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RAPID DESTRUCTION OF APPARENTLY COMPATIBLE RED CELLS

BY

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As serological tests have improved, it has become progressively easier to avoid the transfusion of incompatible blood. When, owing to weak reactions of the blood-group antibody *in vitro*, incompatibility of a sample of red cells is overlooked, transfusion of the cells is usually followed only by a mild haemolytic reaction.

The case reported here is remarkable in that transfusions of red cells which seemed to be perfectly compatible, judged by tests *in vitro*, were repeatedly followed by severe reactions, with haemoglobinuria.

Case Report

A married woman aged 46 was found in 1955 to have reticulum-cell sarcoma. In 1956 she received deep x-ray therapy. During the course of treatment her haemoglobin concentration dropped from 84% to 44%. She was given several blood transfusions, but the notes state that these were "not tolerated." According to the patient the first transfusion took place in February, 1956; she received 2 pints (1 litre) and developed a slight fever, but no other symptoms. The next blood transfusion was given three or four weeks later, and was followed by shivering and high temperature; the next day she was jaundiced.

Later in 1956 she was found to have enlarged glands in both groins. Further deep x-ray therapy was given. In May, 1957, she received another course of x-ray therapy, and a transfusion of 2 pints (1 litre) of blood. The transfusion produced only a transient increase in haemoglobin concentration. In June she was severely anaemic; the results of a blood examination were as follows: haemoglobin, 4.9 g./100 ml.; red cell count,

1,400,000/c.mm.; P.C.V., 15%; reticulocytes, 10%; W.B.C., 1,700/c.mm. (lymphocytes 17%, neutrophils 70%, monocytes 11%, metamyelocytes 2%); 4 nucleated red cells/100 W.B.C.; platelets 51,000/c.mm. The patient had petechial haemorrhages and was bleeding from the gums.

A transfusion with blood which was compatible by the indirect Coombs test and the albumin technique was given, but had to be abandoned after approximately 350 ml. had been transfused because of fever and haemoglobinuria. Treatment with prednisone, 5 mg. four times a day, was then begun. Five days later (June 7), a transfusion of red cells, labelled with ^{51}Cr and washed three times in saline, was given. After the patient had received about half of this over the course of several hours, she felt ill and the transfusion had to be stopped. The urine passed shortly after the end of this transfusion contained haemoglobin; a blood sample showed that most of the injected cells had already been eliminated. The patient's clinical condition improved slightly, but she still suffered from petechial haemorrhages, and her haemoglobin concentration was only 4.5 g./100 ml., with a white cell count of 3,100/c.mm. and a platelet count of 18,000/c.mm. On June 14 the prednisone was increased to 25 mg. four times a day. On July 5 the haemoglobin concentration was 4.8 g./100 ml., and the patient now improved rapidly. By July 25 the haemoglobin concentration had risen to 9.3 g./100 ml., with a platelet count of 187,000/c.mm. The patient was discharged from hospital on a reduced dosage of prednisone (15 mg. three times a day).

When seen in the out-patient department in September her haemoglobin concentration had risen to 12.2 g./100 ml. and her white cell count to 7,800/c.mm. She died suddenly at home in December, 1957.

Red Cell Survival Tests

As mentioned above, a test with ^{51}Cr -labelled red cells was made on June 7, and this showed clearly that the haemolytic reactions were due to destruction of the donor's red cells rather than those of the recipient. On June 13 an attempt was made to measure more precisely the mode of elimination of the injected red cells. Accordingly, a sample of blood was taken from a compatible donor, and 1 ml. of cells was labelled with radioactive chromium and injected. As a control, a sample of the patient's own red cells was labelled with ^{32}P and injected. From the ^{32}P counts in the patient's blood after the transfusion the number of ^{51}Cr

Survival in the patient's circulation of her own red cells contrasted with the survival of red cells from a donor whose red cells were "compatible," judged by tests *in vitro*. The results were obtained by labelling the cells with ^{51}Cr , and the estimates shown in the figure have been corrected for elution of Cr.

counts expected, if 100% of the injected ^{51}Cr -labelled red cells survived, could be predicted. A sample taken eight minutes after injection contained 99% of the expected number of ^{51}Cr -labelled cells; a sample taken 33 minutes after injection contained only 91%, while a sample taken at three hours contained 55%. A sample taken 22 hours after injection contained only 1% of cells (see Chart). The amount of radioactivity in the plasma was measured in all samples, and the largest amount (representing 6.7% of the total ^{51}Cr injected) was found in the three-hour sample.

On June 24 a sample of the patient's own cells was labelled with ^{51}Cr and reinjected to estimate the average life-span of the patient's own cells in her own circulation. The ^{51}Cr -labelled cells were removed relatively slowly, and the average life-span was estimated to be 11 days (see Chart).

Serological Findings

The patient's full blood groups were determined by Dr. D. Parkin, of the Blood Groups Research Unit of the Lister Institute, as follows: O, CcDE, N, S-, P+, Lu(a-b+), K-, k+, Le(a+b-), Fy(a+), Jk(a+b-), Vel+, Yt(a+).

The donor, whose red cells were labelled with ^{51}Cr , had the following blood groups: O, cddEe, M, S-, P+, Lu(a-), K-, Le(a+b-), Fy(a+). Cells of this donor were tested with the patient's serum before they were injected, and were tested again on two subsequent occasions. No reaction of any kind could be demonstrated using the following tests: agglutination in saline; agglutination in albumin; agglutination of enzyme-treated cells; indirect antiglobulin (Coombs) test against untreated cells; and indirect antiglobulin test against enzyme-treated cells. In case the serum was anticomplementary, the indirect antiglobulin test was carried out in two stages, the cells being first incubated with the patient's serum, then washed and resuspended in fresh serum from a normal donor before being finally washed and tested with the antiglobulin serum.

Haemolysis could not be demonstrated with any of these tests, either when human serum or when rabbit serum was used as a source of complement. (For the possible advantages of using rabbit serum as a source of complement in detecting human blood group antibodies, see P. L. Mollison and Ann R. Thomas, 1959, to be published.) The patient's serum was also tested by Dr. Parkin, who reported that no blood-group antibodies could be found using a series of tests, including the "trypsin-Coombs" test.

Discussion

When transfused red cells undergo complete destruction within 24 hours it is to be expected that an antibody, incompatible with the donor's red cells, will be found in the patient's serum. Fudenberg and Allen (1957) have described some cases in which transfused red cells were rapidly destroyed, with haemoglobinuria in one instance, even though no antibody was demonstrable at the time of transfusion. However, in all these cases antibody was either demonstrated some days after transfusion or was known to have been present some time before transfusion.

A diminished survival of transfused red cells due almost certainly to incompatibility but without demonstrable antibody is now well recognized (Loutit, Mollison, and Young, 1943; Mollison, 1956; Jandl and Greenberg, 1957; Adner and Sjölin, 1957), but in these cases the elimination of the donor's red cells takes some days or weeks.

The present case is remarkable in that such rapid destruction occurred in the absence of a demonstrable antibody.

Summary

A case is described in which the patient repeatedly suffered severe haemolytic reactions after the transfusion

of apparently compatible blood. It was demonstrated that the transfused red cells were completely eliminated from the circulation within 24 hours of the transfusion, but all known tests for blood-group antibodies failed to reveal any incompatibility *in vitro*.

We thank Mrs. Crookston (formerly Miss Marie Cutbush) for carrying out most of the serological tests; Dr. Dorothy Parkin for determining the full blood groups of the patient and of one of the donors; and Miss M. D. Snelling for permission to publish clinical details of this case.

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BECLAMIDE IN INTRACTABLE EPILEPSY: A CONTROLLED TRIAL

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Though several powerful anticonvulsants have served to transform the management of patients suffering from major epilepsy, there remain a number of epileptics whose attacks are poorly controlled. In such a group of cases attending an epileptic clinic in Newcastle upon Tyne we decided to try the effect of beclamide ("nydrane"; "hibicon"; N-benzyl-B-chloropropionamide). This promising drug is structurally quite different from the conventional anticonvulsants, and has the additional advantage of being relatively non-toxic in therapeutic doses. Its exact mode of action has not yet been determined.

Several favourable reports have already appeared (Hawkes, 1952; Hoenig *et al.*, 1956; Merlis and Martin, 1956; Robinson, 1957; Sharpe, Dutton, and Mirrey, 1958), and we wish to record here our experiences of a double-blind controlled trial using this remedy.

Clinical Material and Methods

Among the patients attending the epileptic clinic of the Royal Victoria Infirmary at the beginning of the proposed trial (September, 1957) were 16 whose attacks were clearly uncontrolled despite substantial doses of the commoner anticonvulsants in many different combinations. Three of these patients were deemed unsuitable for the trial: the first was pregnant, the second was a psychopathic adolescent girl who was subsequently admitted to a mental hospital, and the third was a mentally defective woman of 34 whose