Dr. Paul to see ✓ Office Hepatitis File

J.C.41.

CONFIDENTIAL REPORT TO THE MEDICAL RESEARCH COUNCIL ON THE INCIDENCE OF JAUNDICE IN PATIENTS GIVEN SERUM, PLASMA OR WHOLE BLOOD IN THE AREA OF THE U.K. LONDON BLOOD SUPPLY DEPOT

OBJECT OF INVESTIGATION.

A follow-up of patients known to have received transfusion fluids issued by the U.K. London Blood Supply Depot has been carried out between 1st October 1944 and 31st January 1946. This has been done in order to discover the number of patients who developed jaundice during the five months following their transfusion. A preliminary report on the findings up to 1st April 1945 and the methods employed (J.C.32) has already been given. This dealt only with patients receiving serum and/or plasma. The present report includes a series of 1284 patients given whole blood only, and a corresponding control series who received no transfusion.

NUMBER OF PATIENTS AND GEOGRAPHICAL DISTRIBUTION.

The survey of patients given serum and/or plasma has been carried out in 78 Hospitals, and an attempt has been made to trace all patients known to have been transfused with these fluids between 1940 and July 1945. The follow-up of patients receiving whole blood was started in May 1945, and up to date the records of only 23 Hospitals have been investigated. The majority of patients concerned have been those transfused in 1944 and the first half of 1945, although in addition, a few of the earlier ones have been followed up. (These patients have received whole blood alone, if serum or plasma has been given as well the patients are included in the previous group).

CONTROL SERIES

Simultaneously with the follow-up of patients who have received whole blood, a survey of a control group has been carried out in an attempt to assess the incidence of jaundice in the non-transfused Hospital patient. This group has been chosen from the records of the Hospitals where the patients transfused with whole blood have been followed up, and is composed of patients who were in Hospital at the same time as those transfused. For every

transfused patient, a control has been selected of the same sex and age group, if possible from the same ward, but regardless of diagnosis. The age groups taken are 0 - 19 years, 20 - 39 years, 40 - 59 years, and 60 years and over.

As stated in the previous report (J.C.32) no transfused patient has been followed up until five months after the transfusion on account of the latent period that may occur before the development of jaundice. Similarly, in the case of the control group, no patient has been followed up until five months after the date of discharge from Hospital.

CHARACTER OF PATIENTS INVESTIGATED.

Most of the patients followed up have been civilians. Only a few service personnel have been included in the survey, as it was found to be extremely difficult to trace these patients, although the authorities concerned have given as much help as possible. Many of the patients transfused with serum and/or plasma have been air raid casualties, which fact accounts, in this group, for the large proportion of deaths within two months of transfusion. The majority of them, in fact, occurred almost immediately, or a few hours after the transfusion. In every case where the patient has died more than two months after transfusion, it has been ascertained that death was due to causes other than hepatic disease, and that an attack of jaundice did not occur in the intervening period.

SERUM AND PLASMA.

In this group a total of 2040 patients has been followed up. The serum and plasma which they received came from well over 400 pools, and included Canadian and other extracted material.

The following figures show the final result:-

TABLE 1.

Particulars of patients given serum and/or plasma

Total no. of patients followed up	2040
No. of patients who could not be traced	186
Proportion which could not be traced	9%

Table 1 (contd.)

No. of patients who were traced	1854	
No. of patients who died within five months of transfusion	800	
Proportion of traced patients who died within five months of transfusion	43%	
No. of surviving patients upon whom the incidence of jaundice is based	1054	100%
No. of patients with no history of jaundice within five months of transfusion	963	91.4%
No. of patients who developed jaundice within five months of transfusion	77	7.3%
No. of patients who developed jaundice but doubtful if due to transfusion. See Appendix .	14	1.3%

Analysis of deaths.

No. of patients who died:-		
Under 2 months after transfusion	769	96.2%
2 - 3 " " "	16	2%
3 - 4 " " "	5	.6%
4 - 5 " " "	10	1.2%
Total	800	100%

COMMENTS

Of the 2040 patients who were followed up, 9% could not be traced. A much larger proportion, 43% of those traced, had died before it could be determined whether or not they would develop jaundice following their transfusion. The observed incidence of post-transfusion jaundice following serum and plasma has, therefore, to be based upon approximately half those originally exposed to risk. The very great majority of deaths, however, took place shortly after transfusion and there is no reason to suppose that the inevitable absence of evidence relating to them would affect the relative incidence, and that they would have been either more or less likely to develop jaundice if they had lived than the survivors. The few who died later had time in which to develop jaundice, but were not exposed to the full five months. If, however, this 31 be debited with a full exposure,

the observed incidence rate of 7.3% would only be reduced to 7.1% so that they can make but little difference to the upshot.

The untraced cases raise the more difficult point as to whether such a patient is more or less likely to have had jaundice. For example, it might be more difficult to follow up a patient who has died, and such a patient might have died of jaundice. With this proviso the figures show an incidence rate of jaundice within five months of transfusion with serum and/or plasma of 7.3%.

Character of jaundice.

Of the 77 cases of jaundice investigated, only one was serious, the patient being in a comatose condition for several days. No deaths occurred among the proven cases of post-transfusion. Two occurred in the doubtful group. One of these was a patient with carcinoma of the bronchus, and the second was an old man of 86 said to have died of senile decay, with jaundice and bronchitis as secondary causes.

The ages of the 77 patients developing jaundice varied from four to eighty years, 30 patients being male and 47 being female.

In every case of jaundice the possibility of an infective source has been investigated. If there has been any evidence at all that the patient might have been in contact with a case of jaundice it has been classified as "doubtful".

It has been found that the incubation period has varied from 45 days to 146 days, the majority of cases occurring 60 to 90 days after transfusion (See Table 2).

TABLE 2.
Time incidence.

No. of patients who developed jaundice:-

40 - 44 days after transfusion	NIL
45 - 49 " " "	5
50 - 54 " " "	3
55 - 59 " " "	4
60 - 64 " " "	7
65 - 69 " " "	11

Table 2 (contd.)

70 - 74	days	after	transfusion	 8
75 - 79	"	"	"	 6
80 - 84	"	"	"	 4
85 - 89	"	"	"	 6
90 - 94	"	"	"	 4
95 - 99	"	"	"	 4
100 -104	"	"	"	 1
105 -109	"	"	"	 2
110 -114	"	"	"	.....NIL
115 -119	"	"	"	 4
120 -150	"	"	"	 8

Symptoms.

Of the 77 cases of jaundice investigated 76 were mild in character, and one was severe. No case of death has been discovered. The symptoms complained of were as follows:-

41 complained of vomiting
20 " " depression
16 " " skin rashes
5 " " urticaria
19 " " joint pains

17 patients complained only of slight nausea or lassitude accompanied by pale stools, dark urine and a yellow tinge of skin and sclerotics.

WHOLE BLOOD.

Although most of the patients transfused with whole blood who have been followed up are maternity and gynaecological cases, a large group of patients with Lematemesis, as well as general medical and surgical cases, has also been investigated. In Table 3 are given the figures relating to the follow-up.

TABLE 3.

Particulars of patients given whole blood.

Total no. of patients followed up (No. of bottles 3468)	1284	
No. of patients who could not be traced (No. of bottles 404)	170	
Proportion which could not be traced		13%
No. of patients who were traced (No. of bottles 3064)	1114	
No. of patients who died within five months of transfusion (No. of bottles) 786)	223	
Proportion of traced patients who died within five months of transfusion		20%
No. of surviving patients upon whom the incidence of jaundice is based (No. of bottles 2278)	891	100%
No. of patients with no history of jaundice within five months of transfusion (No. of bottles 2248)	885	99.4%
No. of patients who developed jaundice within five months of transfusion (No. of bottles NIL)	NIL	
No. of patients who developed jaundice but doubtful if due to transfusion (No. of bottles 30)	6	.6%

Analysis of deaths.

No. of patients who died:-

Under 2 months after transfusion (No. of bottles 679)	192	85%
2-3 months after transfusion (No. of bottles 36)	13	5.8%
3-4 months after transfusion (No. of bottles 54)	13	5.8%
4-5 months after transfusion (No. of bottles 17)	5	2.2%
Total	223	100%

Comments.

Among these patients a larger proportion has been untraceable than among the patients receiving serum and/or plasma. The death rate in this group, however, is lower, and the observed incidence of post-transfusion jaundice is, therefore, based upon

a larger proportion of patients exposed to risk than in the previous group.

All deaths occurring 40 days or more after transfusion have been investigated and, as in the case of the serum and plasma patients it has been verified that the cause was not hepatic disease, and that an attack of jaundice did not occur in the intervening period.

CONTROLS.

In this group, no case of jaundice within five months of discharge from Hospital has been notified to the Depot, although two patients developed jaundice ten months and five and a half months respectively after discharge. Neither of these could give any history of contact with a case of jaundice. Both complained of vomiting, depression and dark urine accompanied by icterus. In both cases the attack was mild. The final results are tabulated below (Table 4.).

Table 4.

Particulars of control patients.

Total no. of patients followed up.....	1284	
No. of patients who could not be traced.....	408	
Proportion which could not be traced.....	32%	
No. of patients who were traced.....	876	
No. of patients who died.....	65	
Proportion of traced patients who died.....	7%	
No. of surviving patients upon whom the incidence of jaundice is based.....	811	100%
No. of patients with no history of jaundice within five months of discharge from Hospital.....	809	99.6%
No. of patients who developed jaundice within five months of discharge from Hospital.....	NIL	
No. of patients who developed jaundice six months or more after discharge from Hospital.....	2	.4%

Comments.

Although the death rate in this group is low, the evidence on which the figures are based is poor owing to the very high lapse rate.

DISCUSSION.

As stated in a recent leading article in the British Medical Journal, the importance of recording the pool and bottle numbers of transfusion fluids should be recognised. In the area of the N.W.London Blood Supply Depot this has been done, the method employed being described in the previous report (J.C.32) referred to above. As a result, certain pools of serum and plasma have been found to be more ictorogenic than others, although in no case has it been possible to trace every bottle of any one particular pool. For example, of 29 traced patients transfused from one pool (LS6) of serum, 9 (31%) gave no history of jaundice, 9 (31%) subsequently developed jaundice within five months of transfusion, and 1 (3.4%) had a doubtful attack. The remaining 10 patients died within five months of transfusion. In all, 38 bottles were involved, 13 (30%) being given to the negative patients, 11 (28%) to the patients who developed jaundice, and 1 (2%) to the patient who had the doubtful attack. The remaining 13 bottles were given to the patients who died. In contrast, only 1% or 2% of the patients transfused from other pools subsequently developed jaundice. When two or more patients have been found to develop jaundice following transfusion from any one pool, the remaining bottles of the pool have been withdrawn from circulation, thus curtailing the risk of further cases of jaundice.

Although 77 cases of post-transfusion jaundice in this area have come to light as a result of the 16 months' investigation, the mild character of the disease must be stressed. Other writers (leading article B.M.J. 1944; Steiner, 1944) report cases of death due to jaundice following transfusion with serum and/or plasma. No death, however, has been notified to this Depot, and in only one case did the patient become

comatose. (The high lapse rate encountered in the survey must, however, be borne in mind when considering this point. See p.4 of this report). The only symptoms manifested by 22% of the patients developing jaundice were slight nausea or lassitude accompanied by pale stools, dark urine and icterus.

No case of jaundice attributable to transfusion with blood alone has been discovered. Although this indicates that the risk of homologous serum jaundice is less with whole blood than with serum or plasma, the facts relating to the figures given above must be considered further. Owing to the pooling of the latter material, many more patients receiving serum and/or plasma are laid open to the risk of developing jaundice from a specified donor than those receiving whole blood. In order to get an exact incidence rate for whole blood it would be necessary to carry out an investigation of a far larger group of patients receiving this material than has been done in this survey. The fact that no case of jaundice was observed in nearly 900 patients suggests, however, that the risk is certainly very small.

CONCLUSIONS.

1. The incidence of jaundice occurring within five months of transfusion in 1054 patients transfused with serum and/or plasma in the area of the N.W.London Blood Supply Depot was 7.3%.
2. No proven case of jaundice within five months of transfusion has been discovered among 890 patients transfused with blood alone.
3. No proven case of jaundice within five months of discharge from Hospital has been discovered among a control group of 811 non-transfused patients.
4. No death from hepatic necrosis has been notified to the Depot.
5. Of 77 cases of homologous serum jaundice only one was serious.
6. Certain pools of serum and plasma have been proved to be more icterogenic than others.
7. In order to get an exact incidence rate of jaundice following transfusion with whole blood, a considerably larger group of patients receiving this material should be investigated.

REFERENCES.

Leading article, British Medical Journal, 1944, 2, 279.

Steiner, R.E. (1944). Ibid., 1, 110.

February 22nd 1946. Nancy M. Spurling, A.I.A.

APPENDIX A.

DOUBTFUL CASES OF JAUNDICE FOLLOWING SERUM AND/OR PLASMA

GRO-A Age 50 years	Died jaundiced 4½ months after transfusion. Carcinoma bronchus.
GRO-A Age 56 years	Carcinoma rectum. Considerable liver metastases. Died 5 months after attack.
GRO-A Age 71 years	Developed jaundice 3 months after transfusion. Diagnosed as obstructive jaundice. Cholecystogram showed definite evidence of cholelithiasis.
GRO-A Age 70 years	Jaundice developed more than 5 months after transfusion.
GRO-A Age 55 years	D.U. ??malignant. Seen 7 months after attack and still jaundiced. Followed up again 19 months after attack; still getting attacks of jaundice.
GRO-A Age 15 years	Gun shot wound. Definite liver damage. Still gets "liver attacks".
GRO-A Age 38 years	Jaundice developed 178 days after transfusion.
GRO-A Age 57 years	Jaundice developed while in Redhill Hospital. Diagnosed as carcinoma head of pancreas. Cholecystenterostomy performed.
GRO-A Age 17 months	Jaundice developed 10 months after transfusion.
GRO-A Age 28 years	Jaundice developed 13 months after transfusion.
GRO-A Age 52 years	Refused to give any information about attack.
GRO-A Age 36 years	Attack reported by his doctor to be of epidemic origin.
GRO-A Age 87 years	2 members of the family subsequently developed jaundice 28-30 days after onset of patient's attack.
GRO-A Age 20 years	Attack said by his doctor not to have been jaundice. ?? diaphragmatic pleurisy.

APPENDIX D.

DOUBTFUL CASES OF JAUNDICE FOLLOWING WHOLE BLOOD

GRO-A P.P.H. Age 26 years	Jaundice developed only 17 days after transfusion. No infective source known. Donors had no history of jaundice.
GRO-A Anaemia Age 46 years	"Jaundice" 8 months after transfusion. Lumbago and pale stools only. No icterus.
GRO-A Oophorectomy and appendicectomy Age 30 years	Jaundice 68 days after transfusion. ?? true attack. Had had similar attacks previously. Jaundiced only on one previous occasion.
GRO-A Aplastic anaemia Age 58 years	Transfused March and April 1944, and July-September 1944. Jaundice 15.11.44. Diagnosed at Guys Hospital as acholuric jaundice. Splenectomy performed 19.12.44. Condition improved.
GRO-A Age 28 years Threatened abortion	Jaundice developed 19 months after transfusion.
GRO-A Hematemesis Age 30 years	Date of onset of attack doubtful. Definite evidence of an infective source. Donors had no history of jaundice.