.07 in 1946, and 0.04 in 1947 in a population of 2,600,000 (McFarlan—personal communication).

In the production of small-pool plasma a record of the donors who contributed to each pool was available, and a follow-up of these donors was carried out so far as was possible, but in only one out of the 63 donors traced was there a history of jaundice. In this case jaundice occurred three months after blood donation. No information such as history of contact with infective hepatitis or of inoculation was given. The donors whose bloods were involved in homologous serum jaundice in the whole-blood series were also followed up, but with negative results.

Summary

In the follow-up of 4,430 patients who had received transfusion therapy 134 (3%) cases of jaundice were discovered, of which seven (0.2%) terminated fatally.

Large-pool plasma and combined large-pool plasma and blood transfusions were responsible for 100 (74.6%) of the cases, six of which were fatal.

The incidence rates of homologous serum jaundice for small-pool plasma (1.3%) and for whole blood (0.8%) are not significantly different (difference/S.E. of difference = 1, approx.), but these rates differ very considerably from that of large-pool plasma (11.9%).

The findings suggest that at least 0.35% of donors are probably carriers of the icterogenic virus.

REFERENCES

- Brightman, I. J., and Korns, R. F. (1947). *J. Amer. med. Ass.*, **135**, 268.
Lancet, 1943, **1**, 83. (Memo by Medical Officers of the Ministry of Health.)
 MacNalty, A. S. (1938). Annual Report of the Chief Medical Officer, Ministry of Health for 1937, London, p. 38.
 Sawyer, W. A., Meyer, K. F., Eaton, M. D., Bauer, I. H., Putnam, P., and Schwentker, F. F. (1944). *Amer. J. Hyg.*, **39**, 337; **40**, 35.
 Spurling, N., Shone, J., and Vaughan, J. (1946). *British Medical Journal*, **2**, 409.

One of the German casualties of the war was the *Archiv für Schiffs- und Tropenhygiene*, and for over four years the Germans have been without a national journal devoted to tropical medicine. This gap has now been filled by the publication of the *Zeitschrift für Tropenmedizin und Parasitologie*, which is edited by workers at the Bernhard Nocht-Institut für Schiffs- und Tropenkrankheiten, Hamburg, and published by Georg Thieme, of Stuttgart. In their prefatory note the editors point out that, while opportunities for German workers in the Tropics are now almost non-existent, many problems concerning tropical medicine can be investigated in the laboratory at home, and that as a result of the war many cases of tropical disease in Germany make ample material available for clinical investigation. Subscription to the new journal is approximately £4 per annum. Dutch investigators also suffered a setback when publication of the *Geneeskundig Tijdschrift voor Nederlandsch Indië* was stopped by the Japanese in March, 1942, after having appeared without interruption since 1852. This journal was replaced in 1946 by the *Medisch Maandblad*. Both these journals have the disadvantage, so far as English readers are concerned, of being almost entirely in Dutch. To overcome this difficulty the Dutch have now commenced publication of an English-language quarterly journal of tropical medicine and hygiene, *Documenta Neerlandica et Indonesica de Morbis Tropicis*, with an editorial board representative both of the Netherlands and its overseas territories. Subscription to this journal is £1 2s. 6d. per annum, and it is published at Rivierenlaan 268, Amsterdam Z.

ISO-IMMUNIZATION BY BLOOD-GROUP FACTORS A AND B IN MAN

BY

PIERRE O. HUBINONT, M.D.

(From the Laboratoires d'Hygiène et de Bactériologie de la Faculté de Médecine, Université Libre de Bruxelles)

Much has been written about the possibility of the blood-group factors A and B acting in the same way as the Rh factor in the pathogenesis of haemolytic disease of the newborn. Jonsson (1936) gave the first immunological evidence, of a statistical nature, that heterospecific blood-group pregnancy (where the O or B mother bears a foetus of group A or AB) was accompanied by a rise of the anti-A haemolysin. Smith (1945) demonstrated that the anti-A or anti-B agglutinin titre rose only in the cases in which the heterospecific foetus was a secretor. The heterospecific pregnancy is then capable of inducing an immune response, but there are very few heterospecific foetuses that demonstrate haemolytic disease. In consequence, there must be some protective mechanism, several of which were reviewed by Tovey (1945).

There are, however, certain facts which focus the attention on the antibody itself. In 1946 we found in the blood of pregnant women who had previously been delivered of stillborn babies anti-A agglutinins reacting far more strongly at 37° than at 4° C. (Millet and Hubinont, 1946a; Hubinont and Millet, 1946). Bruynoghe (1947) found an anti-B agglutinin of the same type in a case of haemolytic disease of the newborn. Since then we have met with several similar cases in which the clinical course was somewhat different from the classical haemolytic disease of the newborn. In all cases the foetus died *in utero* a few days before delivery or during labour.

Many authors—the first of them being Levine, Katzin, and Burnham (1940)—have emphasized that anti-Rh agglutinins react more strongly at 37° than at 4° C. Inversely, it is very well known that natural anti-A or anti-B agglutinins possess a thermal optimum at 4° C.

We verified that several normal agglutinins of rabbit serum (Millet and Hubinont, 1946b; Hubinont, 1948a) and guinea-pig serum (Hubinont, 1947) showed, through immunization, the same change of thermal optimum that we found in our patients. Further investigations on the rabbit showed that hyperimmunization with sheep erythrocytes was often followed by the production of a blocking antibody, giving a prozone phenomenon in quantitative agglutination tests (Hubinont, 1948b).

We recently had the opportunity of studying the immune-response of a group B individual who was transfused by mistake with A₁ blood and eventually recovered: 75 ml. of whole blood had been injected before alarming symptoms appeared.

The serum was tested at regular intervals with A₁ and A₂ cells collected from the same donors. The tests were performed by the usual technique in tubes, using 0.9% saline as diluent, each test being performed simultaneously at 4° and 37° C. The results are shown in the Table.

On the day of transfusion both A₁ and A₂ cells were agglutinated with the same titre and thermal optimum. On the fourth day there was a small increase in titre, noticeably higher for A₁ than for A₂ cells. On the eighth day the thermal optimum for A₁ agglutination turned to 37° C. Finally, on the 30th day the agglutination was stronger at