Before delivery, posterior pituitary extract should be used with great care. Certain criteria for the relatively safe employment of this substance are indicated.

High multiparity provides certain problems, one of which is the possibility of spontaneous rupture of the uterus. The causes of dystocia in the multipara are summarized.

Brow presentation should always be considered when the foetal head fails to descend in the second stage of labour, especially in the multipara.

Precipitate labour may cause serious trauma to mother and foetus.

Women who have had plastic cervical and vaginal operations should be delivered in hospital.

Spontaneous rupture of the vaginal and supravaginal cervix with extension into the broad ligament is described, with illustrative cases.

Four clinical varieties of rupture are described. The "quiet" and "delayed" varieties are easily missed. Stress is laid upon early diagnosis.

Treatment is summarized. The value of transfusion is stressed.

The incidence of rupture and perforation of the uterus in association with pregnancy was 1 in 1,200 of all deliveries in the service of the two hospitals.

BIBLIOGRAPHY

- Barry, A. P. (1949-54). Annual Reports of the National Maternity Hospital, Dublin. Published in *Irish Journal of Medical Science*.
 Beacham, W. D., and Beacham, D. W. (1951). *Amer. J. Obstet. Gynec.*, **61**, 824.
 — and Varino, G. A. (1945). *New Orleans med. surg. J.*, **98**, 91.
 Bill, A. H., Barney, W. R., and Melody, G. F. (1944). *Amer. J. Obstet. Gynec.*, **47**, 712.
 Bonney, V. (1946). *The Technical Minutiae of Extended Myomectomy and Ovarian Cystectomy*. Cassell, London.
 Browne, O'D. (1951). *J. Obstet. Gynaec. Brit. Emp.*, **58**, 555.
 Cosgrove, S. A., and Norton, J. F. (1942). *J. Amer. med. Ass.*, **118**, 201.
 Decio, J. (1951). *Rev. Obstet. Gynec. S. Paulo*, **6**, 235.
 Delfs, E., and Eastman, N. J. (1945). *Canad. med. Ass. J.*, **52**, 376.
 Dewhurst, C. J., and Rowley, H. A. (1951). *J. Obstet. Gynaec. Brit. Emp.*, **58**, 630.
 Donald, Ian (1955). *Practical Obstetrical Problems*. Lloyd-Luke, London.
 Donnelly, J. P. (1951). *Amer. J. Surg.*, **82**, 354.
 Duggar, J. H. (1945). *Surg. Clin. N. Amer.*, **25**, 1414.
 Feeney, J. K. (1950-4). Annual Reports of the Coombe Lying-in Hospital, Dublin. Published in *Irish Journal of Medical Science*.
 — (1953). *J. Irish med. Ass.*, **32**, 36.
 — and Barry, A. P. (1954). *J. Obstet. Gynaec. Brit. Emp.*, **61**, 652.
 FitzGibbon, G. (1950). Personal communication.
 Frid, I. J. (1943). *Ann. Inst. Matern.*, **5**, 125.
 Gandolfo, R. (1946). *Journada Rioplat. Obstet. Gynec.*, **6**, 265.
 Gordon, C. A., and Rosenthal, A. H. (1943). *Surg. Gynec. Obstet.*, **77**, 26.
 — and O'Leary, J. L. (1950). *Amer. J. Surg.*, **80**, 259.
 Greenhill, J. P. (1945). *Year Book of Obstetrics and Gynaecology*, p. 174. Year Book Publishers, Chicago.
 — (1953). *Ibid.*, p. 159.
 Ingram, J. M., Alter, R. L., and Carter, B. (1952). *Amer. J. Obstet. Gynec.*, **64**, 527.
 Kerr, J. M. Munro, and Moir, J. Chassar (1949). *Operative Obstetrics*, 5th ed., p. 823. Baillière, Tindall and Cox, London.
 Lynch, F. J. (1939). *New Engl. J. Med.*, **22**, 847.
 Morrison, J. H., and Douglass, L. H. (1945). *Amer. J. Obstet. Gynec.*, **50**, 330.
 Parker, J. C., and Jones, G. R. (1951). *Ibid.*, **62**, 330.
 Sadowsky, A. (1942). *Amer. J. Surg.*, **55**, 544.
 Shaw, W. Fletcher, (1930). *J. Obstet. Gynaec. Brit. Emp.*, **37**, 74.
 Sheffery, J. B. (1945). *Amer. J. Obstet. Gynec.*, **49**, 423.
 Simons, P. (1950). *J. Obstet. Gynaec. Brit. Emp.*, **57**, 953.
 Taylor, J. S. (1947). *Penn. med. J.*, **50**, 801.
 Tollefson, D. G. (1945). *West. J. Surg.*, **53**, 54.

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ACQUIRED HAEMOLYTIC ANAEMIA CLINICAL AND SEROLOGICAL OBSERVATIONS OF TWO CASES

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The clinical and serological picture of cases of acquired haemolytic anaemia (A.H.A.) has been the subject of many recent publications. In spite of the clarification of some problems, it would appear that we are still some way from a full understanding of this condition, and in all likelihood different clinical and pathological entities are still summarized under the one heading. There is no doubt that further observations and accurate recording of laboratory findings will help to distinguish clinical and pathological entities within this syndrome and will in the long run give us a better understanding of the many problems as yet unsolved. With this in view, we are reporting the clinical, haematological, and haemato-serological findings in two patients treated more or less simultaneously in two different hospitals. Both were diagnosed as cases of acute haemolytic anaemia, but they presented different clinical and haemato-serological pictures.

The disease under discussion has been given different names by different authors. The name "acquired haemolytic anaemia" (A.H.A.) is used throughout this paper.

Case 1

A man aged 47, who worked in a granary, was admitted to hospital on May 17, 1954. He gave a history of auricular fibrillation of unknown aetiology since 1941, and of dyspnoea, fatigue, pallor, and giddiness for nine weeks. He had had some nausea but no vomiting and had been sweating excessively. There was a history of pains and swelling of the joints at the age of 15, although he had not been admitted to hospital. He had had whooping-cough in 1948 and influenza in 1950. He was not old enough to serve in the first world war, and at the beginning of the second was rejected for military service on account of his heart condition. There was no family history of anaemia or jaundice.

On examination the skin showed café-au-lait colour with slight conjunctival icterus; heart apex rate 108, with complete irregularity. Apical systolic and diastolic murmurs were audible, the latter only after exercise. There was slight clubbing of the fingers. Breath sounds were harsh in the left midzone. The spleen was one fingerbreadth below the costal margin. The provisional diagnosis was subacute bacterial endocarditis complicating mitral disease.

Investigations.—Repeated blood cultures were sterile. Urine: no red cells. Chest x-ray examination: patchy infiltration in left upper lobe suggestive of pneumonia or tuberculosis. Blood: Hb, 8 g./100 ml. (54%); haematocrit, 25%; white cells, 9,200 (metamyelocytes 180 (2%), polymorphs 6,990 (76%), lymphocytes 1,470 (16%), monocytes 550 (6%)); reticulocytes, 0.5%. Biochemistry: serum bilirubin, 2.5 mg./100 ml.; direct van den Bergh reaction, negative; serum proteins, 7.39 g. (albumin 4.24 g., globulin 3.15 g.); thymol turbidity, 5 units; E.S.R., 20 mm. an hour. Mantoux: positive 1/100, negative 1/1,000 and 1/10,000. No cold agglutinins or heterophil antibodies. Bacteriological and viral serological studies: negative for *Br. abortus*, enteric group, influenza, psittacosis, lymphogranuloma

venereum, Q fever, and streptococcus M.G. Repeated sputum examinations failed to reveal the tubercle bacillus, malignant cells, or fungi.

Progress

The patient ran a mild intermittent pyrexia and the pulse deficit was controlled with digoxin. A course of penicillin and streptomycin was started on May 17 and 2 pints (1,140 ml.) of Group O rhesus-positive blood (see below) were given for the anaemia on May 21. On two occasions (May 11 and 18) the haemoglobin was found to be 7.6 g. per 100 ml. On May 27 it was 8.5 g. and on June 1, 8.1 g. The rise was therefore not quite as high as would be expected after 2 pints of blood, but the fact that the rise persisted for some time might be significant. In the middle of June the pulmonary and radiological changes were unaltered, the blood picture was similar to that on admission, the E.S.R. remained at 20 mm. an hour, and the spleen was still palpable.

The diagnosis of subacute bacterial endocarditis was given up, and as the pulmonary condition seemed most likely to be tuberculous the penicillin was stopped and P.A.S. given with the streptomycin instead.

By the end of July there was a slight improvement in the lung x-ray film and the E.S.R. was 10 mm. an hour, but there was growing clinical evidence of periodic exacerbations of the patient's illness, during which he suffered loss of appetite, vomited, and appeared more jaundiced. Further investigation yielded the following results. Blood: Hb, 10 g./100 ml. (68%); reticulocytes, 10%; direct Coombs test, strongly positive; serum bilirubin, 4.1 mg./100 ml.; saline fragility test, normal values. The urine contained an excess of urobilinogen.

With the demonstration of this active haemolytic process all treatment was stopped and on August 10 300 mg. of cortisone daily was started; this was reduced to 250 mg. daily on August 19, being continued at this level until September 29. The patient's appetite improved, he put on weight, and after some fluctuation the Hb steadily rose simultaneously with a decrease in the reticulocyte count. However, the radiological changes in the chest had become more marked. As the patient was becoming oedematous, cortisone was reduced on September 30 to 150 mg. and then to 100 mg. daily. He improved steadily. The pulmonary findings were virtually unchanged, but produced no symptoms: their aetiology was still obscure: the mitral stenosis and auricular fibrillation were thought to be of rheumatic origin. By March 11, 1955, his Hb was 12.7 g./100 ml. (85%) and reticulocytes 3.6%. The dosage of cortisone had been gradually reduced to 37.5 mg. daily, which seemed to be enough to maintain his haematological values. The direct Coombs test was still positive.

Case 2

A housewife aged 50 was admitted to hospital on September 7, 1954, for investigation of profound anaemia associated with jaundice and a purpuric rash. Her childhood had been healthy. At age 26 she had epilepsy, which was controlled initially with bromides and latterly with phenobarbitone, $\frac{1}{2}$ gr. (32 mg.) twice daily, and phenytoin, $1\frac{1}{2}$ gr. (100 mg.) each morning. (She had had phenobarbitone continuously for the previous nine years, and was in the habit of doubling the dosage for a few days whenever a "burst" of fits occurred—once or twice yearly on average.) She had had winter bronchitis for many years. The menopause occurred in 1952. There was no history of blood dyscrasia. The family history revealed nothing significant.

The patient had been well up to March, 1954, when an exacerbation of her chest condition and fever occurred. At the same time she had a series of fits. Penicillin was given for her bronchitis. During convalescence she noticed for the first time widespread bruising and purpuric eruptions on her legs, abdomen, and arms. This eruption had persisted intermittently until her admission. Since April, 1954, she felt weak and had occasional severe headaches. Her friends had noted her pallor. In August she had another

severe cold "on her chest," again necessitating penicillin. Her general condition rapidly deteriorated, with fever, increasing pallor, and definite jaundice at the beginning of September. On admission she was found to be obese, very pale, and moderately jaundiced; widespread ecchymoses and purpura were present, particularly on the trunk and legs, but also on the palate and fundi. She was febrile. There was a haemic murmur over the base of the heart. The B.P. was 145/65. The spleen was just palpable.

Investigations.—The initial blood count showed: Hb, 3.55 g./100 ml. (24%); P.C.V., 14%; white cells, 7,800 (polymorphs 5,460 (70%), lymphocytes 2,028 (26%), monocytes 78 (1%), late normoblasts 234 (3%); reticulocytes, 50%; platelets, fewer than 1,500 per c.mm. Biochemistry: bilirubin, 1.7 mg./100 ml.; serum proteins, 7 g./100 ml. (albumin 4.6 g., globulin 2.4 g.); thymol turbidity, 1; colloidal gold, 0; alkaline phosphatase, 8 units per 100 ml. X-ray examination of the chest was clear. Urine: no albumin, sugar, or acetone. The direct Coombs test was strongly positive. A diagnosis of haemolytic anaemia and thrombocytopenic purpura was made.

Progress

As the anaemia seemed to be endangering her life, an emergency transfusion of 2 pints (1,140 ml.) of Group A rhesus-positive blood was given. This raised her Hb from 3.55 g./100 ml. (24%) to 7.4 g./100 ml. (50%) on September 10, but it had again fallen to 3.8 g./100 ml. (26%) by the 12th, and to 2.8 g./100 ml. (19%) on the 15th. It was 1.5 g./100 ml. (10%) on the 16th. On this day the patient was so ill that a further 3 pints (1,700 ml.) of blood had to be given in spite of doubts about its compatibility. This transfusion raised her Hb to 6.8 g./100 ml. (46%). (For details of the blood given, see below.)

It was obvious from the clinical and haematological findings that transfusion treatment produced only very temporary improvement. The fall in the Hb level and the increase of jaundice which followed the transfusion made it apparent that the blood was very rapidly destroyed. On September 17, therefore, 300 mg. of cortisone daily was started. This resulted in a rapid improvement of her condition, and though on September 21 the Hb had fallen to 5.4 g./100 ml. (37%), it had risen on the 25th to 6.9 g./100 ml. (47%), and was 9.6 g./100 ml. (70%) by the end of October. Platelets, however, still remained very scanty, though no new ecchymoses had appeared. The patient was discharged home on a maintenance dose of 25 mg. of cortisone daily on November 13.

However, on November 26, she developed an infection of the upper respiratory tract and a sore throat. Within a day or two there was a further haemolytic crisis, necessitating readmission on December 2. A good response to cortisone was obtained and she was again discharged on December 23 on 75 mg. of cortisone daily. Clinically she was very well. Another cold developed almost immediately and she had to be readmitted on December 30 in a severe haemolytic crisis. This time there was also considerable bleeding from her gums and nose. She was also suffering from severe headaches. An increase of the cortisone dosage produced a clinical remission, and up to the time of writing (March, 1955) the patient had remained well on 62.5 mg. of cortisone daily. She was doing all her housework and her blood values were as follows: Hb, 11.1 g./100 ml. (75%); reticulocytes, 7%.

Serological Investigations

The direct Coombs test,* rhesus typing, and investigation for the presence of antibodies were carried out according to the methods described by Weiner *et al.* (1953).

Indirect Coombs Test.—Cells washed three times were firmly packed and 1 volume was deposited at the bottom of a precipitin tube. To this was added 5 volumes of serum or eluate respectively. After the contents of the precipitin

*We are indebted to Dr. P. Kidd, of Worcester, for the excellent anti-human-globulin serum which he prepared and made available to us. It was used exclusively in this investigation and had an exceedingly high titre (1:1,500 against weakly sensitized D-positive cells).

tubes had been thoroughly mixed by vigorous shaking, the tubes were closed with a rubber bung and incubated for two hours at least in an incubator at 37° C. (Volumes used were approximately 0.02 ml. packed cells and 0.1 ml. serum or eluate.) After incubation the contents of the precipitin tubes were transferred with a clean Pasteur pipette into Kahn tubes. These were then filled up with saline and the cells thoroughly suspended. The cells were washed in the usual way three times and the same procedure was followed as for the performance of the direct Coombs test.

Preparation of Eluates.—The eluates were prepared by a method which will be described in detail elsewhere.

Results in Case 1

The patient's cells gave on all occasions a strongly positive direct Coombs test. They were found to be Group O and rhesus-positive; were agglutinated by anti-C, anti-D, and anti-c; and were not agglutinated by anti-E. This result corresponds to the phenotype CcDee, and the most frequent genotype within this phenotype is CDe/cde. This investigation was repeated next day and gave identical results. The sera used were the routine sera used in the Blood Transfusion Service laboratory for this type of investigation and had, of course, not only been used on many previous occasions with consistent results but, as pointed out above, there had been suitable controls with every run. In particular, the anti-E antiserum was a saline agglutinating serum of high potency obtained from a CDe/cde donor who had formed it in response to a stimulation by pregnancy. Its titre was at least 64 against single dose E-positive cells. For this investigation it was used in a 1:1 dilution and the control (a cell of the genotype CDe/CDE) gave a ++ reaction. The serum was investigated simultaneously, and it contained an anti-E antibody giving a good double-dose reaction with EE cells and acting best by means of the indirect Coombs test. These results were taken to mean that the antibody in the serum had been produced by the previous transfusion and the genotype obtained fitted this assumption well.

An eluate prepared from the patient's cells overnight and investigated next day gave, however, a most unexpected result, which necessitated a complete revision of our assumptions. Most surprisingly the eluate showed a very strong anti-E activity—even stronger than the one found in the serum. It was obvious that the eluate contained an anti-E antibody which must have been fixed to the cells and had been eluted from them. This naturally necessitated the assumption that the cells contained the E antigen. However, this assumption again seemed to conflict with our findings of the day before, when the cells did not react with the anti-E antiserum and were therefore regarded as E-negative. The investigation for the genotype of the patient was for this reason repeated, but again a negative result was obtained with the anti-E antiserum.

To resolve, if possible, these conflicting results, the investigations were repeated 10 days later on a fresh specimen of blood. The cells were now tested not only with the anti-E antiserum used previously but with a further six anti-E antisera. Each, including the original one, now gave a positive reaction. The phenotype of the patient as now determined was CcDE, with its most likely genotype CDe/CDE. The results of an extensive family investigation fully supported this assumption. The wrong result obtained in the first investigation can only be explained by the fact that the anti-E antibody fixed to the cells blocked the E antigen and prevented agglutination of the cells by the agglutinating serum used. The "blocking" effect in anti-rhesus antisera was simultaneously discovered by Race (1944) and Wiener (1944) independently, and we believe that we were dealing here with the same phenomenon.

The two donors who had contributed to the one transfusion the patient had (see above) were reinvestigated with the following results:—First donor: most likely genotype CDe/CDE (phenotype CCDee); second donor: most likely genotype CDe/cde (phenotype CcDee). This result makes

it obvious that neither of the two donors has an E and could not, therefore, have stimulated the production of this antibody in the patient, and provided additional proof that the antibody found in the patient's serum and eluate was not due to the transfusion given previously.

The blocking effect of the patient's own anti-E antibody on his own cells became much weaker later on, but we could show it experimentally with the originally prepared eluate and the original serum. E-positive cells were used which were incubated in parallel with the patient's serum, the eluate, and normal AB serum respectively. They were used after incubation without washing and also after they had been washed three times in normal saline. The action of anti-D was not inhibited at all, and the cells incubated with AB serum reacted as strongly as before to anti-E antisera. A much weaker reaction with the same anti-E antiserum was obtained, however, on the cells which had been incubated with both the eluate and the serum, particularly after they had been washed.

Results in Case 2

The specimen from this patient was found to be Group A and rhesus-positive, and genotyping was possible only after the cells had been washed eight times to abolish a certain degree of auto-agglutination. The phenotype found was cDEe, corresponding most likely to the genotype CDe/cde. The serum of this specimen contained an anti-E antibody, but the investigation of the eluate gave at first somewhat confusing results. It undoubtedly contained an anti-E reacting with all E-positive cells immediately and strongly. Agglutination, however, occurred with some E-negative cells as well, though after a longer interval and causing smaller agglutinates. This was shown to be due to an anti-c. No trace of this latter antibody could be found in the serum. All five donors used were Group A and rhesus-positive, and had the following genotypes (phenotypes): *1st transfusion*—first donor genotype CDe/CDE (phenotype CcDE); second donor genotype CDe/CDe (phenotype CCDee); *2nd transfusion*—third donor genotype CDe/cde (phenotype CcDee); fourth donor genotype CDe/CDe (phenotype CCDee); fifth donor genotype cDE/cde (phenotype ccDEe).

Three donors (first, third, and fifth) carried either one or two antigens (c or c + E) against which the patient possessed an antibody. Four donors had the C antigen. Only the blood from the fifth donor was truly homologous—though incompatible.

It was, of course, tempting to think that the thrombocytopenia found in this patient was also due to immunological causes (Evans *et al.*, 1951; Stefanini *et al.*, 1953). We were, however, unsuccessful in demonstrating platelet agglutinins either in the serum or in the eluate of the patient.

Clinical Aspect

The first case presented with such a variety of symptoms and signs that the diagnosis of haemolytic anaemia was not at first contemplated. A connexion between the heart lesion and the haemolytic anaemia would seem to be unlikely. The same need not necessarily be true of the lung condition found in this patient. The connexion between A.H.A. and virus pneumonia has now been firmly established. The serum was investigated extensively for the presence of antiviral antibodies, and, though nothing significant was found, it is tempting to think that a virus may have played some part in the aetiology of his disease. The radiological appearances are similar to those in the case described by Weiner *et al.* (1953). They could not establish a definite diagnosis of the lung condition during life, but since the publication of their paper the patient has died and a necropsy performed by Dr. B. T. Davis showed fibrotic changes only, which contained doubly refractile bodies. (The patient had never been exposed to silica.) The occurrence of a rather similar lung condition in two cases of a rare disease might perhaps be suggestive of a more intimate relationship between the two conditions, and it might be interesting to find out whether similar lung changes occur in other cases of A.H.A.

Case 2 presented primarily with purpura. No connexion could be established with the medication, as its cessation did not bring about any improvement. Cortisone treatment had a beneficial effect, but it is interesting to note that, though the purpura and bleeding stopped, the platelet count did not go up significantly. This behaviour may be indicative of the involvement of the vascular endothelium in the immunological process. Dameshek (1953) and Stefanini and Dameshek (1954) have on several occasions pointed out that this system may participate in the immunological process, and it seems remarkable that, in spite of the fact that the platelets did not rise under treatment, the purpura decreased greatly when the patient was in remission.

Both patients were treated with liberal doses of cortisone. The haemolytic crises were controlled by this medication, and the first patient had been keeping well on a maintenance dose of 37.5 mg. daily. The second patient was on a maintenance dose of 62.5 mg. a day and was doing all her housework. She claimed to be fitter than for a long time past.

Serological Aspect

Since Weiner *et al.* (1953) described the finding of a specific antibody directed against an antigen on the patient's own cells numerous papers dealing with the same subject have been published confirming the occurrence of specific antibodies in A.H.A. (Holländer, 1953; van Loghem and van der Hart, 1954a, 1954b; Dacie, 1953; Dacie and Cutbush, 1954; Flückiger *et al.*, 1955). The antibodies so far found by the various authors were directed against the following antigens: e, c, D, Jk^a, Kell, and B. Nearly all of these antigens were within the rhesus system. The antibodies were always found in the eluates and sometimes also in the sera. Cases 1 and 2 showed an anti-E antibody which so far has not been reported as a "spontaneous" antibody in A.H.A.* In both sera and eluates this antibody was present to a fairly high titre. Anti-c was present in the eluate (Case 2) but absent from the serum. This is probably explained by the assumption that this antibody was produced in smaller quantities than the anti-E antibody and that all of it was attached to the surface of the cells. Serologically it must be of the same importance as an antibody found both in the serum and in the eluate.

Treatment

If confronted with severe anaemia in people who are gravely ill, one's thought would first turn to treatment by blood transfusion. This, in the light of our present knowledge, produces considerable difficulties. In the normal run of events, one would expect a homologous transfusion to be compatible if by homologous is understood that the blood to be transfused should, so far as possible, have the same antigenic structure as the blood of the patient who is to receive it. In A.H.A., conditions are entirely different, as the papers quoted above and our own cases have shown. If a compatible transfusion is defined as a transfusion given to a patient whose serum does not contain an antibody directed against any antigen carried on the donor's cells, homologous transfusions in patients suffering from A.H.A. cannot, in the light of our present knowledge, be regarded as compatible. Both patients had an anti-E antibody in their sera, and compatible blood would have had to be E-negative.

In Case 1 the blood to be given should have been one of the following genotypes: CDe/CDe, CDe/cde, cDe/cde, cDe/cde, to mention only the most frequent ones. CDe/cde, cDe/cde, and cde/cde would, of course, have been incompatible in Case 2 as it could be shown that the eluate contained an anti-c antibody. The only two types of blood suitable for this patient would have been CDe/CDe or CDe/Cde. Neither of these types in the strict sense constitutes a homologous transfusion. That this is not simply a theoretical consideration but has practical importance is clear if one considers the effect of the transfused blood in

the recipient. The first patient received 2 pints (1,140 ml.) of compatible (though non-homologous) blood and derived some benefit from this transfusion, as shown in the follow-up of his Hb. The transfusion was given on May 21, when his Hb was 7.6 g./100 ml.; six days later it was 8.5 g./100 ml., and a fortnight later it was still 8.1 g./100 ml. This fall does not seem to be unduly severe considering that his own blood was probably being rapidly destroyed.

In contrast, the second patient received on admission, when her Hb was 3.55 g./100 ml., two bottles of blood which raised the Hb to 7.4 g./100 ml. Two days later it had fallen again to 3.8 g., and the next day to 1.8 g. The lowest Hb was found on the following day, when it was 1.5 g. The extremely critical condition of the patient made immediate transfusion imperative. There was no time to perform a full cross-match before the blood was transfused. It was later found that the Coombs test with one bottle (fifth donor) gave a weakly positive reaction. The improvement in the patient's condition was only very temporary. It is obvious that she destroyed practically everything she was given almost immediately, and no benefit resulted. Similar conditions obtained in the case of Weiner *et al.* (1953), which had an anti-e antibody in the eluate and in the serum and whose cells had the genotype CDe/CDe. On one occasion cDe/cDe blood was transfused and cells from this transfusion could be shown to be present in the patient's circulation a long time afterwards. Unfortunately, neither in this patient nor in our two cases was it possible to do survival studies.

If transfusion treatment is decided on in A.H.A. the blood to be given must be selected by criteria different from those used in other conditions. Normally, if homologous blood is selected the transfusion can be assumed to be compatible. Homologous blood, however, will, in the light of the above findings, be incompatible in A.H.A. The question also arises whether serum is sufficient for cross-matching blood for these patients. It has long been known that sera from some cases of A.H.A. whose cells show a strongly positive direct Coombs test do not seem to contain any demonstrable antibodies. It may be that on very rare occasions the antibody developed by the patient is directed against an antigen on the patient's cells, which is so rare as to be classed as a "familial" or "personal" antigen. If that happens the cells from the patient would give a positive Coombs test, but the serum would seem to have no antibody content at all even if it contained the same antibody as found on the surface of the cells. A cell having the same antigen as the patient's cells would in all likelihood not be available as a test cell even in a very large panel.

In this setting one would not expect the eluate, even if properly prepared, to react with any of the cells available. One would also expect that all blood transfused would survive normally. So far, we have not come across this particular serology, but have found on quite frequent occasions that the serum did not react with any test cell at all, whereas the properly prepared eluate did. This behaviour can probably be explained by the antibody being produced in relatively small quantities only, and being completely attached to the cells at the site of its formation so that nothing will be found in the serum. The serum will then give a compatible cross-match with cells which, if transfused, would nevertheless be immediately coated.

In our second case this pattern was seen together with the more usual serology. Though an anti-E antibody was present in the serum and in the eluate, an anti-c antibody which gave a good single-dose effect in the eluate was completely absent from the serum even when the latter was tested against cells containing two c's. By using serum for cross-matching purposes, blood containing the c antigen would be considered compatible, as in actual fact happened. It would appear, therefore, to be essential that if transfusion treatment is to be considered at all, blood should be selected, using the eluate from the patient's cells as a reagent in parallel with the serum. It is, however, quite conceivable that compatible blood might not be found for some cases of A.H.A. It would be possible on theoretical grounds that antibodies would be formed against both allelomorphs

*Since this paper was written Dr. F. Stratton has published a case of A.H.A. with an anti-E antibody both in the eluate and in the serum. (*Modern Trends in Blood Diseases*. Edited by John F. Wilkinson. Butterworth, 1955.)

carried on the patient's cells—for instance, C and c or E and e. If this should happen, these antibodies would present as a panagglutinin, as apart from very few exceptions (-D/-D-) (Race *et al.*, 1951) all cells contain one or both allelomorphs. A serological definition and separation of these antibodies might be extremely difficult (Race *et al.*, 1951). It would be of theoretical importance only, as from the practical point of view no blood would be found to be compatible. All blood transfused would be destroyed rapidly.

As compatible blood in A.H.A. will, of necessity, be non-homologous blood, antigens not found in the patient's cells will be introduced into his or her circulation. Patients suffering from A.H.A. are "good reactors" and often produce antibodies to even weak antigens. One therefore runs the risk of stimulating the formation of additional antibodies against the introduced antigen. This must have happened many times in the past after blood transfusion. These additional antibodies produced to the stimulus of introduced antigens may also make transfusion treatment quite impossible. It is conceivable that a patient, having developed an immunologically "idiopathic" anti-c antibody, may be stimulated to produce anti-C in addition. The same condition would then obtain which has been described above—that is, that, apart from a very few cells, no cell would be compatible. It is perhaps true that dramatic transfusion reactions do not occur very frequently in A.H.A. even if the eluate and/or the serum contains the homologous antibody against the antigen introduced. There is no doubt, however, that the blood is destroyed very rapidly in these cases, and often the only effect the transfusion has for the patient is to increase the haemosiderosis which is so marked a feature in the cases of A.H.A. that come to necropsy after prolonged transfusion treatment.

From the above it would appear to be imperative to use not only the serum but also the eluate for cross-matching. Loutit and Mollison (1946) have shown that the survival of normal cells in A.H.A. is shorter than in the congenital variety. The blood used was presumably selected after a cross-match, using serum for the test, had been performed. The short survival is no doubt due to the above-mentioned mechanism. Compatible cells should have the normal life expectancy even in cases of A.H.A.

For the reasons given we have refrained, once the diagnosis had been made and the serology clarified, from treating either of these patients with further transfusions. Though the first patient derived some benefit from the 2 pints (1,140 ml.) he received, the remission was produced by cortisone. Within the rhesus system no foreign antigen was introduced, but, of course, we cannot claim the same from antigens belonging to different systems. The second patient received blood containing a non-homologous C antigen. The latter is known to be rather poor in its antigenic properties. Neither of the two patients has so far produced evidence of the presence of an additional antibody due to the transfusion treatment.

Summary

Two patients suffering from acquired haemolytic anaemia are described. They presented with a variety of symptoms and signs. The occurrence of a lung lesion in one patient is discussed and its possible importance pointed out. The other patient showed the not unusual combination of A.H.A. and thrombocytopenic purpura. The serology showed that both patients had developed an anti-E antibody and one patient an anti-c in addition. The anti-E antibody was present in the sera and eluates of both patients, whereas the anti-c antibody could be recovered from the eluate only. The importance of these findings is discussed with particular reference to transfusion treatment. A revision of compatibility tests in these cases is suggested in view of these findings. It would appear to be essential that cross-matches for selecting blood for these patients be performed using not only the serum but also the eluate prepared from the cells of these patients. Cortisone treatment in both

patients was effective in controlling the haemolysis, and both patients achieved a good remission.

The patients were admitted under the care of Dr. S. R. F. Whittaker and Dr. J. V. S. A. Davies, and we thank them for their most helpful attitude, for free access to notes, and for permission to investigate both patients so fully. We also thank Dr. A. P. Prior and Dr. J. C. Ford for their help. We are grateful to Professor S. P. Bedson for his advice on the virology. The staff of the Transfusion Service have generously contributed the "test cells," which involved numerous pricks in the literal sense of the word. We are indebted to all of them, as without the generous supply of these cells the tests could not have been performed. We also thank Miss D. A. Battey for rechecking donor No. 2, and Miss P. M. Young for the secretarial work.

REFERENCES

- Dacie, J. V. (1953). *Fourth Congress of the European Society of Haematology*. Amsterdam.
 — and Cutbush, Marie (1954). *J. clin. Path.*, 7, 18.
 Dameshek, W. (1953). *Blood*, 8, 382.
 Evans, R. S., Takahashi, K., Duane, R. T., Payne, R., and Liu, C. K. (1951). *Arch. intern. Med.*, 87, 48.
 Flückiger, P., Ricci, C., and Usteri, C. (1955). *Acta Haemat. (Basel)*, 13, 53.
 Höllander, L. (1953). *Experientia (Basel)*, 9, 468.
 Loghem, J. J. van, and Hart, M. van der (1954a). *Vox Sanguinis (Amst.)*, 4, 2.
 — (1954b). *Ibid.*, 4, 98, 120.
 Loutit, J. F., and Mollison, P. L. (1946). *J. Path. Bact.*, 58, 711.
 Race, R. R. (1944). *Nature (Lond.)*, 153, 771.
 — Sanger, Ruth, and Selwyn, J. G. (1951). *Brit. J. exp. Path.*, 32, 124.
 Stefanini, M., and Dameshek, W. (1954). *Ann. Rev. Med.*, 5, 87.
 — Chatterjee, J. B., Adelson, E., and Mednicoff, I. B. (1953). *Blood*, 8, 26.
 Weiner, W., Battey, D. A., Cleghorn, T. E., Marson, F. G. W., and Meynell, M. J. (1953). *British Medical Journal*, 2, 125.
 Wiener, A. S. (1944). *Proc. Soc. exp. Biol. (N.Y.)*, 56, 173.

DISSECTING ANEURYSM DURING METHONIUM THERAPY

A REPORT ON NINE CASES TREATED FOR HYPERTENSION

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Nine out of a series of 44 hypertensive patients who came to necropsy after methonium or pentolinium therapy have had dissecting aneurysms. We think that this incidence is beyond chance expectation. Three of the cases have been mentioned elsewhere (Doniach *et al.*, 1954; Goldsmith *et al.*, 1955).

Of the 44 cases, 34 were suffering from malignant hypertension and 10 from "benign" hypertension, the latter with major complications or severe symptoms. While we now accept malignant hypertensives for treatment only when they are non-uraemic or have a blood urea of less than 110 mg. per 100 ml., eight cases with more severe uraemia than this were included in our earlier therapeutic trials.

Control data on untreated malignant hypertension were obtained from a study of such cases admitted to Hammersmith Hospital during the period 1935–50; data on benign hypertension were obtained from 200 consecutive post-mortem examinations on patients with benign essential hypertension, confirmed pathologically, and with a record of at least one blood-pressure reading of 190/110 mm. Hg or over during life.

Case 1

A male clerk aged 50 was admitted to Hammersmith Hospital on January 8, 1952, complaining of dyspnoea on exertion, and, recently, at night.