Nocturnal tooth-grinding is shown to be a cause of bleeding into the mouth. Tests of lesser sensitivity are recommended.

The advantages of the newly introduced simplified benzidine test are enumerated.

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TRANSFUSION TREATMENT OF WOMEN OF CHILD-BEARING AGE

A STATISTICAL STUDY OF THE INCIDENCE OF ANTI-RHESUS IMMUNIZATION

BY

W. WEINER, M.D.

Director of the Midland Regional Blood Transfusion Service

VERA NORRIS, Ph.D., M.B., Ch.B.

Department of Medical Statistics, University of Birmingham

AND

S. DAVIDSON, M.B., Ch.B., F.R.C.S.Ed.
M.R.C.O.G.Honorary Obstetric Surgeon, Birmingham Maternity
Hospital

The increased use of blood transfusion in the treatment of a great number of conditions has brought into the foreground complications which in the past must have been more or less rarities. The immediate effects of transfusion in saving the lives of many patients has on certain occasions been followed by the production of antibodies. Some of these antibodies may play a decided part in the future life of the patient. Serologically the great majority of the antigens carried on or in the red cells of man seem to be poor antigens, but even poor antigens will produce antibodies in "good reactors," particularly if given in sufficient quantity.

By far the most important antigen of the cells in this respect—apart from the antigen responsible for the ABO specificity—is the rhesus antigen. Compared with other blood-group antigens it provides a comparatively potent stimulus for antibody production, and is thus

capable of immunizing an appreciable percentage of patients lacking the antigen themselves. Diamond (1946) has shown, in an investigation performed on war veterans, that approximately 46% of rhesus-negative men who were transfused in the field were found to be immunized against the rhesus factor. The blood given in most of these emergencies was presumably rhesus-positive blood. Although the production of antibodies in the male might have serious consequences if the patient should later require a further transfusion, the sequelae in the female are far more serious, since the presence of antibodies may, under certain circumstances, prevent her from ever having a healthy child. Among the mothers who bore children affected with haemolytic disease of the newborn are a certain number whose immunization had either been started or been greatly stimulated by one or more previous transfusions of rhesus-positive blood. The percentage of immunized women is very much higher among those who have received a previous transfusion than among those who were not so treated. The growing knowledge of the dangers of immunization by transfusion has, generally speaking, resulted in an improved technique and fewer cases of immunization. This investigation was undertaken in order to find out whether the number of patients whose immunization has been precipitated by transfusion treatment in the past has declined lately.

Material and Methods

The material has been taken from the Regional Transfusion Service, Birmingham, and consists of the records of approximately 82,000 patients whose blood samples were investigated up to the end of 1949. This investigation consisted always in the determination of the group and the rhesus type of the patient. In all cases which were found to be rhesus-negative an investigation for the presence of antibodies was performed routinely. For the latter investigation the following method was used. Eight random samples of rhesus-positive saline-suspended cells and two samples of rhesus-positive and two of rhesus-negative albumin-suspended cells were put up in precipitin tubes as recommended by the Medical Research Council (1943). An equal amount of the patient's serum was then added to the test cells and the mixture was incubated at 37°C. for two hours. The tests were always read under the low power of the microscope on a slide. If in this screening test agglutination was found in either the saline- or the albumin-suspended test-sample cells, a fuller investigation was carried out.

This same fuller investigation was also done if the history of the patient indicated immunization or if a transfusion had been given at some time previously in her life. The method used was as follows. The serum of the patient was put up with ten random rhesus-positive and two random rhesus-negative saline-suspended cells. The same cells were used as test cells in albumin suspension and simultaneously incubated with the saline-suspended cells (incubation two hours at least). Indirect Coombs tests, using CDE, cDE, and cde cells, were also performed with every sample.

All the patients in whose sera antibodies were discovered were followed up by frequent investigations until delivery. In most cases the diagnosis was confirmed either by the result of the pregnancy (hydrops) and/or a Coombs test on the baby's blood. In many cases a sample of blood taken from the husband was investigated for its genotype. The clinical data concerning the patients were obtained from the medical officers in charge of the hospitals and antenatal clinics on the usual antenatal forms. Further information was obtained in special cases. The data were transferred to a filing-card, on to which were entered also the result of the serological investigation and any subsequent development. The cases were arranged according to the date on

which the transfusion had taken place. Arbitrarily the date of December, 1947, was taken as a dividing-line. This date was chosen because at this time, approximately, the knowledge of the dangers of non-homologous transfusions became more widespread and the supply of rhesus-negative blood of all groups had become somewhat more plentiful by a revised bleeding programme.

Results

Among approximately 82,000 cases investigated up to the end of 1949 were found 13,169 patients who were rhesus-negative. Of the latter, 515 (3.9%) were found to be immunized against the rhesus factor (D). Among the total of 13,169 patients investigated, 243 gave a history of having received a blood transfusion at some time during their lives or blood injections of untyped blood which was given as a therapeutic measure. It is possible that the number of women who, as girls or babies, had received blood injections is greater than the actual number found among our patients, as these data depend very often only on the recollection of their parents, who might not have informed their children. Of the 243 patients who had been treated with blood transfusion or injections, 87 were found to be immunized against the rhesus factor. This leaves 428 who, with no history of a previous transfusion, were found to be immunized.

Before 1947 many patients will have received, particularly in emergencies, transfusions of untyped or rhesus-positive blood. The chance of a rhesus-negative patient receiving initially 1 pint (570 ml.) of rhesus-positive blood is about 85 in 100, but the chance of receiving at least 1 pint (570 ml.) of rhesus-positive blood increases with successive transfusions (second, 977 in 1,000; third, 997 in 1,000). As pointed out above, both the knowledge of the dangers of immunization and the availability of rhesus-negative blood increased after 1947. In the Birmingham Blood Transfusion Centre the average monthly number of blood samples from pregnant women which were investigated for the rhesus factor ("D screening") increased as follows:

Second half of 1947 ..	2,334	Second half of 1949 ..	5,869
First .. 1948 ..	3,340	First .. 1950 ..	6,306
Second .. 1948 ..	4,469	Second .. 1950 ..	6,015
First .. 1949 ..	5,700	First .. 1951 ..	6,602

The numbers of pints of rhesus-negative blood issued annually were as follows: in 1947, 1,551; in 1948, 2,447; in 1949, 4,953; and in 1950, 6,824.

Table I sets out in detail the occurrences of immunization among transfused persons. It will be seen that in most of the years previous to 1947 over 40% of the transfused

TABLE I.—Immunization Among Transfused Persons

	'40*	'41	'42	'43	'44	'45	'46	'47	'48	'49	Total
Primigravidae transfused and immunized	2	1					1		1	1	6
Multigravidae transfused and immunized	10	2	4	6	8	12	15	12	10	2	81
Primigravidae transfused and not immunized	1		2	1	1	2	3	4	3	12	29
Multigravidae transfused and not immunized	13	4	7	7	8	8	17	24	26	13	127
Total ..	26	6	14	14	17	22	36	40	40	28	243
Percentage of immunized women	46	33	36	43	47	54	44	30	27	11	36

* Includes some cases that occurred before 1940.

rhesus-negative women were immunized. The percentage declined in 1947 and 1948, and in 1949 it was much less.

Table II shows the difference of the percentage of immunization among the transfused persons: 41.7% before and including 1947, 20.6% after 1947. The difference of 21.1% has an estimated standard deviation of 6.8%; thus the probability of so large a difference occurring by chance is about 1 in 500. In the second part of this table a comparison is

TABLE II.—Immunization Among Transfused Rhesus-negative Women

Period	Total No. of Transfused Women	% Immunized	Difference %	Estimated Standard Deviation %	P
Transfusions: 1940-7 ..	175	41.7	} 21.1	6.8	0.002
1948-9 ..	68	20.6			
Transfusions: 1944-7 ..	115	41.7	} 21.1	7.3	<0.003
1948-9 ..	68	20.6			

made between transfusions known to have taken place in the period 1944 to 1947 and those in 1948-9. The difference is 21.1%, its estimated standard deviation 7.3%, and the probability of such a difference occurring by chance is less than 1 in 100.

In Table III the incidence of immunized persons in two-year groups, up to and including 1947, is compared with that in the period 1948-9. In each case the difference is too large

TABLE III

Period	No. of Transfused Women	% Immunized	Difference %	Estimated Standard Deviation %	P
1940-1 ..	32	43.7	} 23.1	9.6	0.016
1948-9 ..	68	20.6			
1942-3 ..	28	39.3	} 18.7	9.8	0.057
1948-9 ..	68	20.6			
1944-5 ..	39	51.3	} 30.7	9.4	0.001
1948-9 ..	68	20.6			
1946-7 ..	76	36.8	} 16.2	7.6	0.036
1948-9 ..	68	20.6			
1944-5 ..	39	51.3	} 14.5	9.7	0.134
1946-7 ..	76	36.8			

to be regarded as a chance effect. The period with the highest percentage (1944-5) is compared with that having the lowest percentage (1946-7), 1948-9 being excluded. The difference of 14.5% is probably due to chance, since it might be elicited 13 times out of 100.

Table IV shows the actual and expected numbers of immunized women up to the end of 1947. There is little dif-

TABLE IV

Period	No. of Transfusions				Total
	With Immunization		Without Immunization		
	Actual	Expected	Actual	Expected	
1940-1 ..	14	13.35	18	18.65	32
1942-3 ..	11	11.68	17	16.32	28
1944-5 ..	20	16.27	19	22.73	39
1946-7 ..	28	31.71	48	44.29	76
Total ..	73	73.01	102	101.99	175

$$\chi^2 = 2.327. \quad 0.70 > P > 0.50.$$

ference between the actual and the expected numbers, since they may occur by chance about seven times out of ten.

Table V shows the actual and expected numbers when the period 1948-9 is included. In this case the actual number

TABLE V

Period	No. of Transfusions				Total
	With Immunization		Without Immunization		
	Actual	Expected	Actual	Expected	
1940-1 ..	14	11.46	18	20.54	32
1942-3 ..	11	10.02	17	17.98	28
1944-5 ..	20	13.96	19	25.04	39
1946-7 ..	28	27.21	48	48.79	76
1948-9 ..	14	24.34	54	43.66	68
Total ..	87	86.99	156	156.01	243

$$\chi^2 = 11.98. \quad P = 0.02.$$

of cases is less than the expected number in the last period only (1948-9); the actual number exceeds the expected in each of the other periods. The probability of this difference being due to chance is only 1 in 50.

From the above it seems to be quite clear that the number of women immunized by a transfusion was greater before the end of 1947 than after this period. With and without transfusion, a certain number of rhesus-negative mothers are bound to become immunized if the foetus is rhesus-positive, but the figures will be much higher if precautions are not taken to prevent artificial immunization by transfusion in the rhesus-negative population.

Discussion

Though the figures show a definite improvement in the two years under review as compared with previous years, they seem to be still too high to be accepted with complacency. It would appear to be imperative to adopt effective measures to reduce these figures still further, and no case of immunization by transfusion in a female should ever occur. As the great majority of transfusions are "cold" transfusions there is usually enough time to group and type the patient so that homologous blood can be given. Most hospitals have by now a blood bank run by the pathological laboratory; blood grouping and typing has reached in most parts of the country a very high standard indeed, and technical mistakes are very rare.

With regard to emergency transfusions, a simple procedure would serve to prevent immunization and at the same time save the rare rhesus-negative blood, particularly of Group O: a female patient admitted in an emergency is treated, to start with, as if she was rhesus-negative, and rhesus-negative blood is given. If the group is known or if there is enough time at least to determine the group, rhesus-negative blood of the same ABO group may be given if available. Before the transfusion is begun an adequate sample of blood from the patient is put into a test-tube and sent immediately to the laboratory, where grouping, typing, and cross-matching can be performed. If further blood is needed for the patient, this can then be given as homologous blood, and rhesus-positive patients will receive positive blood. The great amount of antenatal care and the issue of grouping cards by the transfusion centres have further increased the safety of transfusion treatment. The flying squad, for instance, in Birmingham during 1946 and 1947 was issued with rhesus-negative blood only. Lately it has been found possible to make use of rhesus-positive blood, as many emergency patients can now produce their blood-grouping cards on request. If the patient has been typed as rhesus-positive, homologous rhesus-positive blood is given.

The scarcity of anti-rhesus serum, which at one time seemed to limit a further expansion of antenatal typing, will, it is hoped, be overcome in the future if pathologists and clinicians realize the importance of its availability and will help to persuade immunized mothers to contribute some serum to the common pool.

Conclusion and Summary

Using the figures obtained from the records of the Regional Transfusion Service in the Midlands, it has been shown that the percentage of immunization among rhesus-negative mothers due to previous transfusions has gone down significantly in the two years 1948 and 1949 as compared with previous periods. It is felt, however, that no immunization should ever occur if simple precautions are taken in the treatment of girls and women of pre-child-bearing or child-bearing age.

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INFECTIOUS MONONUCLEOSIS WITH THROMBOCYTOPENIC PURPURA

BY

C. M. OGILVIE, M.B., M.R.C.P.

Medical First Assistant, The London Hospital

AND

T. E. PARRY, M.B., M.R.C.P.

Consultant Pathologist, United Cardiff Hospitals

A tendency to abnormal bleeding in patients with infectious mononucleosis has been noted for many years, but a true thrombocytopenic purpura has been recognized only since Magner and Brooks (1942) reported a case. Accounts of nine other cases have now been published, six of these during the past two years. Despite this increased recognition of the condition, only one instance has been reported in the European literature (Finlayson, 1951). Thrombocytopenia is not mentioned in many recent accounts of infectious mononucleosis published in this country, but it is still quoted as diagnostic evidence of acute leukaemia in the differentiation of this condition from infectious mononucleosis. We describe a further case of thrombocytopenic purpura in infectious mononucleosis and review the literature on this complication.

Case Report

An unmarried girl aged 20 was admitted to the Liverpool Royal Infirmary as a case of purpura on May 11, 1951. She complained of lassitude, sore throat, swollen glands, and a rash on her arms and chest. Her previous health had always been good, and neither the patient nor her family had ever shown abnormal bleeding tendencies. She had not recently taken drugs in any form and was not exposed to toxic substances at her work.

On admission she stated that she had felt tired and "run-down" for about a month but had remained at work. For the same period she had been aware of enlarged glands behind her right ear; these had not altered in size. Three days before admission red spots appeared over the neck, the upper part of the chest, the upper arms, and the radial border of the left forearm. This rash developed in about 48 hours and gradually faded during the ensuing fortnight. On the day of admission she complained of sore throat, which remained for about a week. A menstrual period two weeks before the rash appeared was not excessive.

Examination revealed a lively and well-nourished girl showing no pallor or jaundice. Her temperature on three evenings during the first week in hospital was 100-101° F. (37.8-38.3° C.), and thereafter remained normal. Crops of petechiae were found on the left arm and breast, and larger purpuric areas on the right upper arm and left thigh. Hess's test for capillary fragility was negative. Firm, discrete mobile lymph nodes were palpated behind the upper part of the right sternomastoid, and one node was felt in a similar position on the left side. Inguinal and axillary lymph nodes were normal and the spleen was not palpable. The faucial pillars were injected and a mucous exudate partially covered the tonsils, but the mucous membranes were otherwise normal and no haemorrhagic lesions were seen in the mouth. The examination revealed no other abnormal features.

A blood examination on admission showed no anaemia. There were changes in the white cells typical of infectious mononucleosis, and this diagnosis was confirmed by a strongly positive Paul-Bunnell reaction. A platelet count revealed a marked thrombocytopenia (the haematological findings are enumerated in the accompanying table).