with copper in alkaline solution (Jacobsson and Hansen, 1953), but these same authors have pointed out that this occurs only when a method such as that of Lehmann (1944) is used in which there is no initial precipitation of the proteins.

As they have shown, and we have confirmed, the disturbing influence of dextran is, for practical purposes, eliminated by precipitating the protein with trichloroacetic acid.

Serum cholesterol was estimated by the modification (King, 1951) of the method of Sackett (1925).

Summary

The diuretic action of dextran in renal oedema has been investigated and confirmed.

Attention is drawn to the large increases in blood volume produced in these patients by intravenous infusions of dextran.

Headache and nausea, usually of slight degree, occurred in most of our patients, and it is postulated that these symptoms were due to overloading of the circulation. Vomiting and dyspnoea were less frequent.

In an attempt to find the optimal molecular size of dextran to promote diuresis four preparations with differing molecular distribution were used. There was little difference in the amount of diuresis produced, but the most severe side-effects, accompanied by the greatest increases in blood volume, occurred after infusion of the preparation containing the greatest proportion of small molecules. The most prolonged diuresis was effected by the large-molecule dextran.

Attention is drawn to the fact that the presence of dextran does not interfere with the estimation of plasma proteins by the biuret reaction provided the proteins are first precipitated by trichloroacetic acid.

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THROMBOCYTOPENIC PURPURA AFTER ADMINISTRATION OF GOLD COMPARISON OF TREATMENT WITH DIMERCAPROL, A.C.T.H., AND CORTISONE

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Various authors, reporting on the incidence of toxic reactions to gold salts, record percentages varying from 20 to 77. Severe reactions occur in approximately 6%. Amongst the most serious are thrombocytopenic purpura, agranulocytosis, and aplastic anaemia. Hartfall *et al.* (1937), in a series of 750 cases of rheumatoid arthritis given gold, noted toxic reactions of greater or lesser severity in 40% of patients, which included nine cases of thrombocytopenic purpura. Three of these patients died. Wintrobe *et al.* (1939), in a review of the literature, reported seven cases of purpura, four of which were fatal. Cecil *et al.* (1942) recorded three cases of purpura, one fatal, in a series of 245 cases given gold. Price and Leichtentritt (1943), in a series of 101 patients, noted three with purpura, one of whom died. Short *et al.* (1946) reported one fatal case of purpura in a series of 47 patients. Nyström (1950) encountered one fatal case of purpura among 572 patients given gold. Mettler *et al.* (1948), on the other hand, recorded four cases of purpura among 160 patients, none of which were fatal. Various other workers have reported isolated cases, but the incidence of this complication of gold therapy has declined in recent years, presumably owing to a better appreciation of the dangers of gold administration.

The introduction of 2,3-dimercaptopropanol (dimer-caprol, "B.A.L.") by Peters *et al.* (1947) as a therapeutic agent in the treatment of poisoning by arsenic and other heavy metals quickly led to its use in the treatment of toxic reactions due to gold. Many of the less serious reactions, such as dermatitis, rapidly improved following the use of dimercaprol (Ragan and Boots, 1947; Cohen *et al.*, 1947; Macleod, 1948; Montgomery, 1950; Edström, 1950; Kirsch, 1951). Good results have been recorded in cases of thrombocytopenic purpura, but only a few have been reported in detail. Lockie *et al.* (1947) describe a case of thrombocytopenic purpura due to gold which had shown no response to various methods of treatment over a period of three months and ultimately developed a subarachnoid haemorrhage. Dimercaprol was administered in doses of 180 mg. four-hourly for two days, then twice daily for ten days (total 5.7 g.), and the patient made a good recovery. The platelet level rose from 36,000 to 120,000 in three weeks, and was at approximately the same level three months later. Kroese (1949) described two cases of purpura following gold administration. In one case the response to dimercaprol was excellent. The drug was given immediately the symptoms appeared. The

second case was of five months' duration and showed no response to dimercaprol. Brodthagen (1950) reported one case in which 2 ml. of 5% dimercaprol was given daily for three days, but the patient died on the third day.

Initially dimercaprol was used mainly by intramuscular injection in the doses recommended by Peters *et al.* (1947). A course consisted of four injections, each of 2 ml. of 5% dimercaprol, at four-hourly intervals on the first day (400 mg.), followed on the second, third, and fourth days by 2 ml. twice daily. On the fifth and sixth days a single injection of 2 ml. was given (total dose 1.2 g.). In severely ill patients nearly double these doses were given, but "with considerable trepidation" (Longcope and Luetscher, 1946).

Only a small number of cases of thrombocytopenic purpura due to gold administration and subsequently treated with dimercaprol have been described in detail. In view of this it was considered important to report in full two further cases, in one of which the total amount of dimercaprol far exceeded the recommended dose, without ill effect.

Case 1

This patient, a man aged 49, was first seen as an out-patient in October, 1948. He had suffered from rheumatoid arthritis since 1946. He was treated conservatively until 1949, when a course of gold was recommended. Three days after the fifteenth injection (total 0.22 g.) a purpuric eruption appeared. He was admitted to hospital two days later.

On admission there was evidence of a recent epistaxis with haemorrhagic bullae present on the tongue and mucous membrane of the mouth, and a widespread purpuric eruption on the hands, feet, shoulders, neck, and face. He complained of a feeling of weakness, but was not distressed. His blood pressure was 170/110. Nothing abnormal was found in the cardiovascular, respiratory, nervous, and renal systems. The spleen was palpable, and enlarged lymph nodes were present in both axillae. There was typical spindling of the proximal interphalangeal joints of the fingers. Pain, swelling, and limitation of movement were also present in the wrists, elbows, ankles, and feet. At this time his haemoglobin was 90%, white blood cells 10,000 per c.mm. E.S.R. 46 mm. per hour, and platelets 163,000 per c.mm. Examination of a sternal marrow smear showed some hyaline degeneration of the megakaryocytes.

A transfusion of 2 pints (1,140 ml.) of whole blood was given and the bleeding stopped for three days. Epistaxis then recurred, and the patient complained of abdominal pain, nausea, headache, and diplopia. Haematuria developed and a subconjunctival haemorrhage appeared in the right eye. Ptosis became apparent and the power of accommodation was lost. Some weakness of the left leg was noted and the knee-jerk could not be elicited. There was no evidence of sensory loss. Paralysis of the third cranial nerve on the right side became complete. A further 2 pints of whole blood was transfused, but this did not control the bleeding. At this stage the platelet count had fallen to 20,000 per c.mm. The white-cell count was within the range of 5,600 to 8,200 per c.mm. The haemoglobin was 102%.

In view of the failure of transfusions to control bleeding, and the presence of a persistently low platelet count, dimercaprol was given in doses of 150 mg. six-hourly. After the second injection the patient complained of a feeling of constriction in the chest, with flushing. The individual dose was reduced to 100 mg. and no further reactions occurred. A total of 1.3 g. was given over six days. The bleeding diminished, and ceased during the course of treatment with dimercaprol. After withdrawal of the drug no further haemorrhage occurred. The platelet count remained low during dimercaprol treatment, values between 30,000 and

50,000 per c.mm. being recorded. A further transfusion of 1½ pints (850 ml.) of fresh whole blood was given without appreciable effect on the platelet count. Power in the left leg gradually improved, but the knee-jerk did not return for about eighteen months. Paralysis of the right third cranial nerve slowly improved and recovery was complete in seven months.

Comment.—Although the administration of dimercaprol coincided with the cessation of haemorrhage there was no appreciable rise in the platelet count for a further 25 days, and it is doubtful if dimercaprol, in the doses given, materially influenced the course of the disease. The most remarkable feature in this case was the localized lesions of the nervous system. Damage to the central nervous system can undoubtedly complicate the administration of gold. Mollard (1935) reported a case which developed bulbar palsy and paralysis of the right facial nerve. Hinault and Mollard (1934) described a patient in whom facial neuralgia, impairment of accommodation, and transitory blindness arose during the administration of gold. Sundelin (1941) collected 107 cases in which some evidence of neurological damage had occurred as a result of gold therapy. Hartfall *et al.* (1937), Cohen *et al.* (1947), and Doyle and Cannon (1950) reported cases of severe peripheral neuritis, in all of which recovery was eventually complete. In the present case it is difficult to be certain whether the neurological symptoms were due to the direct effect of the gold on the central nervous system or to small haemorrhages into the brain stem and cord. In view of the widespread purpura, the latter is considered to be the more likely explanation.

Case 2

This patient, a woman aged 44, was admitted to hospital with a history of profuse vaginal bleeding and widespread purpura for 12 days. She had suffered from rheumatoid arthritis of a very mild type for three years. Six months before admission her symptoms became much more acute and a course of gold was recommended. Injections were given at weekly intervals. A substantial clinical improvement was noted when a total of 0.85 g. had been given. After an interval of three weeks she received three further injections, each of 0.05 g. She noticed a metallic taste in her mouth and complained of general malaise. Menstruation began at the normal time, but bleeding became profuse and continuous. A generalized purpuric eruption appeared. She was admitted to another hospital and found to be severely anaemic. She received 4 pints (2,280 ml.) of blood before transfer to the rheumatic unit.

On admission her haemoglobin was 35%, red blood cells, 2,000,000 per c.mm.; white blood cells, 2,050 per c.mm.; and platelets, 20,100 per c.mm. The bleeding-time was raised to 20 minutes. Purpura and ecchymoses were present on the hands, thighs, and buttocks. Physical examination revealed only minimal evidence of rheumatoid arthritis in the small peripheral joints. The spleen was not palpable and no other abnormality was discovered. Vaginal haemorrhage continued. Her condition improved somewhat with repeated transfusions, 5 pints (2,840 ml.) of packed cells being given initially. The haemoglobin rose to 53% and the red cells to 3,270,000. In view of the value of A.C.T.H. and cortisone in idiopathic thrombocytopenic purpura (Bethell *et al.*, 1951; Wilson and Eisemann, 1952; Faloon *et al.*, 1952) and in other varieties of toxic reaction to drugs (Steinberg and Roodenburg, 1951), it was decided to explore their value in this condition. A total of 100 mg. of A.C.T.H. was given by the intravenous route, in the course of three days, combined with 40 mg. of "acthar gel" twice daily. Little evidence of haematological response appeared. The platelet count remained less than 40,000 per c.mm. and the bleeding-time remained over 10 minutes. The red-cell count and haemoglobin level fell from their post-transfusion levels to 2,780,000 per c.mm. and 47% respectively.

The dose of acthar gel was therefore increased to 60 mg. twice daily from the fourth day of treatment and, in addition, 100 mg. of cortisone was given daily by mouth. Apart

from a transitory fall in the bleeding-time, there was no evidence of any improvement. The dose of cortisone was increased to 125 mg. and subsequently to 150 mg. daily, while the dose of A.C.T.H. was reduced to 40 mg. daily. Signs of fluid retention appeared, in the form of ankle and sacral oedema, basal pulmonary crepitations, and a rise in systolic blood pressure. The bleeding-time remained over 10 minutes. Vaginal bleeding continued. The haemoglobin had fallen to 42%, red-cell count to 2,410,000, and platelets to 18,000 by the fourteenth day of treatment. The white-cell count was reduced to 2,500 per c.mm. A further 3 pints (1,700 ml.) of blood was given.

In view of the complete absence of any signs of improvement in the haematological condition, it was not considered justifiable to continue with cortisone or A.C.T.H. When the hormones were finally withdrawn, a total of 1.41 g. of A.C.T.H. and 1.75 g. of cortisone had been given. It would appear, therefore, that these hormones may be of little value in the treatment of severe cases of thrombocytopenic purpura following the administration of gold. It is of interest to note that the E.S.R. fell from initially high levels of 120 and 130 mm. in one hour to within normal limits during the period of hormone therapy and rose rapidly after withdrawal. The capillary resistance, measured by the method described by Robson and Duthie (1950), also rose during the period of hormonal treatment and fell after withdrawal. A similar effect on the blood pressure was noted. Eosinophils were absent from the peripheral blood during the period of hormonal therapy.

Dimercaprol was then given in doses of 150 mg. eight-hourly for 10 days. There was an immediate and dramatic response (see Chart). Haemorrhage ceased, the bleeding-

time fell rapidly, while the platelet count rose from 20,000 to 200,000 per c.mm. and the haemoglobin level rose from 52% to 60%. On the abrupt withdrawal of dimercaprol this improvement was quickly reversed. The platelet count and haemoglobin level fell, the bleeding-time rose again, and there were further episodes of haemorrhage, this time from the rectum and nose.

After an interval of six days dimercaprol was again given in doses of 450 mg. daily and the haematological response was unequivocal (see Chart). Five days later the dose was reduced to 300 mg., but some deterioration again took place. The dose was restored to the former level of 450 mg. daily and continued for a further 12 days. During this time normal menstruation occurred, and it was thought to be safe to begin withdrawal of the drug. This was done during the course of 10 days, without any sign of relapse. The patient's condition improved rapidly and there has been no relapse for one year. A feature of interest that occurred during administration of the second course of dimercaprol was a marked eosinophilia. The eosinophil count rose abruptly to 1,200 per c.mm. from its previous level of 50. This marked eosinophilia persisted during the second course of dimercaprol and subsided slowly as the drug was withdrawn.

No flare-up in the joints occurred after the withdrawal of cortisone, A.C.T.H., or dimercaprol.

Discussion

Several points of interest emerge from a study of the response to treatment of these two patients. In Case 1 purpura and thrombocytopenia appeared after the administration of a relatively small amount of gold (0.22 g.).

Dimercaprol given in the recommended doses (total 1.2 g.) appeared to have little immediate effect on the course of the condition. The platelet count remained at a very low level for 25 days after its administration was stopped. The fact that the cessation of haemorrhage coincided fairly closely with the administration of dimercaprol may be of little significance, as bleeding was not a prominent feature and anaemia did not develop. The neurological complications in this patient have already been discussed.

In Case 2 1 g. of gold had been given before purpura appeared. Haemorrhage was severe and continuous. A marked degree of anaemia rapidly developed. Repeated transfusions were necessary as a life-saving measure, but were of very temporary benefit. Large doses of A.C.T.H. and cortisone had no significant effect on the platelet count or the anaemia. The bleeding-time did show some improvement, and the capillary resistance, as measured by the negative-pressure method (Robson and Duthie, 1950), rose sharply from an initially subnormal level. This is an observation of some interest, as it would suggest that the reduction in the strength of the capillary wall found in thrombocytopenia of both the idiopathic and the toxic type may be of little importance as a cause of haemorrhage. The findings in this patient would suggest that there is a closer inter-relationship with the platelet count, but other as yet unknown factors must be concerned, as low counts are not infrequently found in the absence of bleeding (see Case 1). The failure of these hormones is in marked contrast to their effects in the idiopathic variety of thrombocytopenic purpura, in which a response occurs in most cases, although it may be incomplete and temporary.

Davidson *et al.* (1952) have also reported the failure of A.C.T.H. to influence the haematological condition in one case of thrombocytopenic purpura following the administration of gold. Virkkunen (1952), however, describes the effect of A.C.T.H. and cortisone in two cases with severe thrombocytopenic purpura after gold therapy. In one case a short course of cortisone produced a substantial rise in the platelet level, with an immediate fall on withdrawal. A subsequent more prolonged course produced a permanent return of the platelet level to normal. In the other case a total of 2 g. of A.C.T.H. was administered over one month, without any improvement in the extremely low platelet count. Clinically the patient improved without further haemorrhagic phenomena, but the thrombocytopenia persisted until four months after treatment, when a spontaneous remission occurred.

In Case 2 the response to dimercaprol was prompt and unequivocal. Cessation of treatment was followed by deterioration. Resumption of dimercaprol restored the position, but reduction of the daily dose to 300 mg. was again followed by relapse. The critical dose at this time lay between 300 and 450 mg. daily. The occurrence of normal menstruation was thought to indicate that dimercaprol might safely be withdrawn, and this proved to be the case. This patient received a total of 15.575 g. of the drug without any evidence of toxic effects. An interesting finding was the marked eosinophilia during the second course of dimercaprol. This is difficult to explain, as the patient had no clinical signs of hypersensitivity such as rash or fever. The presence of a persistent leucopenia would suggest a depression of all the cellular elements of the bone marrow. It may be that the adequate removal of the gold in the tissues by dimercaprol prevented further damage of the marrow and thereby avoided the possible onset of agranulocytosis or aplastic anaemia.

The pharmacological properties and therapeutic uses of dimercaprol have been reviewed by Weatherall (1948). Its action depends on its ability to form stable complexes with the heavy metals. By so doing it transfers the toxic element from the cells to the tissue fluids, from which it is excreted in the urine. In doses above 5 mg. per kg. body weight it may cause lacrimation, salivation, vomiting, and a rise in blood pressure, but permanent damage to organs has not been reported. It is not known why certain individuals develop toxic reactions to gold, but in such individuals it

would appear necessary to protect any susceptible tissues from the damaging action of gold until it is no longer being absorbed from tissue depots in significant quantities. This point is well illustrated in Case 2. It would seem that in the past some of the poor results reported in the treatment of thrombocytopenic purpura with dimercaprol may have been due to failure to give the drug in large enough doses for long enough periods. Results are likely to be more satisfactory if dimercaprol is given immediately toxic effects appear, as in these circumstances it may be possible to clear gold both from the damaged tissues and from the tissue depots, thus protecting susceptible cells from further injury. In recent years the successful use of much higher doses has been reported. Montgomery (1950), in two cases of gold dermatitis, gave a total of 9.6 g. in one case and 11.9 g. to the other over periods of 12 and 8 weeks respectively. One patient developed skin sensitivity to dimercaprol, but suffered no other ill effects.

Summary

Two cases of thrombocytopenic purpura following gold administration are described.

Unusual neurological signs occurred in one case, probably due to small haemorrhages into the cord and brain stem.

One case appeared to show no response to dimercaprol, but it is now considered that the total dosage given was inadequate.

One case showed no response to large doses of A.C.T.H. and cortisone, but responded promptly to dimercaprol.

The need for a higher daily dose and more prolonged courses of dimercaprol are discussed.

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