of chloroquine alkaloid, whereas Bagnall prescribed only 150 mg. base. Our maintenance dose was 300 mg. base daily.

Discussion

If antimalarial drugs, chloroquine in particular, have a beneficial effect on the disease process of rheumatoid arthritis, the question of its mode of action arises. Haydu investigated the effects of chloroquine as an adenosine triphosphatase inhibitor in rheumatoid arthritis. He regarded the high tissue requirements for adenosine triphosphate and the lack of corticoid support—for example, during infection and mental stress—in certain constitutional types as the basis of rheumatoid arthritis. Kurnick (1956) found that chloroquine combined with desoxyribonucleic acid and thereby prevented its depolymerization. This breakdown of the molecule is the preliminary to sequestration of the nuclear material and to phagocytosis, which represent the L.E.-cell phenomena. In other words, the addition of chloroquine *in vitro* to a system otherwise positive for the L.E.-cell phenomena will prevent the reaction taking place.

Experience gained in treating and following up 39 patients suffering from rheumatoid arthritis up to four years does not justify sweeping statements about the effect of a new drug. It was our original intention to publish a five-year review of our observations, but the recent interest aroused in chloroquine as a potentially useful drug in the management of rheumatoid arthritis has induced us to publish this report.

The assessment of any new treatment of rheumatoid arthritis is not easy, as remissions—some of them permanent—may occur at almost any stage of the disease. It is unlikely, however, that anyone experienced in the management of rheumatoid arthritis would attribute a maintained state of remission in over two-thirds of cases under observation to the natural course of the disease. The *Lancet* (1958) dealt with prognosis in rheumatoid arthritis based on observations in the Rheumatic Unit in Edinburgh between 1948 and 1951. 43% of cases admitted in the first year of illness but only 10% of those admitted between the fifth and tenth years were free from any restriction in activity six years later. Hospital treatment comprised bed rest, plaster splints, salicylates, and physiotherapy. These "sound and uncontroversial methods" and ancillary measures (induced pyrexia and transfusions) have in the past failed to bring an arrest of the condition in the majority of cases. The best results have been achieved by long-continued chrysotherapy, using small weekly doses. Gold failed, however, quite frequently even in cases with a short history of illness. Chloroquine does not seem to distinguish between old and recent cases so long as the disease process is active. We have given up corticosteroids for systemic treatment of rheumatoid arthritis altogether and use them only as hydrocortisone acetate for local injections into single joints to achieve mobility and overcome contractures during the first few weeks, until chloroquine takes effect.

It is too early yet to know how patients with rheumatoid arthritis treated with chloroquine will fare after five to ten years. Long-term maintenance treatment with chloroquine has been planned for the patients under review until the day when the enigma of rheumatoid arthritis has been solved and a more specific and radical cure has been discovered.

In the meantime, we believe that further trials of chloroquine in the treatment of rheumatoid arthritis are justifiable in view of the results achieved so far and the lack of dangerous side-effects of the drug.

Summary

The literature on the use of chloroquine in the management of rheumatoid arthritis is reviewed.

Results in treatment and following up 39 patients from three months to four years are described.

Complete remission of the disease process was obtained in 30% of cases, a major improvement occurred in 50%, and insignificant or no benefit was noted in about 20% of the patients.

The drug proved harmless and was well tolerated in larger doses than used by other authors. Relapses whilst on chloroquine were not observed in our series.

We recommend a regime of treatment consisting in bed rest, induced pyrexia, blood transfusions, and salicylates during the first three weeks of treatment, and tablets of chloroquine sulphate, 200 mg. t.d.s., throughout the treatment or immediately after induced fever—this dose of chloroquine to be continued until a remission has been obtained, when the dose may be decreased to 400 mg. daily (equals 300 mg. base). The maintenance therapy may be required for 12 months or longer.

REFERENCES

- Bagnall, A. W. (1957). *Canad. med. Ass. J.*, 77, 182.
Escarpenter-Oriol, J., Carreras Bayés, A., and Sarios Gomez, M. (1955). *Medizinische*, p. 1083. Quoted by Bagnall (1957).
Forestier, J., and Certoncin, A. (1954). *Rev. Rhum.*, 21, 395.
Freedman, A. (1956). *Ann. rheum. Dis.*, 15, 251.
Fuld, H. (1958). *Rheumatism*, 14, 1, 12.
Haydu, G. G. (1953). *Amer. J. med. Sci.*, 225, 71.
Kurnick, N. B. (1956). *A.M.A. Arch. intern. Med.*, 97, 562.
Lacépède, J., Monier, H., and Vial, G. (1954). *Rev. Rhum.*, 21, 389.
Lancet, 1958, 1, 894.
Page, F. (1951). *Lancet*, 2, 755.
Rinehart, R. E. (1955). *Northw. Med. (Seattle)*, 54, 713.
— Rosenbaum, E. E., and Hopkins, C. E. (1957). *Ibid.*, 56, 703.
Scherbel, A. L., Schuchter, S. L., and Harrison, J. W. (1957). *Cleveland clin. Quart.*, 24, 98.
— Harrison, J. W., and Ardjian, M. (1958). *Ibid.*, 25, 95.

UNCONTROLLABLE POST-OPERATIVE HAEMORRHAGE AFTER INCOMPATIBLE BLOOD TRANSFUSION

BY

JAMES M. MOORE, F.R.C.S.Ed., F.R.F.P.S.
Senior Registrar, Hairmyres Hospital, East Kilbride

It has often been reported that a defect of coagulation may occur in obstetrical conditions and in pulmonary and prostatic surgery. For example, it has been noted in accidental haemorrhage, amniotic fluid embolism, intrauterine foetal death, and missed abortion (De Lee, 1901; Dieckmann, 1936; Moloney *et al.*, 1949; Schneider, 1951; Reid *et al.*, 1953; Barry *et al.*, 1955), following pulmonary lobectomy (Soulier *et al.*, 1952), and in metastatic carcinoma of the prostate (Tagnon *et al.*, 1952; Swan *et al.*, 1957). One of the features of these cases has been hypofibrinogenemia.

That abnormal bleeding may occur as a transfusion reaction is not so well known, although it has been recorded by American authors on a number of occasions since it was mentioned by Drinker and Brittingham (1919). Muirhead (1951) found nine cases, while Friesen *et al.* (1952) investigated 11. Other examples are given by Wiener (1954) and Stefanini and Dameshek (1955). Krevans *et al.* (1957) studied two instances, and in a survey of the literature found 11 additional reports. No report of a case has been traced in British literature, although Mollison (1956) refers to the condition.

It is the object of this paper to give a clinical account of such a case which had a fatal termination.

Case Report

The patient was a single woman aged 25 suffering from a chronic gastric ulcer. In the past she had undergone appendicectomy and tonsillectomy, and no excessive bleeding had been noted. Menstrual blood loss had been normal. There was no history suggestive of any allergic upset.

Operation.—A Billroth I partial gastrectomy was carried out, and it was uneventful. The anaesthetic consisted of

thiopentone sodium, tubocurarine chloride, gallamine triethiodide, and nitrous oxide, and a pint (540 ml.) of carefully matched homologous group O rhesus-negative blood was given. The operation was completed at 12 noon.

A second bottle of blood was started at 12.30 p.m. When examined 15 minutes later the patient was rather pale, with a slight cyanotic tinge, and there was a little staining from a stab drainage wound. There was little change during the next two hours. At 2.45 p.m., when about two-thirds of the second bottle of blood (360 ml.) had been given, it was discovered that it was in fact group A rhesus-positive blood which had inadvertently been transfused. Immediately, carefully matched blood of the correct group was substituted and 1 pint (540 ml.) of 50% dextrose given in an attempt to minimize renal complications.

At 4 p.m. it was noted that venous blood sent for further cross-matching would not clot, and by then there was considerable fresh bleeding from the stab wound. Only a small amount of altered blood had been aspirated from the gastric tube during the afternoon, but at 6 p.m. there was 15 oz. (450 ml.) of fresh blood and the main wound had started to ooze. The patient became weaker despite continued transfusion, and another laparotomy was carried out at 7.45 p.m.

Second Operation.—About 4 pints (2 litres) of blood was found in the peritoneal cavity with a few clots. There was a general ooze from many areas involved in the previous operation. On opening the stomach more blood escaped, but again this arose from numerous areas, many not at the suture lines. Despite all attempts at haemostasis the ooze continued. The supply of matched blood for transfusion was temporarily exhausted during the operation, and 2 pints (1 litre) of 6% dextran in saline ("dextraven" and "intradex") was given. As nothing further of benefit could be done, the stomach opening was repaired and the abdomen closed with two drainage tubes.

It was now obvious that the patient had developed an abnormal haemorrhagic tendency.

Treatment.—4 ml. of "adrenoxyl" (1.5 mg. of adrenochrome monosemicarbazone dihydrate) and 100 mg. of vitamin K analogue ("synkavit") were given intramuscularly. 10 ml. of 10% calcium gluconate was given intravenously and a rapid transfusion of matched group O rhesus-negative blood continued. After consultation with the director of the regional transfusion centre at 10 p.m. the patient was given 4 pints (2 litres) of fresh dried plasma alternating with blood, and 2 g. of concentrated fibrinogen fraction. At this stage there appeared to be a slight temporary decrease in the rate of blood loss. Fresh frozen plasma was requested for her, but her condition deteriorated and she died at 1.45 a.m. on the day following operation, before it could be given.

She had received a total of 17 pints (9 litres) of blood, 3 pints (1.5 litres) of processed plasma, and 2 pints (1 litre) of dextran, as well as the 4 pints (2 litres) of fresh dried plasma and fibrinogen mentioned above. In all, this represents the administration of approximately 20 g. of fibrinogen, of which half had been given after the haemorrhagic defect had been recognized. In spite of this, up to the time of death, bleeding continued from the drainage tubes in the abdomen and from the gastric tube.

Relevant Post-mortem Findings

There was a large amount of blood and clot in the peritoneal cavity. The stomach was filled with a well-formed clot equivalent to about a pint (0.5 litre) of blood. No open vessels were identified, but there appeared to have been diffuse haemorrhage from the gastric mucosa, in which there were numerous slit-like defects several millimetres in length apparently communicating with submucosal haematomata. The liver and spleen were normal. Histological examination of kidney showed amorphous eosinophilic material, and desquamated epithelial cells in a few convoluted tubules. The lungs appeared oedematous, but there

were no histological changes, and selective staining showed no significant intravascular deposits of fibrin.

Blood Examination.—A specimen of venous blood taken at 3.30 p.m. on the day of operation failed to clot in 24 hours, even after the addition of thrombin in excess, indicating afibrinogenaemia. Marked haemoglobinaemia was noted soon after withdrawal, proving rapid destruction of the incompatible blood. A similar specimen taken two days before operation clotted normally.

Investigations at the regional transfusion centre confirmed that the patient was group O, rhesus negative, and that she had received group A blood, which had been rapidly destroyed. The pre-transfusion serum of the patient contained an anti-A haemolysin, and it was considered that this was responsible for the rapid haemolysis of the incompatible cells.

Discussion

The patient undoubtedly developed a haemorrhagic defect associated with afibrinogenaemia. The development of hypofibrinogenaemia has been described by Stefanini and Damashek (1955). Among the conditions mentioned as leading to the syndrome are haemorrhagic shock and haemolytic transfusion reactions. The patient's condition was good immediately after operation, which had not been associated with significant loss of blood. Therefore, even if haemorrhagic shock can produce such a syndrome, it seems unlikely that it was initially responsible for the onset of the fibrinogen deficiency in this case. The trigger mechanism was almost certainly the transfusion of blood of the wrong group.

Acquired hypofibrinogenaemia might theoretically result from (a) defective formation of fibrinogen; (b) intravascular clotting following the entrance of thromboplastic material into the circulation, with consumption of fibrinogen; or (c) depletion of fibrinogen by fibrinolytic or proteolytic enzymes in the blood. In this case it is unlikely that there was any defect in the formation of fibrinogen, as there was no evidence of impaired liver function. It is possible that intravascular clotting was the cause of the haemorrhagic state, because Quick *et al.* (1954) have demonstrated the thromboplastin-like activity of lysed red blood cells. However, there was no evidence histologically of abnormal fibrin deposition in tissues; nevertheless a fibrin deposit could have been destroyed by fibrinolytic enzymes, the presence of which has been reported in some cases of this syndrome.

The response to treatment was disappointing although there was post-mortem evidence of clotting. Stefanini and Damashek (1955) suggested that the average amount of fibrinogen required in treatment was 2–4 g., but mentioned that 8–20 g. might be necessary. Barry *et al.* (1955) recommended 2–6 g. of the fibrinogen fraction in the treatment of hypofibrinogenaemia of pregnancy, but if this was not available found triple- or quadruple-strength raw plasma equally effective (1 pint (0.5 litre) of the latter strength yielding 4.4 g. of fibrinogen). In this case approximately 10 g. of fibrinogen was given after the haemorrhagic defect had been recognized, but it is possible that this amount might have produced a greater effect if more of the fibrinogen had been in a concentrated form and had been administered over a shorter period. However, the failure of the patient to respond suggests that there may well have been additional factors involved.

Other coagulation elements may have been absent or diminished—for example, prothrombin, Factor V, and platelets (Greenwalt and Triantaphyllopoulos, 1954). Krevens *et al.* (1957) studied two patients after 500 ml. of incompatible blood and in both found hypofibrinogenaemia, hypoprothrombinaemia, and thrombocytopenia, with reduction of Factor V activity in one. (Incidentally, they could find no evidence of increased fibrinolytic activity, and favoured intravascular coagulation as a probable cause of these changes.) In treatment they advised fresh whole blood supplemented by fibrinogen. It may be that the fresh frozen plasma, containing some of these factors, would have been of benefit.

Two pints (1 litre) of dextran 6% in saline was given when matched blood and plasma were temporarily unavailable. In retrospect it is clear that this was inadvisable, as a number of reports have incriminated dextran as a cause of a haemorrhagic tendency (Carbone *et al.*, 1954; Scott, 1955; McKenzie and Langlands, 1956). The mechanism of the process is not clear, and suggestions made include interaction of dextran with fibrinogen, haemodilution, production of thrombocytopenia, and prolongation of the bleeding-time. The patient, of course, had developed abnormal bleeding before the dextran was given, but it is possible that the dextran aggravated the haemorrhagic tendency.

Friesen *et al.* (1952) described similar cases in which post-operative bleeding occurred as a result of a haemolytic transfusion reaction, when over 250 ml. of incompatible blood had been given. They felt that fibrinolysis was an important factor, but considered that a "heparinoid disturbance" was present. Toluidine-blue dye, given intravenously to two patients in a dosage of 15 mg. per kg. of body weight, apparently corrected the bleeding tendency. Such treatment might be worthy of a trial in any refractory case.

Treatment with corticotrophin (200 units intramuscularly) or cortisone (400 mg. intravenously) has been recommended, in addition to fibrinogen, by Stefanini and Dameshek (1955).

If the possibility of a bleeding state after incompatible transfusion had been known, the second laparotomy would probably not have been carried out, and appropriate treatment might have been started earlier.

Summary and Conclusions

A case is described in which there was fatal post-operative bleeding, associated with afibrinogenaemia, following a haemolytic transfusion reaction.

Treatment is discussed, and the following points may be of value in controlling such a condition: (1) early recognition of the fact that a haemorrhagic state has developed; (2) administration of large amounts of the fibrinogen fraction—for example, 2–6 g., repeated if necessary—or the use of quadruple-strength reconstituted raw dried plasma if fibrinogen is not available; (3) fresh frozen plasma, or fresh blood, if there is a poor response to adequate fibrinogen; (4) avoidance of dextran; (5) corticotrophin, cortisone, or toluidine-blue dye intravenously, if not responding.

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REFERENCES

- Barry, A. P., Geoghegan, F., and Shea, S. M. (1955). *Brit. med. J.*, 2, 287.
 Carbone, J. V., Furth, F. W., Scott, R., jun., and Crosby, W. H. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, 85, 101.
 De Lee, J. B. (1901). *Amer. J. Obstet. Dis. Wom.*, 44, 785.
 Dieckmann, W. J. (1936). *Amer. J. Obstet. Gynec.*, 31, 734.
 Drinker, C. K., and Brittinsham, H. H. (1919). *Arch. intern. Med.*, 23, 133.
 Friesen, S. R., Harsha, W. N., and McCroskey, C. H. (1952). *Surgery*, 32, 520.
 Greenwalt, T. J., and Triantaphyllopoulos, D. C. (1954). *Amer. J. clin. Path.*, 24, 1246.
 Krevans, J. R., Jackson, D. P., Conley, C. L., and Hartmann, R. C. (1957). *Blood*, 12, 834.
 McKenzie, J. M., and Langlands, A. C. (1956). *Scot. med. J.*, 1, 323.
 Mollison, P. L. (1956). *Blood Transfusion in Clinical Medicine*, 2nd ed., p. 367. Blackwell Scientific Publ., Oxford.
 Moloney, W. C., Egan, W. J., and Gorman, A. J. (1949). *New Engl. J. Med.*, 240, 596.
 Muirhead, E. E. (1951). *Surg. Gynec. Obstet.*, 92, 734.
 Quick, A. J., Georgakos, J. G., and Hussey, C. V. (1954). *Amer. J. med. Sci.*, 228, 207.
 Reid, D. E., Weiner, A. E., and Roby, C. C. (1953). *Amer. J. Obstet. Gynec.*, 66, 465.
 Schneider, C. L. (1951). *Surg. Gynec. Obstet.*, 92, 27.
 Scott, J. S. (1955). *Brit. med. J.*, 2, 290.
 Soulier, J. P., Mathey, J., Bolloch, A. G. Le, Daumet, Ph., and Fayet, H. (1952). *Rev. Hémat.*, 7, 30.
 Stefanini, M., and Dameshek, W. (1955). *The Hemorrhagic Disorders*, pp. 190, 214. Grune and Stratton, New York and London.
 Swan, H. T., Wood, K. F., and Daniel, O. (1957). *Brit. med. J.*, 1, 495.
 Tagnon, H. J., Schulman, P., Whitmore, W. F., and Kravitz, S. C. (1952). *J. clin. Invest.*, 31, 666.
 Wiener, A. S. (1954). *N.Y. St. J. Med.*, 54, 3071.

THE ISOLATION OF TRYPANOSOMA RHODESIENSE FROM A BUSHBUCK

BY

R. B. HEISCH, M.D.

J. P. McMAHON, O.B.E.

AND

P. E. C. MANSON-BAHR, M.D., M.R.C.P.

From the Division of Insect-borne Diseases, Medical Research Laboratory, Kenya

It has long been believed that an animal reservoir of Rhodesian sleeping sickness exists, but only one serious attempt has been made to isolate polymorphic trypanosomes from game animals and to test their pathogenicity in man. This was done recently by Ashcroft (1958), who killed 74 animals of various species in two endemic areas in Tanganyika and inoculated blood from them into rats. One polymorphic strain was isolated from a Coke's hartebeest (*Alcelaphus cokei*) near Babati in the Mbulu District and inoculated into man with negative results; this strain was presumably *Trypanosoma brucei*. It must be stressed that the only sure way of differentiating *T. rhodesiense* from *T. brucei* is by the inoculation of man. *T. rhodesiense* infects man while *T. brucei* does not: both trypanosomes are morphologically identical.

The present experiment was carried out on Utonga Ridge, a small peninsula projecting into Lake Victoria about 40 miles west of Kisumu in the Nyanza Province of Kenya. This area was chosen because not only were a few natives suffering from Rhodesian sleeping sickness found near by but because *T. rhodesiense* had been isolated from *Glossina pallidipes*, which is now the predominant tsetse fly on the ridge. Between April and August, 1958, 24 animals, which included 13 duikers, 10 bushbucks, and one serval cat were shot and their blood inoculated into rats. The serval cat was negative, but a strain of polymorphic trypanosomes and *T. congolense* were isolated from the duiker, and two polymorphic strains and two strains of *T. congolense* from the bushbuck. The polymorphic strains were inoculated into human volunteers and one of those from the bushbuck (*Tragelaphus scriptus* Fall.) was pathogenic to man (see below). This strain, which is highly pathogenic to rats and produced numerous posternuclear forms, is presumably *T. rhodesiense*. This is the first time that *T. rhodesiense* has been isolated from animals and establishes finally that Rhodesian sleeping sickness is a zoonosis.

The bushbuck strain was inoculated into the forearm of Mr. C. A. W. Guggisberg, mammalogist on our staff. The inoculum was heavily infected and consisted of 25 ml. of blood from a subinoculated rat with numerous trypanosomes in its blood (over 100 per oil-immersion field). On the seventh day there was a hardish lump at the site of the inoculation and trypanosomes were seen in material aspirated from the swelling. On the eighth day scanty trypanosomes appeared in the blood and the temperature rose to 103° F. (39.4° C.). On the ninth day the arm was very swollen, with a hard inflamed area about 3 in. (7.5 cm.) in diameter on which was a blister about the size of a half-crown. Fluid from the blister contained about three trypanosomes per oil-immersion field. At 11 p.m. the temperature rose to 106.9° F. (41.6° C.) and the patient felt very ill. At 11.45 a.m. he was given his first injection of antypol. Response to treatment was dramatic and recovery uneventful. Rats inoculated on the ninth day with exudate from the blister and blood taken from an earlobe became infected.

The technique employed is considered of great importance. It is essential to inoculate enough blood (30 ml. at