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REACTIONS AFTER TRANSFUSION OF STORED BLOOD

BY

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The transfusion of stored blood for many conditions has now become an established practice, and it may therefore be worth while to record some observations made on the incidence of reactions after its use.

Reliable statistics about reaction rates both from stored and from fresh blood transfusions are exceedingly difficult to obtain, mainly because there is little uniformity of opinion as to what constitutes a "reaction." Moreover, the reaction rate will vary with the person who carries out the transfusion, the method employed, the rate of administration, and the condition of the patient. Two disasters which cannot rightly be termed "reactions" but which may develop equally after the use of either fresh or stored blood result from an incomplete understanding of the technique of blood transfusion. They are: (1) pulmonary oedema with cardiac failure, due to overloading of the circulation of a patient whose heart is already embarrassed; and (2) renal failure due to transfusion of blood of an incompatible group. The more usual type of reaction that is apt to occur after a blood transfusion is a febrile reaction. It is unnecessary here to discuss the theories of the causes of such a reaction, although it is generally thought that the introduction of foreign protein into the blood stream plays an important part.

Reactions after Transfusion of Fresh Blood

The febrile reaction may be of variable severity. A simple rise of temperature without shivering or rigor is exceedingly common. Kordenat and Smithies (1925) maintain that nearly all transfusions of fresh blood are associated with some rise of temperature, even though this may be symptomless. Riddell (1939) is in agreement with this statement. Other observers believe that about 50% of fresh blood transfusions are associated with a rise of temperature or a rigor. A mere rise of temperature without constitutional effects is of little significance, but a rigor is more distressing and may even precipitate cardiac failure.

In considering the incidence of transfusion reactions, therefore, it is necessary that the reactions be divided into grades. The following classification is made by Riddell: *Grade I*, associated with a rise of temperature to 100° F., but no other objective features. *Grade II*, associated with a similar or greater rise of temperature and subjectively with feeling cold and shivery, but without having an actual rigor. *Grade III*, associated with a definite rigor. Riddell, giving his figures for his last 100 transfusions with fresh blood, noted rigors (*Grade III* reaction) in 11%. Fell (1938), analysing 500 cases, found reports of rigors in 4.8%. Edwards and Davie (1940) gave the following statistics of reactions after 100 consecutive transfusions of fresh citrated blood at the Liverpool Royal Infirmary: none, 37%; doubtful, 15%; *Grade I*, 15%; *Grade II*, 25%; *Grade III*, 8%. *Grade III* reactions are the most striking and easily recognized. Their average incidence in these three careful investigations on the use of fresh blood is 7.9%.

Reactions after Transfusion of Stored Blood

Edwards and Davie report that out of 1,364 bottles of stored blood administered by numerous surgeons in a variety of hospitals 69 (5%) gave rise to a *Grade III* reaction. These and other results with preserved blood, some of which are quoted by them, are tabulated below:

	No. of Transfusions	Grade III Reactions
Liverpool Royal Infirmary (Edwards and Davie, 1940)	1,364	5.0%
Milton Road Infirmary	—	4.0%
Walton Hospital	—	12.0%
Lundy, Tuohy, and Adams (1937)	149	4.2%
Cameron and Ferguson (1939)	1,000	2.8%
Elliott, Macfarlane, and Vaughan (1939)	50	8.0%
Hamilton-Paterson (1939)	46	6.0%
Biddle and Langley (1939)	150	5.0%
DeGowin and Hardin (1940)	1,458	3.9%
Brewer, Maizels, Oliver, and Vaughan (1940)	56	5.4%

The average incidence of *Grade III* reactions in all these transfusions with stored blood is 5.6%.

In order to determine the reaction rate and other results of the use of stored blood from the North-East London depot a label was attached to every bottle of blood sent out. This label consisted of a detachable reply-paid post-card which the medical officer who gave the transfusion was asked to fill in and return. Investigations suggest that in perhaps half of the transfusions carried out this request was complied with. The first 700 labels returned have been analysed, with the following results:

TABLE I.—Results of Transfusion of 700 Bottles of Stored Blood. Average Age of Blood, 10.8 Days

No. of transfusions	389	
Grade I reactions	44 (11.3%)	
" II "	17 (4.4%)	} 8.5% = 19.8 per 100 transfusions
" III "	16 (4.1%)	
Jaundice	6 cases	= 0.86%
Urticaria	4 cases	= 0.57%

Riddell's classification was slightly modified in that *Grade I* reactions were those in which any rise of temperature above 99° F. was reported but in which there was

no shivering or rigor. Grade II reactions included shivering attacks and mild chills. Grade III reactions were obvious rigors.

Thus the total incidence of Grade II and Grade III reactions was 8.5%, while marked rigors (Grade III reactions) occurred in only 4.1% of cases. These results compare favourably with those of the transfusion of fresh blood to which reference has already been made.

Because of the unreliability of statistics based on a comparatively small total number, and because of the uncertainty as to the proportion of labels that were returned after transfusions, each group of 100 labels was analysed separately, and it will be seen that the figures in each group are in fairly close agreement with each other (Table II). Each bottle contained 360 c.cm. of blood and 180 c.cm. of anticoagulant fluid (composed of 1.05% sodium citrate and 3% glucose in 0.85% sodium chloride solution). The Medical Research Council depots are now using a modification of this mixture (see M.R.C. War Memorandum No. 1, 1940).

TABLE II

Hundred Bottles :	First	Second	Third	Fourth
No. of transfusions	62	63	57	52
Grade I reactions	14.5%	14.3%	12.3%	7.7%
" II "	1.6%	4.8%	5.3%	3.8%
" III "	4.8%	1.6%	3.5%	7.7%
Total ..	20.9%	20.7%	21.1%	19.2%
Average age of blood	8.3 days	9.6 days	9 days	10.5 days

Hundred Bottles :	Fifth	Sixth	Seventh
No. of transfusions	52	49	54
Grade I reactions	11.5%	10.1%	7.4%
" II "	5.8%	0	9.3%
" III "	0	4.0%	7.4%
Total ..	17.3%	14.1%	24.1%
Average age of blood	13.5 days	11.5 days	13.3 days

These findings bear out the opinion of other investigators such as Biddle and Langley, who state: "We are well satisfied that stored citrated blood produces no more complications than does fresh citrated blood, and the advantages of the former cannot be exaggerated." DeGowin and Hardin (1940) state that, in their experience, "no types of reaction were observed from the transfusion of preserved blood which were not already known to be associated with the use of fresh blood. . . . The incidence of various types of reaction did not increase or decrease with the period of storage of the blood mixtures."

In my own series 58 of the bottles of blood were 21 or more days old, but the average age of the blood causing Grade II reactions was 13.4 days, while the average age of the blood causing Grade III reactions was 12.7 days. Reactions were by no means confined to the older blood. Thus, shortly after receiving one bottle of 3-day-old blood one patient had a rigor for ten minutes with a sense of constriction in the chest and headache. On the other hand, two bottles of 21-day-old blood and one bottle of 28-day-old blood were given to another patient without any reactions developing. The oldest blood used consisted of two bottles that had been stored for 33 days. This was given to a patient with salpingitis and a urinary infection whose haemoglobin was 59%. There was no reaction or discomfort during the transfusion, but one hour afterwards she had a rigor. Her temperature fell to normal within forty-eight hours and remained so. There was no jaundice or other untoward reaction, and her haemoglobin had risen to 71% the day following the transfusion. Eight days after the transfusion she was given another bottle of blood—this time 28 days old. There was no rigor or discomfort on this occasion. Her temperature rose slightly

(to 99.4° F.) in the evening, but the next day and thereafter it remained normal.

The 4 cases of urticaria resulted from transfusion of blood stored for 1 day, 3 days, 12 days, and 19 days. The six cases of jaundice, however, seemed to be the result of transfusion of somewhat older blood, since in all but one instance it had been stored for 14 or more days.

Red Cell Destruction

Since even fresh blood contains many aged erythrocytes, rapid destruction of these is to be expected after their transfusion. When stored blood is used the degree of destruction increases with the age of the blood. These facts have been demonstrated by Ashby's (1919) method of estimating cell survival after transfusion. Maizels and Hamilton-Paterson (1940) have found, however, that when the blood had been stored for 7 to 14 days more than 75% of the cells survived in the patients' blood stream after six days, and in some instances transfused cells were found months after transfusion. Mollison and Young (1940) found that when blood over 20 days old was transfused a great deal of destruction took place within a few hours of transfusion, although the time taken for the complete disappearance of the transfused cells was little less than that found for fresh blood.

It thus appears that the rapid initial fall in the number of transfused cells of stored blood is due to the destruction of effete corpuscles and that those that do not quickly succumb are relatively resistant to haemolysis. The early destruction of effete cells results in a transient increase in the bilirubin content of the patient's plasma and the presence of urobilin in the urine. If the amount of red cell destruction is excessive the patient may become jaundiced, but this is of very brief duration, since the excess of bilirubin is rapidly removed from the blood stream.

Using the preservative solution described it is found that most of the degenerative changes in the blood, other than the disintegration of the red cells, occur within the first two weeks of storage. Up to three weeks the amount of *in-vitro* haemolysis is negligible. The subsequent amount of haemolysis in previously undisturbed blood, estimated by the method described by Hudson (1940), was as follows:

TABLE III

Length of Storage	Average Haemolysis	No. of Bloods Examined
3 weeks	1.0%	9
4 "	2.9%	12
5 "	3.8%	13
6 "	8.1%	7

Further haemolysis is likely to occur when the stored blood is transfused into a patient, and this can be shown by pipetting off from a centrifuged specimen all the supernatant plasma and replacing it by isotonic saline or fresh normal serum. If this is gently mixed and allowed to stand or is centrifuged, considerable additional haemolysis is observed, and it is found on measurement to be more than that in the original plasma.

It is therefore important as a routine not to use blood preserved under present conditions for more than three weeks, since the haemolysis both *in vitro* and *in vivo* may result in transient jaundice and possibly be the cause of other reactions. Bushby, Kekwick, Marriott, and Whitby (1940) have proved that the increase in plasma bilirubin of the recipient is due not to free haemoglobin in the transfused specimen but to *in-vivo* haemolysis of transfused cells. Amberson (1937) concluded that haemoglobin is not toxic to vertebrates if it has been properly freed from stroma, and Duesberg (1934) has injected haemoglobin intravenously into man in amounts varying

from 2 to 6 grammes without ill effect. Hamilton Fairley (1940) has successfully injected considerably larger amounts after careful alkalization of the urine.

It is therefore likely that the febrile reactions after transfusion of very old blood are due to products of red cell disruption and degeneration rather than to the mere presence of free haemoglobin in solution.

Though it is not relevant here to discuss the merits of various preservative solutions it is important to use mixtures that are most likely to prevent the early breakdown of the red cells. That haemolysis is impeded by the presence of glucose is now well known. Table IV shows the average haemolysis in five samples of blood, each preserved with and without glucose, over a period of six weeks.

TABLE IV.—*Comparison of Haemolysis with and without Glucose*

Weeks	With Glucose	Without Glucose
3	0.91%	4.99%
4	1.76%	13.24%
5	3.46%	24.75%
6	8.17%	37.4%

Blood preserved in solutions containing no glucose might therefore be expected to lead to a greater incidence of transfusion reactions owing to the additional *in-vitro* and *in-vivo* haemolysis, and this has been found to be so. Thus in the transfusion of fifty bottles of blood preserved without glucose the results of transfusion were as follows:

TABLE V.—*Fifty Bottles of Blood Preserved without Glucose. Average Age of Blood, 11.1 Days*

No. of transfusions	.. 33								
Grade I reactions	.. 18.2%								
" II "	.. 15.1%								
" III "	.. 12.1%								
} 27.2% } = 45.5 per 100 transfusions									
Jaundice	..	..	..	..	..	..	..	..	1 case = 3%
Urticaria	..	..	..	..	..	..	..	..	1 case = 3%

The total number of bottles of non-glucose blood used is not large, but the reaction rate is considerably higher than in any group of 100 bottles of blood preserved with glucose.

Stored blood can never be better than fresh blood, but its ready availability is an immense advantage, particularly in an emergency, and this outweighs any slightly smaller rise of haemoglobin percentage in the recipient that may occur. The disadvantage of stored blood has been seen to resolve itself chiefly into the question of haemolysis, but with modifications of the preservative solution the life of the red cells can be further prolonged. Fortunately there is now less need to attempt to preserve emergency supplies of blood for long periods of time, since plasma or serum, capable of independent storage for many months, can be given as an emergency measure in place of whole blood in certain cases, when whole stored blood is not immediately available.

Conclusions

There is no significant difference in the nature or number of reactions which tend to occur after the transfusion of fresh blood and blood stored up to three weeks under standard M.R.C. conditions. Such difference as may occur seems to be in favour of stored blood.

When standard stored blood is used a febrile reaction is to be expected in about 20% of transfusions and an obvious rigor in about 5%.

The incidence of jaundice and febrile reactions tends to increase when blood more haemolysed than this is used. These reactions appear to be caused not so much by the free haemoglobin introduced as by the early disruption of effete red cells after transfusion.

Stored blood, as originally prepared, can safely be used for three weeks and in some cases for longer. Modifications of the preservative solution may further increase the useful life of the blood, though the introduction of preserved plasma and serum now renders this less necessary.

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CARRIERS OF TUBERCULOSIS

BY

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The fact that many infectious diseases may be contracted from contact with individuals who are not themselves suffering from any of those diseases at the time of contact is well known. Typhoid fever, scarlet fever, and some other streptococcal infections, cerebrospinal fever, diphtheria, and acute poliomyelitis are examples that come to mind at once, but there may be many other diseases which are spread in this way. The exanthemata and even the common cold, though usually contracted in epidemics from known sources, sometimes appear in a sporadic form which suggests the possibility of contact with a carrier.

Types of Carrier

Clinically there are two types of carrier—the known and the unsuspected. A known carrier has had the disease in question and has never been shown to become bacteriologically negative, although he no longer suffers in any way from the infection; in such a case the organisms appear to be saprophytic only. Carriers of this type are usually kept under observation until eventually the organisms are eradicated by some means or other; in any case they are a known danger and can therefore be controlled to some extent. The unsuspected type of carrier is much more dangerous, for his very existence may not be even suspected until extensive damage has been done. Such persons may have had their infection in an abortive or aberrant form, the true nature of which was not recognized at the time, or, more difficult still, they may never have had the disease in their lives so far as the most careful clinical investigation can discover.

In view of the great amount of work which has been done on the carrier problem it is surprising to note that little attention has apparently been paid to the possibility of the existence of carriers of tuberculosis. Of course it is well known that sufferers from chronic pulmonary tuberculosis may eject tubercle bacilli in the sputum for years, but a point often overlooked is that those who have