dation. It was part of his concept that all grades of mental hospital staff should be offered part-time appointments, thus encouraging diverse extramural activities, and that general hospitals and mental hospitals should have staff in common.

Although many general hospital patients may never enter a mental hospital there is certainly no natural clinical cleavage between those who do and those who do not. Experience underlines similarities rather than the opposite, especially in techniques of management. If, then, one envisages a policy of treating as many psychiatric patients as possible in the general hospital, how is it best achieved? Henderson and Gillespie (1950) thought that treatment in the wards of a general hospital should be regarded as a provisional arrangement pending the establishment of specially constructed and equipped psychiatric clinics within general hospitals. Apart from observation wards, whose special function excludes them, the York Clinic stands out in this country as almost the only deliberate attempt at achieving such an aim, with close physical contiguity to other parts of the hospital. Such a unit is essentially what most mental hospitals try to supply in the form of admission wards. But can anything else be attempted? In an address to the Association of Occupational Therapists Lord Webb-Johnson (1951) is reported to have said that one of his own great ambitions was to see all voluntary patients, and all borderline patients, treated in a general hospital. This would be a revolution indeed, and if widely developed it would inevitably mean bringing the present staffs of mental hospitals to work with in-patients in the general hospitals also. Sargant and Slater (1946) are among those who have suggested its clinical practicability. It would also be in line with the ideals of the joint memorandum already quoted.

But is this not really a question which should be explored in a purposeful, experimental way, to supplement evidence which is at present tenuous? For example, would it not be possible to arrange a clear-cut long-term experiment, within the ordinary administrative arrangements of a progressive general hospital, by which beds therein could become the part-time responsibility of a mental hospital consultant, assisted by his staff, and admission to which would be only by transfer from the mental hospital? The mental hospital consultant would, in effect, be given general-hospital facilities for the experiment. We have to discover the answers to two main questions: first, how many patients can be treated successfully in the general hospital who are at present treated successfully in the mental hospital? and, secondly, what special administrative arrangements and regimes would be necessary for this? One has in mind the serial group relationships mentioned earlier, as well as such matters as provision of day-rooms, problems of staffing, and the use of convalescent homes for prolonged rehabilitation. The answers to these two questions cannot safely be assumed, and their investigation could play a powerful part in encouraging further integration of psychological and physical medicine.

I am glad to acknowledge Professor D. R. MacCalman's permission and encouragement in dealing with, and describing, these patients.

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At the annual general meeting of the Royal Institute of Public Health and Hygiene, held in London on July 2, Mr. Walter Elliot, C.H., F.R.S., presented certificates of Honorary Fellowship to Mr. F. J. M. Bengué, founder of the Bengué Memorial Award, and to Mr. H. H. Gerrans, Secretary of the Institute.

SEROLOGICAL FINDINGS IN A CASE OF HAEMOLYTIC ANAEMIA

WITH SOME GENERAL OBSERVATIONS ON THE PATHOGENESIS OF THIS SYNDROME

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The application of new serological methods has made a further classification of the syndrome "haemolytic anaemia" easier. Whereas up to a short time ago a classification into "familial" and "acquired" types (excluding acquired haemolytic anaemia due to known aetiological agents) was possible only by clinical means and family investigations, the discovery that one type of acquired haemolytic anaemia is accompanied by the presence of antibodies in the blood of the patient made it possible to separate this type from the rest.

Antibodies had been postulated already in 1940 by Dameshek and Schwartz as the causative agents of all haemolytic anaemias. Definite proof, however, of their presence in certain types of haemolytic anaemia was obtained only in 1946, when Boorman, Dodd, and Loutit used the Coombs test (anti-human globulin test) for the investigation of their cases. They found that the cells of certain patients suffering from the acute and obviously acquired type of the disease gave a positive Coombs reaction, and interpreted these findings as proof of the presence of antibody globulin on the surface of the cells of these patients. They also reported that the sera of their patients who were found to have a positive Coombs reaction gave no indication of containing an antibody other than a low-titred "cold" agglutinin or "pseudo"-agglutinin. Since then, however, a number of cases have been described in which the presence of antibodies in the serum of the patient could be demonstrated by means of the indirect Coombs test. These antibodies were designated pan-agglutinins, since they acted upon all red cells tested, and on occasion, in consequence, no donor compatible with the patient could be found. Kidd (1949) eluted the antibodies from the red-blood cells of his patients and found them to act on all cells of his panel. He states that "to date, no human red cell has been found which cannot be fully coated or sensitized by exposure to the action of these eluates."

In our experience, previous cases of acquired haemolytic anaemias in which the direct Coombs test was positive had shown similar behaviour, and, though the strength of the reaction varied, eluates from previous cases showed the same lack of specificity as the eluates prepared by Kidd (unpublished observation).

The serological findings in the case described below are remarkable in that the antibody both in the serum

and in the eluate from the cells has been shown to be specific against a well-defined blood-group antigen which is also present on the patient's cells.

Case History

The patient was a male clerk aged 32 when first admitted to the General Hospital, Birmingham, in September, 1941. He complained of a painless lump on the foreskin of a few weeks' duration. Mr. Welsh performed a circumcision and local resection of the lesion, which proved histologically to be an epithelioma. The excision was followed by deep *x*-ray therapy administered locally. In 1942 he was admitted as an emergency to another hospital following accidental carbon monoxide poisoning, and has suffered a winter cough since that time. He was confined to bed during the first four months of 1946 with symptoms attributed to acute bronchitis. A radiograph of the chest in January, 1947, showed some shadowing of the right lung field. No cause for this was ascertained. A further radiograph, some four months later, showed partial resolution of the shadowing. In July, 1948, there was a recurrence of the lump on the penis. This failed to respond to deep *x*-ray therapy, and Mr. Welsh performed an amputation of the penis in November, 1948. Microscopy again revealed an epithelioma. At no time was there any evidence suggesting the presence of metastases. Haematological examination at the time revealed: red cells, 5,670,000; Hb, 16.5 g.% (112%); C.I., 1.0; white cells, 7,300, with a normal differential count.

The patient first attended Professor A. P. Thomson's outpatient clinic on December 17, 1950. He complained of lack of energy and dyspnoea on exertion. Both symptoms had been present for two years and had become rapidly worse during the previous two months. Examination revealed a pale, slightly jaundiced man aged 41, with moderate finger-clubbing. The spleen was palpable two finger-breadths below the costal margin. A few rales were present in the right side of the chest. No further abnormal physical signs were elicited. The urine was free from albumin and contained an excess of urobilinogen. There was no family history of anaemia or jaundice. Apart from the history stated above he had suffered no serious illnesses. A tentative diagnosis of haemolytic anaemia was made and the patient was admitted for further investigation.

Investigations.—Blood: red cells, 3,510,000; Hb, 11 g.% (74%); C.I., 1.05; white cells, 9,600 (polymorphs 83.5%, eosinophils 1%, lymphocytes 10%, monocytes 3.5%, N. metamyelocytes 1.5%, N. myelocytes 0.5%); platelets, 189,000 per c.mm.; reticulocytes, 19%. Saline fragility test:—patient: commencing haemolysis, 0.68%; complete haemolysis, 0.32%. Control: commencing haemolysis, 0.48%; complete haemolysis, 0.32%. Direct Coombs test, positive; Donath–Landsteiner test, negative; acid haemolysins, negative; cold agglutinins at 5° C. were positive to 1:32; Wassermann and Kahn reactions, negative. Bacteriological and viral serological studies were negative for leptospirosis; influenza; Q fever; psittacosis, L.G.V.; and streptococcus M.G. Malaria parasites were not seen. Sickling of the red cells was not found. Sternal marrow films showed hypercellularity and erythroid hyperplasia. Serum proteins, 6.37 g. (albumin 4 g., globulin 2.37 g.); serum bilirubin, 1 mg. per 100 ml. Direct van den Bergh reaction negative. A radiograph of the chest showed "some consolidation in the right upper lobe with a small effusion at the right base." Repeated sputum tests for tubercle bacilli and malignant cells were negative.

The patient was discharged three weeks after admission, with a diagnosis of acquired idiopathic haemolytic anaemia. The changes in the lung were thought to represent fibrosis with bronchiectasis following pneumonia in 1946.

Progress

March, 1951.—The patient was readmitted to hospital, complaining of right-sided chest pain of six weeks' duration. Examination revealed the presence of a large right pleural effusion, and 45 oz. (1,300 ml.) of straw-coloured fluid was aspirated. It was sterile and contained 85% lymphocytes and 15% polymorphs. The blood count was essentially the same as that seen on the first admission. A further radiograph of the chest, after aspiration of the effusion, showed an increase in shadowing on the right side.

August, 1951.—The patient was readmitted. His general weakness had increased for three months. A blood count showed a haemoglobin value of 9.7 g.% (66%) and reticulocytes 19.4%. A further radiograph revealed no change in the pulmonary shadows. In view of his continued ill-health, splenectomy was performed on August 31 (Mr. Watson). The spleen was easily mobilized and removed. It weighed 700 g. and histological examination revealed gross engorgement with red-blood cells which largely obliterated the normal splenic architecture. There was no other recognizable abnormality.

After splenectomy his condition rapidly deteriorated and the haemoglobin value fell to 4.7 g.% (32%) by September 10. A pint (570 ml.) of compatible blood was obtained with great difficulty (see below), and following transfusion the haemoglobin rose to 6.8 g.% (46%). By this date the jaundice, which was only slight before splenectomy, had become pronounced. The motions were now pale and the urine contained bile pigments. Four days later a femoral vein thrombosis was noticed, and sudden onset of severe pain in the left chest suggested a pulmonary embolism. Two days later (September 16) he complained of upper abdominal pain. The liver could be palpated a hand's breadth below the costal margin. The neck veins were not distended. Within a few days his condition became critical. We were unable to obtain further compatible blood at this time, and from September 18 to 24 800 mg. of cortisone was given intramuscularly. His condition began to improve rapidly, and the haemoglobin value, 6.8 g.% (46%) on September 15, rose to 8.8 g.% (60%) by October 19. By this time the liver had returned to normal size and the jaundice had decreased. Liver function tests on October 2 had shown an immediate positive van den Bergh reaction with a serum bilirubin of 2 mg. per 100 ml., total serum protein of 6 g.% (albumin 3.2 g. and globulin 2.8 g.), serum alkaline phosphatase 18 units, thymol turbidity 10 units, thymol flocculation +++, and colloidal gold ++++. The patient improved sufficiently to return home on October 24, approximately two months after splenectomy.

September, 1952.—He was readmitted as an emergency case. His condition had remained fairly stationary until ten days before admission, when he suffered a sudden severe relapse. On admission he was critically ill, and the haemoglobin value had fallen to 3.2 g.% (22%). He was deeply jaundiced, the liver was very much enlarged, and the legs were oedematous. The neck veins were not distended. The urine contained large quantities of bile pigment and urobilinogen. A pint (570 ml.) of compatible blood was transfused on September 19 and a further pint on the following day. Cortisone therapy was started on September 19. Liver-function tests on September 22 were as follows: strongly positive direct van den Bergh reaction; serum bilirubin, 48 mg. per 100 ml.; serum proteins, 5.5 g.% (albumin 2.6 g., globulin 2.9 g.); serum alkaline phosphatase, 16 units; thymol turbidity, 8 units; thymol flocculation ++; and colloidal gold ++++.

Cortisone therapy was continued in a daily dosage of 100 mg. by mouth. The patient's condition gradually improved and the jaundice became less deep. By October 20 the liver enlargement had disappeared, the serum bilirubin had fallen to 7 mg. per 100 ml., and the haemoglobin value had risen to 9.7 g. % (66%). On October 27 it was decided to decrease the daily dosage of cortisone gradually, but the patient's condition relapsed almost immediately and the haemoglobin value fell from 9.7 g.% (66%) on October 27 to 5.4 g.% (37%) on November 3. By this date the cortisone had been reduced to 25 mg. daily. The jaundice deepened and the liver rapidly enlarged. In view of this relapse and a temporary shortage of cortisone the patient

was put on A.C.T.H., starting with 25 mg. daily, administered in an intravenous saline drip. The dose was increased gradually to 40 mg. This induced a further remission, and the haemoglobin value, 5.1 g.% (35%) on November 5, rose to 10.5 g.% (71%) three weeks later.

Material and Methods

Direct Coombs Test.—This was performed on cells washed three times in saline.* They were put on an opaque tile and mixed with an equal amount of suitably diluted anti-human globulin serum.† Tests were read after two and five minutes, using a hand lens (×8). All tests were performed alongside suitable controls, which included AB rhesus-negative cells washed three times in saline and the patient's own cells, to which was added saline instead of anti-human globulin serum.

Rhesus Typing.—The following sera were used for the determination of the genotype of the patient and his family: anti-C, anti-C+, anti-C^w, anti-D, anti-E, anti-c, and anti-e, the latter containing a trace of anti-C. All the tests were run off with suitable controls.

Investigation for Presence of Antibodies.—The antibodies contained in both serum and eluates were investigated by means of a large panel of fully typed cells which were used in saline and albumin suspension and also used by means of the indirect Coombs test.

Indirect Coombs Test.—This was performed as follows: 1 volume of washed cells was mixed with 5 volumes of serum or eluate, thoroughly mixed, and incubated for at least two hours at 37° C. The supernatant was then removed and the cells were washed in saline three times. For reading, the same procedure was followed as in the direct Coombs test.

Preparation of Eluates.—The eluates were prepared from cells washed at least three times and then packed tightly. After the last wash the supernatant saline was removed and a volume of fresh saline equal to the volume of packed cells was added. The eluates were prepared at both 56° C. and 37° C. At the higher temperature the sample was submerged in a 56° C. water-bath and kept there with frequent agitation for approximately 30 minutes. It was then rapidly centrifuged and the supernatant removed. For the preparation of the eluate at 37° C., the cells were treated as before, and the specimen was then put into a 37° C. incubator overnight. Immediately on being taken out of the incubator it was centrifuged and the supernatant removed. The eluates were removed immediately after spinning and stored at −15° C. until used. The eluates prepared in either way showed heavy haemolysis. Generally speaking, eluates prepared at 37° C. worked better than those prepared at 56° C.

Results

Serum.—When it became necessary to transfuse the patient it was found that the serum contained an antibody active at 37° C. against saline- and albumin-suspended cells. It also gave a positive indirect Coombs reaction against the same cells. A large panel of cells was then used, and it was found that at 37° C. only one cell sample (cDE/cDE) was not agglutinated. Identical results were obtained in the indirect Coombs test. As the serum also contained an unspecific "cold" agglutinin it was necessary to incubate all tests carefully. These results were strongly suggestive of the presence of an anti-e in the serum, as no other antigen could be found which was common to the agglutinated cells and lacking from the cells in question. This was confirmed later when a further eight samples of this subtype (cDE/cDE) became available for testing. The titre of the antibody determined against albumin suspended cde/cde cells was 16 and against cDE/cde 4 (double-dose effect) (Race and Sanger, 1950). A very careful history obtained from the patient and his parents and wife showed, surprisingly, that he had never been transfused or received blood injections.

The eluates prepared from several specimens of the patient's cells in the course of his illness gave identical results. They could be made to act mainly by means of the indirect Coombs test, but weak reactions were also obtained when they were investigated with saline- and albumin-suspended cells. The eluates showed the same pattern of reaction as the serum. All cells containing the e antigen gave, when incubated with the eluates, a positive Coombs reaction, whereas E/E cells obtained from various donors always gave a negative result. The identity of the antibody, coated on to the cells and present in the serum, could thus be proved.

Direct Coombs Test.—At all times the cells of the patient showed a strongly positive direct Coombs reaction.

Group and Genotype.—In view of the presence of the antibody described above, it was of more than theoretical importance to define precisely the genotype of the patient. As pointed out, the serum contained a low-titred "cold" agglutinin and the cells persistently showed a moderate degree of auto-agglutination. This was abolished by washing the cells in 56° C. saline, and typing was then facilitated. The following results were obtained: the group was determined as Group O but was not confirmed by serum grouping, as no Group A or Group B donors were found of the subtype cDE/cDE. (All others, of course, showed agglutination due to the presence of the anti-e.)

Genotype.—The cells were agglutinated by anti-C, anti-C + anti-C^w, anti-D, and anti-e, but were not agglutinated by anti-E and anti-c. These results suggested that the most likely genotype was CDe/CDe. It was astonishing to find this genotype in view of the presence of the antibody already found in the patient's serum and on his cells, and it was therefore decided to investigate fully the available members of his family. Their groups and reactions are summarized in the Table. The sera of all members of the family were investigated, but showed no deviation from the norm. The family investigation thus supports the view that the genotype of the patient was CDe/CDe. It is of interest that the cells from all members of the family showed typical behaviour with the antisera available and did not give the impression of containing allelomorphic antigens. We are greatly indebted to Dr. R. R. Race, who was kind enough to check the results and to determine the other antigens on the patient's cells. The cells from the specimen of the patient were found to be M+, N+, S+, P+, Lu(a−), Le(a+ b−), Fy(a−). After the patient had received several transfusions with cDE/cDE cells these cells survived for a considerable period and did not clump on the addition of anti-human globulin serum. The blood transfusions gave rise to no reactions.

The Rhesus Types and ABO Groups of the Patient's Family

	ABO Group	Anti-C*	Anti-C+C^w†	Anti-D‡	Anti-E†	Anti-c†	Anti-e†	Probable Genotype
Patient	OO	+	+	+	−	−	+	CDe/CDe
Father	AO	+	+	+	−	+	+	CDe/cde
Mother	OO	+	+	+	+	+	+	CDe/cDE
Sister	AO	+	+	+	+	+	+	CDe/cDE
Sister	OO	+	+	+	−	+	+	CDe/cde
Brother	AO	+	+	+	−	−	+	CDe/CDe

* One example. † Two examples. ‡ Three examples.

Discussion

It is obvious that an antibody present in the serum of a patient will combine with its homologous antigen. The best example is perhaps the serology as seen in the haemolytic disease of the newborn when an antibody (usually anti-D) which has been passively transmitted to the patient via the placenta combines with its homologous antigen (D). The recognition of the union of antibody and antigen was made possible by the introduction of the Coombs test, which

*Freshly prepared 0.9% saline was used throughout this investigation.

†Anti-human globulin serum was kindly supplied by Dr. A. E. Mourant, of the Lister Institute.

demonstrates the presence of antibody globulin on the surface of the cells. Uncoated cells have always given a negative result. The positive direct Coombs reaction found in cases of acute acquired haemolytic anaemia is therefore taken to indicate the presence of antibody globulins on the surface of the cells. The presence of antibodies in the serum of these patients lends further support to this assumption.

The antibodies present in the serum and in the eluates in acquired haemolytic anaemia have previously been regarded as unspecific, or pan-agglutinins. The diagnosis of the specificity of an antibody depends naturally to a great extent on the size of the available panel of test cells. In our case the diagnosis could only be made through the availability of a cDE/cDE donor. As this subtype is comparatively rare among the British population (1.99%) (Race *et al.*, 1948), it is conceivable that even a large laboratory might not have this particular test cell available. As Kidd (1949) has pointed out, these antibodies were regarded as anti-species-specific, as in his cases no cell could be discovered which would not have been acted upon by the eluates. The test cell which permitted the diagnosis of the specificity of the antibody in our patient is, however, usually available in specialized laboratories. An antibody defining, for instance, the very frequent antigen Tj^a (Levine *et al.*, 1951) would react with all available test cells, as this antigen is so widely distributed and a cell lacking it might not be available at all. A pan-agglutinin would therefore be assumed.

Further difficulties might arise if several antibodies were formed against a variety of antigens. Very carefully performed absorption experiments and choice of test cells would be necessary to differentiate the various antibodies contained in any one serum or eluate. Multiple antibody formation is, of course, well known (Callender, Race, and Paykoc, 1945; Malone and Cowen, 1950).

It has been assumed in the past that no organism will form an antibody against an antigen carried on any of its own circulating cells (horror autotoxicus). This was taken to be a basic "law" of serology (Boyd, 1947). Our case has shown that an organism is capable of forming an antibody active against its own antigens, and the serology of acquired haemolytic anaemia would seem to show that this happens in all these cases. The antibodies attached to the cells and/or present in the serum of these patients must have combined with one or more antigens on the cell surface. Our case is exceptional in one way only—namely, that we were able to define the antigen precisely. Dameshek and Schwartz (1940) have shown that injection of antibodies directed against the cells of their experimental animals produce haemolytic anaemias typical in all respects. It is conceivable that the presence of antibodies in patients with acquired haemolytic anaemia may be the cause of these anaemias, though cases have been known in which, in spite of the persistent direct Coombs reactions, patients have had complete remissions. Further work would seem to be necessary to elucidate fully the mechanism of these types of haemolytic anaemias.

The presence of these antibodies in the serum and on the cells of the patients suffering from acquired haemolytic anaemia is difficult to explain. A tentative explanation might perhaps be offered as follows. It is a common experience that many haemolytic anaemias of the acute and acquired type are initiated by an acute febrile episode sometimes accompanied by the signs and symptoms of an upper respiratory tract infection. One might postulate that these initial febrile episodes have been caused by an agent, possibly viral, which carries an antigen similar in its structure to that present on the cells of the patient. An antibody formed in response to the stimulus of this infecting agent might cross-react with an antigen chemically related to the antigen which stimulated its production. There need not be a biological relationship between the two antigens. Many viral and rickettsial infections are known to produce antibodies which cross-react with unrelated organisms—Weil–Felix reaction and biological false Wassermann reactions after vaccinia and other viral infections (Moore and Mohr, 1952). (In this connexion one might point out that unspecific positive Wassermann reactions are not uncommon in cases of acquired haemolytic anaemia.) This applies particularly if the infection is severe and if the immunizing stimulus has been applied repeatedly. It is common serological experience that repetitive stimulation with one agent produces antibodies which are less specific than antibodies produced with fewer immunizing stimuli. It could also be possible that this antibody production may be initiated by a different pathological process, and the case of Levine *et al.* which produced the anti-Tj^a was shown to be suffering from a neoplasm which specifically absorbed the antibody, the patient's cells lacking the antigen.

Summary

A case of acquired haemolytic anaemia presenting a variety of interesting clinical details is described.

The development of an anti-e in the presence of the homologous red-cell antigen without stimulation by transfusion or blood injection was shown.

The serological findings were discussed and a tentative explanation was offered.

We wish to thank Dr. R. R. Race and Miss Ruth Sanger for the great help and encouragement they have given and for checking the results. Our thanks are also due to Dr. A. E. Mourant and his staff for their help and readily offered co-operation. We would also like to thank Professor A. P. Thomson, under whose care this patient was admitted to the General Hospital, Birmingham, for permission to publish.

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DIAGNOSIS OF "SEDORMID" PURPURA

BY

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Thrombocytopenic purpura following ingestion of the hypnotic "sedormid" (allyl*iso*propylacetylurea) by susceptible individuals is a well-known clinical entity. The pathogenesis of this syndrome was made clearer by the investigations of Ackroyd (1949b, 1949c, 1949d) on three patients who had recovered from such attacks. As a result of his researches, he put forward the hypothesis that thrombocytopenia in these patients was associated with a circulating substance in the blood which, in the presence of sedormid, caused lysis of platelets (Ackroyd, 1949d). This lysis he observed to take place *in vitro*, using suitable preparations of the patients' blood. An alternative method of demonstrating platelet lysis was by using the indirect approach of estimating clot retraction either of whole blood or of plasma. In his patients clot retraction was very much, and consistently, reduced in the presence of sedormid. The value of such tests as these obviously lies in enabling confirmation of the provisional diagnosis to be made without the necessity of