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THE INCIDENCE, INCUBATION PERIOD, AND SYMPTOMATOLOGY OF HOMOLOGOUS SERUM JAUNDICE*

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Jaundice has been recognized with increasing frequency as a sequela of transfusion with whole blood, plasma, or serum (Memorandum, Ministry of Heath, 1943 ; *B.M.J.*, leading article, 1944, 1945). It is generally agreed that such jaundice is indistinguishable from, and of the same aetiology as, the jaundice following the use of convalescent serum, vaccines containing human serum, and syringes contaminated with human blood (Memorandum, Ministry of Health, 1945). This jaundice is commonly called homologous serum jaundice.

Since certain of the cases reported after transfusion have proved fatal it appeared important to determine, if possible, the incidence of this complication, since it might well be that the risk of hepatic necrosis was greater than the risk incurred by withholding transfusion. Records of blood products issued from the N.W. London area since 1940 being available, a follow-up of patients who had received transfusions in this area was therefore instituted in 1944 with a view to determining the incidence of homologous serum jaundice following transfusion, its incubation period, and the symptomatology.

Method of Investigation

Follow-up

In connexion with an earlier investigation, blood, serum, or plasma issued from the depot carried a label. The hospital receiving and using the bottle was asked to fill in answers to certain questions on the label before returning it to the depot. The returned labels were filed ready for reference. The greater part of the information so collected was not relevant to the present inquiry, but the batch number of the material used was entered on the label before issue, and subsequently the name of the hospital and patient, so affording means of following up all those transfused.

In view of the latent period that may occur before the development of jaundice no personal follow-up of a patient was attempted until five months after the date of the transfusion. The hospital was then visited and the patient was interrogated if still in hospital. If discharged, his address was obtained and he was sent a follow-up letter (Appendix I) asking, among other things, whether he had had an attack of jaundice. If an affirmative answer was received the patient was visited and a more elaborate form (Appendix II) was filled in. In two cases, when the patient lived at a great distance, the general practitioner was asked to complete this form. For obvious reasons it was impossible to include cases of subclinical jaundice in a follow-up of the character described. The notes of all patients who died between forty days and seven months of transfusion were checked to determine if death was due to hepatic necrosis, and to ascertain that no attack of jaundice had occurred in the intervening period. At the time the investigation was started the possible significance of a syringe in the transmission of an icterogenic agent was not appreciated, and no note was made as to whether casualties had, for instance, received pentothal (Darmady and Hardwick, 1945) or penicillin (Turner, 1946). The data were not available to allow a follow-up of the donors of batches which proved to be icterogenic, in order to determine if they had recently had jaundice.

Products Transfused

In the first instance, patients who had received serum and plasma were followed up. In many cases such patients had received blood in addition. The serum and plasma came from 400 different pools, varying in size from 30 to 200 litres. Subsequently a series of patients who had received only blood was studied. It is unfortunate that all patients cannot be placed in clear-cut groups as having received only one product, but the majority of serum and plasma transfusions were given to air-raid casualties treated under emergency conditions. Such transfusions were an essential life-saving procedure, and were not given as part of a planned experiment.

Geographical Distribution of Patients

An attempt was made to follow up all patients known to have been transfused with serum or plasma in 78 hospitals in the N.W. London area between 1940 and July, 1945. Patients receiving only blood in 1944 and the first half of 1945 were traced from 23 hospitals. A few earlier patients were included in this group.

Control Series

Simultaneously with the follow-up of patients receiving whole blood a survey of a control group was made to assess the incidence of jaundice in the non-transfused hospital patient. This group was composed of patients in the same hospital at the same time as the patients given blood. For every transfused patient a control was selected of the same age group, sex, and, if possible, in the same ward, but regardless of diagnosis. The age groups taken were 0–19 years, 20–39 years, 40–59 years, and 60 years and over. No control cases were followed up until five months after discharge from hospital. They were then either visited or written to, asking them to complete a questionary not unlike that sent to patients who had received transfusions.

Character of Patients

The majority of patients given serum or plasma were civilian air-raid casualties ; this accounts for the large proportion of deaths within two months. Death in many cases occurred within a few hours, or at most days, of receiving a transfusion. Most of the patients given whole blood were maternity and gynaecological cases ; a large group of patients with haematemesis, and other miscellaneous medical and surgical cases, were, however, included.

Results of Follow-up of Patients Given Serum and/or Plasma

In this group a total of 2,040 patients were followed up. Since jaundice occurred after both serum and plasma no distinction is made between the two in tabulating the results, nor is any distinction made between patients who also received blood and those who did not. It may be stated, however, that a more detailed analysis of the figures showed that jaundice occurred with any combination. The numbers involved were

* A report to the Medical Research Council from the North-West London Blood Supply Depot.

too small to allow conclusions to be drawn as to whether any combination was more likely than another to cause jaundice. The results are shown in Table I. Of the 2,040 patients 9%

TABLE I.—*Particulars of Patients given Serum and/or Plasma*

Total no. of patients followed up		2,040
No. of patients not traced		186
Proportion not traced		9%
No. of patients traced		1,854
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	1,054	(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 III)	14	(1·3%)

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 after their transfusion. The time at which death occurred after transfusion in the 800 patients who died before the five-months period was complete is shown in Table II. 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 great majority of deaths—769—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, or that if they had lived they would have been either more or less likely to develop jaundice than the survivors. Of the surviving 1,054 patients 91.4% gave no history of jaundice within 5 months; 77 (7.3%) gave a history suggestive of homologous serum jaundice; and 14 (1.3%) developed jaundice which could be attributed to other causes, such as malignant disease or exposure to a case of infective hepatitis (see Appendix III).

TABLE II.—*Analysis of Time of Deaths*

Time	Deaths	
Under 2 months after transfusion	769	(96·2%)
2–3 ,, ,, ,,	16	(2·0%)
3–4 ,, ,, ,,	5	(0·6%)
4–5 ,, ,, ,,	10	(1·2%)
	800	(100%)

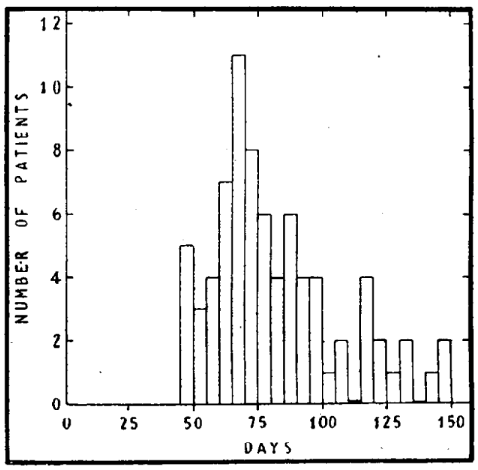
The 31 patients who died between two and five months after transfusion had time in which to develop jaundice, but were not exposed for the full five months. If, however, these 31 patients be debited with a full exposure, the observed incidence rate of 7.3% would only be reduced to 7.1%, so that they can make but little difference to the upshot.

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

Certain pools of both serum and plasma were found to be more icterogenic than others, although in no case was it possible to trace every bottle of one particular pool. For example, of 29 traced patients transfused from one pool of serum (LS 6), 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 patients who did not develop jaundice, 11 (28%) to the patients who did, 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. To some slight extent, but not entirely, this may be attributed to the fact that as soon as the risk of jaundice was appreciated, when two or more patients were found to have developed jaundice following transfusion from any one pool, the remaining bottles were withdrawn from circulation, thus curtailing the further risk of jaundice.

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 proved cases of post-transfusion jaundice, and two occurred in the doubtful group, one of these being a patient with carcinoma of the bronchus and the second 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 4 to 80 years, 30 patients being males and 47 females. The incubation period varied from 45 to 150 days, the majority of cases occurring 60 to 90 days after transfusion (see Graph).



The incubation period in homologous serum jaundice

Symptoms

The incidence of symptoms other than jaundice in 77 cases of jaundice is shown in Table III.

TABLE III.—*Incidence of Symptoms*

Vomiting	41	Urticaria	5
Depression	20	Joint pains	19
Skin rashes	16		

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

Results of Follow-up of Patients Given Whole Blood

In this group 1,284 patients were followed up. They received between them 3,468 bottles of blood. The results are shown in Tables IV and V. The number of patients surviving upon whom the incidence rate is based was 891, receiving between them 2,278 bottles of blood. No patient receiving whole blood developed frank homologous serum jaundice. Notes on 6 doubtful cases are shown in Appendix IV.

TABLE IV.—*Particulars of Patients given Whole Blood*

Total no. of patients followed up (No. of bottles, 3,468)		1,284
No. of patients not traced (No. of bottles, 404)		170
Proportion not traced		13%
No. of patients traced (No. of bottles, 3,064)		1,114
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, 2,278)	891	(100%)
No. of patients with no history of jaundice within five months of transfusion (No. of bottles, 2,248)	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) (See Appendix IV)	6	(0·6%)

TABLE V.—*Analysis of Time of Death*

Time	Deaths
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%)

Among patients receiving blood a larger proportion have 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.

Controls

In this group no case of jaundice within five months of discharge from hospital was noted, 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; and in each case the attack was mild. Results are shown in Table VI. Although the death rate in this group

TABLE VI.—*Particulars of Control Patients*

Total no. of patients followed up	1,284	
No. of patients not traced	408	
Proportion not traced	32%	
No. of patients 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	(0·4%)

is low, the evidence on which the figures are based is poor owing to the high lapse rate—i.e., persons who could not be traced.

Discussion

The results recorded above show an incidence rate of 7.3% of cases developing jaundice after transfusion with serum and/or plasma. No proved case of jaundice following transfusion with whole blood was found. The number of patients given whole blood was smaller than that given serum, but the figures suggest that the risk of homologous serum jaundice is less with whole blood than with pooled serum and/or plasma.

Though no comparable series has been reported, the present findings are in accord with those of other workers, who have almost all been concerned to describe actual cases which developed jaundice after transfusion rather than to assess the incidence of this complication. Jaundice following whole blood appears to be less frequent than jaundice following pooled serum and/or plasma.

Beeson (1943) reported four cases in which jaundice resulted from small transfusions of whole blood within four months, and three cases after the use of plasma. Steiner (1944) records three cases following whole blood alone and two following plasma also. Rappaport (1945), in a series of 33 cases of jaundice after transfusion, mentions two who were given blood only. Loutit and Maunsell (1945) found no case of frank homologous serum jaundice in a follow-up of a selected series of 213 blood transfusions. They record two doubtful cases only. Apart from the cases mentioned above, many which followed the use of pooled serum and/or plasma, either for transfusion or other purposes, have been reviewed at intervals (Memorandum, Ministry of Health, 1943; Bradley *et al.*, 1944; *B.M.J.*, leading article, 1944; *B.M.J.*, leading article, 1945).

The evidence available therefore supports the conclusion to be drawn from the present observations—namely, that jaundice occurs more commonly after serum and/or plasma than after blood. It is obvious, however, that it is easier to incriminate a batch of serum or plasma as the cause than it is to incriminate a bottle of blood, since multiple cases may occur after the use of a batch of the former material, while in the case of blood it is extremely rare for one donor to give blood to more than one recipient within an appreciable time. Unless a single donor's blood results in jaundice of the recipient on repeated occasions it is unsafe to assume that the blood is icterogenic.

It appears probable, on the other hand, that the difference in incidence is not due to any inherent differences between blood and serum or plasma, but rather to the fact that serum and plasma are prepared from big pools and therefore many more patients are likely to receive the icterogenic agent from one donor than when all the affected material is given to one patient, as in the case of a blood transfusion.

Loutit and Maunsell (1945) have shown that no case of homologous serum jaundice was detected when 99 individual sera were each injected into an average of six normal recipients. Transmission experiments have shown, however, that a single serum may be an effective transmitter of jaundice (MacCallum and Bauer, 1944; Neefe *et al.*, 1944; Paul *et al.*, 1945).

The findings of the present inquiry, therefore, emphasize the recommendation of Loutit and Maunsell (1945) that sera for prophylactic use should preferably be individual sera, and that for transfusion purposes pools should be as small as possible. The present observations also stress the importance of labelling with the batch number all material issued, of keeping accurate records of its destination and use, and of creating some machinery for notifying to the regional transfusion officer cases of jaundice following transfusion, so that if necessary the suspected serum or plasma may be withdrawn from circulation. Since certain batches are known to have infected 57% of the cases exposed (Bradley *et al.*, 1944), withdrawal of an infected batch at an early stage should do much to reduce the incidence of jaundice. At present this somewhat cumbersome procedure appears essential, since icterogenic batches cannot be detected by any laboratory or animal test.

The incubation period accorded with that previously noted, varying from 45 to 150 days, the majority of cases occurring between 60 and 90 days after transfusion—so demonstrating yet again the remarkable difference between the incubation period of infective hepatitis and homologous serum jaundice.

The character of the jaundice in the 77 cases here recorded has already been discussed in detail. It was, with one exception, mild. This is in accord with the majority of other observers (Bradley *et al.*, 1944; *B.M.J.*, leading article, 1944; Loutit and Maunsell, 1945), but it must not be forgotten that a definite mortality after both transfusion jaundice and "syringe jaundice" has been noted (Droller, 1945). Few, if any, of the cases were bad enough to go to hospital or to be attended closely by their own doctor; the account of their symptoms is therefore neither detailed nor extremely reliable. It does not differ in any striking way from that described by previous observers (Steiner, 1944; Rappaport, 1945).

Summary

The results are given of a follow-up of 2,040 patients transfused with pooled serum and/or plasma, of 1,284 patients transfused with whole blood only, and of 1,284 control patients, not transfused, who were in hospital at the same time as those receiving whole blood.

The incidence of jaundice in the patients receiving pooled plasma or serum was 7.3%. No patient receiving whole blood developed frank homologous serum jaundice. There was no case of jaundice among the controls within five months of transfusion.

The character of the jaundice was with one exception mild. The symptomatology and incubation period noted were in accord with previous accounts.

It is suggested that to minimize the risk of homologous serum jaundice after transfusion the following procedure should be adopted: (i) human serum for prophylactic purposes should not be pooled; (ii) for transfusion purposes only small pools should be used*; (iii) all blood products issued should carry an identification number; (iv) records should be kept of the number of any bottle given to a particular patient; (v) machinery should be maintained and strengthened for the notification to the regional transfusion officer of jaundice following transfusion, thus enabling icterogenic material to be withdrawn from circulation.

* We understand that only small pools are now used by the Ministry of Health for the preparation of blood products.

APPENDIX I

MEDICAL RESEARCH COUNCIL

N.W. London Blood Supply Depot,
The Social Centre,
Farnham Road,
Slough, Bucks.
Telephone: Slough 22078 and 20291.

Dear ,

We are following up all the people who have been given a transfusion of blood or plasma in this area as we are anxious to know how much benefit they have gained from this treatment. We note from your hospital records that you received a transfusion at ..... Hospital. We should be most grateful if you would write and tell us how you have kept, whether you have had any colds, rheumatism, skin rashes, bilious attacks, jaundice, or any other complaint. It would be helpful to us if you could reply filling in the attached form, giving us your present address, in the enclosed stamped addressed envelope as soon as possible.

With many thanks, yours sincerely,

Medical Director.

Name .....

Address .....

Have you had any Colds ?.....

Rheumatism ?.....

Skin rashes ?.....

Bilious attacks ?.....

Jaundice ?.....

Any other remarks .....

How is your general health ?.....

Signature.....

APPENDIX II

MEDICAL RESEARCH COUNCIL: JAUNDICE COMMITTEE
TRANSFUSION FOLLOW-UP

Name ..... Age ..... Sex .....

Address .....

Letter dispatched .....

Reason given ..... Immediate reaction .....

Date of death, if any ..... Reason given .....

P.M. findings .....

Date	Place and Hospital	Blood	Serum	Plasma	Unknown	Remarks

Previous attacks jaundice:— Date .....

Present attack:—

Date first symptom .....

Urticaria ..... Rashes ..... Joint pains; stiffness .....

Vomiting ..... Stool colour ..... Urine colour .....

Depression ..... History .....

Contact with case of jaundice in 6 weeks before onset:—

At home . At work . In town or village .

(Cross out what does not apply and tick or underline what does)

Household contacts at onset:—

	Number	*Ages*	*Previous Jaundice**	*Subsequent Jaundice**
Male:				
Female:				

* Fill in age of contact concerned and date of attack.

Arsenotherapy ..... Yellow fever vaccine .....

Measles serum ..... Alcohol habits .....

APPENDIX III: DOUBTFUL CASES OF JAUNDICE FOLLOWING SERUM AND/OR PLASMA

L. B. (aged 50).—Died jaundiced 4½ months after transfusion. Carcinoma of bronchus.

F. C. (aged 56).—Carcinoma of rectum. Considerable liver metastases. Died 5 months after attack.

F. D. (aged 71).—Developed jaundice 3 months after transfusion. Diagnosed as obstructive jaundice. Cholecystogram showed definite evidence of cholelithiasis.

C. F. (aged 70).—Jaundice developed more than 5 months after transfusion.

J. H. (aged 55).—D. U., ? malignant. Seen 7 months after attack and still jaundiced. Followed up again 19 months after attack; still getting attacks of jaundice.

E. L. (aged 15).—Gunshot wound. Definite liver damage. Still gets "liver attacks."

D. N. (aged 38).—Jaundice developed 178 days after transfusion.

F. P. (aged 57).—Jaundice developed while in Redhill Hospital. Diagnosed as carcinoma of head of pancreas. Cholecystenterostomy performed.

J. R. (aged 17 months).—Jaundice developed 10 months after transfusion.

W. M. (aged 28).—Jaundice developed 13 months after transfusion.

E. R. (aged 52).—Refused to give any information about attack.

F. T. (aged 36).—Attack reported by his doctor to be of epidemic origin.

J. T. (aged 87).—Two members of the family subsequently developed jaundice 28 to 30 days after onset of patient's attack.

H. T. (aged 20).—Attack said by his doctor not to have been jaundice. ? diaphragmatic pleurisy.

APPENDIX IV: DOUBTFUL CASES OF JAUNDICE FOLLOWING WHOLE BLOOD

A. B. (aged 26).—P. P. H. Jaundice developed only 17 days after transfusion. No infective source known. Donors had no history of jaundice.

P. P. (aged 46).—Anaemia. Jaundice 8 months after transfusion. Lumbago and pale stools only. No icterus.

E. M. (aged 30).—Oophorectomy and appendicectomy. Jaundice 68 days after transfusion. ? true attack. Had had similar attacks previously. Jaundiced on only one previous occasion.

C. S. (aged 58).—Aplastic anaemia. Transfused March and April, 1944, and July/September, 1944. Jaundice Nov. 15, 1944. Diagnosed at Guy's Hospital as acholuric jaundice. Splenectomy performed Dec. 19, 1944. Condition improved.

M. T. (aged 29).—Threatened abortion. Jaundice developed 19 months after transfusion.

T. D. (aged 30).—Haematemesis. Date of onset of attack doubtful. Definite evidence of an infective source. Donors had no history of jaundice.

REFERENCES

Beeson, P. B. (1943). *J. Amer. med. Ass.*, **121**, 1332.
Bradley, W. H., Loutit, J. F., and Maunsell, K. (1944). *British Medical Journal*, **2**, 268.
British Medical Journal (1944). **2**, 279
Ibid. (1945). **1**, 810.
Darmady, E. M., and Hardwick, C. (1945). *Lancet*, **2**, 106.
Droller, H. (1945). *British Medical Journal*, **1**, 623.
Loutit, J. F., and Maunsell, K. (1945). Ibid., **2**, 759.
MacCallum, F. O., and Bauer, D. J. (1944). *Lancet*, **1**, 622.
Memorandum prepared by Medical Officers of the Ministry of Health (1943). *Lancet*, **1**, 83.
—— (1945). Ibid., **2**, 116.
Neefe, J. R., Stokes, J., jun., Reinhold, J. G., and Lukens, F. D. W. (1944). *J. clin. Invest.*, **23**, 836.
Paul, J. R., Havens, W. P., jun., Sabin, A. B., and Philip, C. B. (1945). *J. Amer. med. Ass.*, **128**, 911.
Rappaport, E. M. (1945). Ibid., **128**, 932.
Steiner, R. E. (1944). *British Medical Journal*, **1**, 110.
Turner, R. (1946). *Lancet*, **1**, 108.

The European Regional Office of U.N.R.R.A., has issued from 11, Portland Place, London, W., a series of leaflets, each of which describes the relief and rehabilitation organization at work in one of some ten countries of Europe. Further, to mark the occasion of the recent fifth council session of U.N.R.R.A. in Geneva a special review has been published devoted exclusively to the work of the European missions, and giving for each country the amount of supplies which had been sent up to the middle of 1946. The largest recipients of medical and sanitation supplies were Yugoslavia and Poland, each of which received this form of help to the value of over 27 million American dollars.