HOW IMPORTANT IS TRANSFUSION AS A CAUSE OF HAEMOLYTIC DISEASE OF THE NEWBORN?

BY

GEORGE DISCOMBE, M.D., B.Sc.

AND

H. O. HUGHES, O.B.E., M.R.C.S., L.R.C.P.

(From the Central Middlesex County Hospital)

When transfusion reactions caused by the Rh factor were first recognized (Wiener and Peters, 1940) it was thought that sensitization by transfusion was rare, though once it had developed following repeated pregnancy small transfusions would increase the antibody titre. Attention was therefore directed to the peculiarities of those patients who formed antibodies, and it was thought that subjects suffering from certain diseases (Drummond *et al.*, 1945; Callendar and Paykoc, 1946) were especially apt to produce antibodies to antigens which they lacked. Studies on soldiers transfused during the invasion of Europe led to a change of opinion, Moloney (1945), Hattersley (1947), and Diamond (personal communication, 1947) showing that at least 55% of Rh-negative* males were sensitized by a single transfusion of Rh-positive* blood, while Wiener and Gordon (1947) sensitized five out of nine volunteers, obtaining high titres in two.

Since Levine and others (1941a, 1941b) had shown that haemolytic disease of the newborn is caused by a reaction between a foetal antigen and the corresponding antibody formed by the mother, and that in about nine-tenths of all cases the antigen concerned is the Rh antigen, it becomes important to decide what part transfusion plays in the pathogenesis of haemolytic disease of the newborn. Various authors have noted that transfusion occasionally preceded and apparently caused fatal cases of disease in a first-born child, but Hellmann (1947) studied 27 Rh-negative mothers who had given birth to affected infants and found that seven had been transfused with blood of unknown Rh type before the birth of the first affected infant, whereas only 2% of the generality of mothers had been transfused.

Present Investigation

To compare with these results, the notes of Rh-negative mothers of affected infants born or treated in this hospital were reviewed. The mild cases not clinically distinguishable from "physiological jaundice" were rejected, as were those due apparently to ABO compatibility, but two cases without serological data were retained—these mothers had never received a transfusion. Mothers who had received only Rh-negative blood were classed as "not transfused." Those patients whose hospital notes were not explicit were written to, and all replied. The results are given in Table I, together with the replies of 200 consecutive mothers attending the antenatal clinic, who are described as "unselected." In Table II is shown the mortality of the infants in the two groups into which the mothers of affected infants are placed.

The frequency of transfusion with blood which had not been Rh grouped is therefore 36% among the mothers of infants affected by haemolytic disease of the newborn, compared with 2% among the general population of the clinic. These results could be explained by either of two hypotheses; first, that mothers who gave birth to infants

*Throughout this paper Rh-positive refers to blood possessing the antigen D, and Rh-negative, in the case of recipients, refers to those lacking this antigen; in the case of donors, Rh-negative implies lack of the three major antigens, C, D, and E.

TABLE I.—Comparison of Results

	Mothers of Affected Infants	Mothers Unselected	Total
Transfused ...	9	4	13
Not transfused ..	16	196	212
Total ..	25	200	225

$$\chi^2 = 41.15$$

$$P = < 0.001$$

TABLE II.—Mortality of Infants Affected

Mothers	Infants		
	Died	Survived	Total
Transfused ...	5	4	9
Not transfused ..	9	9	18
Total ..	14	13	27

affected by haemolytic disease are particularly liable to illness which requires transfusion—a hypothesis for which there is no evidence whatsoever; or secondly that transfusion sensitizes the recipient and thus prepares the way for the development of haemolytic disease—a view for which there is plenty of support.

This risk has been recognized for over a year at this hospital, and the Gunz (1946) transfusion form was modified to eliminate it (see accompanying Form). It is

CENTRAL MIDDLESEX COUNTY HOSPITAL

REQUEST FOR BLOOD FOR TRANSFUSION

Patient's Name..... Sex.... Age.... Ward.....

Has patient had any previous transfusion? Yes No

If so, was it followed by a rigor or by jaundice? Yes No

Don't know

If the patient is female:

any pregnancies? Yes 1, 2, 3, 4, more No

any stillbirths? Yes No

any babies jaundiced at birth? Yes No

If previously determined in this Hospital, Group O A B AB

Rhesus Positive Negative

Transfusion will be Immediate Urgent When convenient

No. of pint bottles required 1 2 3 4

Ring the correct answer

Transfusion request form. On the reverse side are instructions for transfusion and space for the laboratory to note the ABO and Rh group and the serial number of bottles supplied.

a rule that no female below the age of 40 years may be transfused unless she has been Rh tested, and if found to be negative she must receive Rh-negative blood. In the rare extreme emergency, when there is no time to test, or in emergency transfusions in domiciliary work, Rh-negative blood is used until the recipient has been tested and shown to be positive. This procedure has been made possible only by the adoption of Chown's (1944) capillary technique, which usually gives a clear-cut result within 10 minutes of setting up or 15 minutes of seeing the patient (Discombe and Meyer, 1948), and by the co-operation of the newspapers which serve the locality in advertising our need for donors.

It is well known that sensitization can be induced by a single injection of quite small quantities of an antigen. There is no reason why the Rh antigen should behave differently, so it must be assumed that injection of any volume of blood, from 0.1 ml. to 1,000 ml., should suffice to establish sensitization: the titre of antibody produced by a single injection will be low, but will rise rapidly if the antigen is again injected after a lapse even of years.

Since for many years the intramuscular injection of parental blood has been recommended for the treatment of haemorrhagic disease of the newborn, it appears useful to calculate the frequency with which this procedure might sensitize the infant to the Rh factor. Of the whole population, about 17% are Rh-negative (rr) and 45% heterozygous Rh-positive (Rr). Rh-negative infants can be born to Rh-positive parents in the matings $Rr \times rr$, constituting 15.2%, and $Rr \times Rr$, forming 19.8% of all matings. Therefore, in the first group three out of four and in the second group one out of four of all children will be Rh-negative, so that one or both parents are Rh-positive when the infant is Rh-negative in about 12.5% of all births. It seems that over 6% of all infants could be sensitized by the injection of parental blood.

If all infants were treated thus, about one in three of all Rh-negative females would be sensitized. Fortunately, haemorrhagic disease of the newborn is not common, but, even if it is rare, treatment by injection of parental blood will sometimes result in the appearance of haemolytic disease in the first-born of an Rh-negative mother. Such possible tragedies can be avoided by the use of a vitamin-K analogue, and the use of parental blood in its place will no doubt in future be regarded as a barbarous and unethical procedure.

Conclusion

A history of having received a blood transfusion without special precautions for Rh matching is 18 times more common among mothers of infants suffering from haemolytic disease of the newborn than among unselected patients at the antenatal clinic.

Such transfusion probably causes the disease.

Injection of paternal or maternal blood into an infant without Rh matching would sensitize about one in three of the Rh-negative females at risk.

It is wrong to inject any female with blood from another individual unless either the recipient is known to be Rh-positive, both recipient and donor to be Rh-negative, or the recipient to be too old to bear children.

This rule must be broken only if the patient is expected to die before Rh-compatible blood can be obtained.

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THE EVOLUTION OF GASTRIC AND DUODENAL ULCERATION

BY

J. DONALDSON CRAIG, M.D., M.R.C.P.

Research Fellow in Medicine, St. Mary's Hospital
Medical School

Acquired disease being the product of disharmony between constitutional and environmental factors, it is inevitable that alterations in mode of life should be accompanied by change in the pattern and distribution of certain diseases. As a preliminary to the present investigation the early literature dealing with peptic ulcer was reviewed and the observations thereon summarized in a previous communication (Craig, 1947). Space will not permit of further detailed discussion of the nature and incidence of peptic ulceration before the present century, but certain broad conclusions may be outlined.

Although gastric ulcer was mentioned by Celsus and was well recognized in the eighteenth century, the disease does not appear to have been at all common until the middle of the nineteenth century, when William Brinton (1857) concluded that about 5% of the population were subject to gastric ulcer at some time or other in their lives. At that time gastric ulcer was predominantly a disease of young women, many of whom suffered from perforation. Haematemesis occurred more commonly in men, generally in the fifth decade, but by the end of the century this complication, too, was one more often affecting young women (Hale White, 1901). Thus, although the overall incidence of gastric ulcer has remained fairly uniform during the past century, the age and sex distribution and its clinical pattern have changed very considerably in that time.

George Hamberger (1746) first described a case of duodenal ulcer, and Abercrombie (1828) gave the first account of the clinical features of the disease, but until the end of the century the amount of interest taken in the condition was out of all proportion to the number of cases encountered. The Fenwicks (1900), for example, were able to quote over 200 references, yet for all their extensive experience and keen interest they could gather together only 68 cases, 25 of them acute ulcers. It is generally believed that the apparent rarity of duodenal ulcer until the present century was the consequence of failure to recognize the condition. Undoubtedly many cases were missed, but when the situation is viewed against the broader background of earlier writings it is difficult to escape the conclusion that improvement in diagnosis was concomitant with an increase in the frequency of the disease. Review of more recent years provides strong evidence of further increase, and this suspicion becomes stronger. Although there is every reason to believe that duodenal ulcer has become very much more common there is no evidence that its clinical features have altered in any way.

Pringle (1753) and MacGregor (1804) in their treatises on military medicine made no mention of dyspepsia in the Army. In the war of 1914–18, digestive diseases of all types were no great problem, but in the recent war, by the end of 1941 no fewer than 23,754 serving personnel had to be invalided from the Army alone on account of peptic ulcer, duodenal ulcer preponderating over gastric ulcer in the ratio of approximately 7:2.

The changing nature and frequency of gastric and duodenal ulceration thus becomes apparent. The evolution of acute gastric ulcer, of chronic gastric ulcer, and of duodenal ulcer has been so different as to raise the strong suspicion that they may be distinct diseases, albeit related to one another. In an attempt to evaluate causal factors

As the result of negotiations between the Northern Ireland Ministry of Health and the Northern Ireland Pharmaceutical Negotiating Committee, the Committee has decided to recommend all chemists in Northern Ireland to enter the Health Service provisionally, pending the outcome of further negotiations. The Minister of Health (said an agreed joint statement) "undertook to appoint a practising accountant to carry out an investigation into dispensing costs in Northern Ireland and, after receiving the Accountant's report, to enter into further negotiations on the basis of this report and that made by the accountants appointed by the chemists, full account to be taken of pharmaceutical practice in Northern Ireland."