days after treatment is stopped. In one case perforation actually occurred 72 hours after stopping phenylbutazone medication (Shields *et al.*). The ulcer-provoking and ulcer-activating effect of phenylbutazone has been compared with that of cortisone. Some authors have postulated that phenylbutazone acts via an adrenal cortex stimulation (Wilhelmi, 1949), but most investigators deny this (Bach, 1952; Currie, 1953; Cudkowicz and Jacobs, 1953; Domenjos, 1953).

Phenylbutazone is a dangerous drug. If it is used it should be administered, after meals, with milk or alkali. It is absolutely contraindicated in patients with peptic ulceration.

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A Fatality Due to the Use of Gold

Until the recent introduction of cortisone, A.C.T.H., and phenylbutazone, the most important drugs available for the treatment of rheumatoid arthritis were the gold salts. They are still widely used, and will continue to be, until the supply and the efficiency of the newer drugs are more satisfactory than at present. The toxic effects of gold salts are well recognized, and yet are generally supposed to be controlled if a careful watch is kept for their early manifestations, and if a certain maximum dose is not exceeded. In the present case an unusually small total dose resulted in fatal damage to the bone marrow, and the first signs of serious toxic effects developed a fortnight after the course of gold had been finished.

CASE REPORT

A married woman aged 27 was admitted to hospital on August 20 on account of menorrhagia. Her menstrual period had begun two days before admission, and she had since suffered from a continuous and very heavy loss. She gave a history of a chronic arthritis which had first shown itself immediately after the birth of her second child two and a half years before. The disease had developed very rapidly and had reached its height only nine weeks after her confinement, remaining thereafter almost stationary. It mainly affected her hands and feet, although her elbows were also involved to some extent. She had been under treatment—as an out-patient at another hospital—since the beginning, and various treatments had been tried: ascorbic acid and deoxycortone acetate, pregnenolone, and insulin. All had produced an initial improvement followed by a relapse. The first and only course of gold was begun in the middle of May.

The preparation used was "myocrisin"; the initial dose was 0.01 g. Subsequent doses at weekly intervals were 0.02, 0.03, 0.03, 0.04, and 0.05 g. This last dose was repeated four times, making a total of 0.38 g. in ten weeks. The course was finished at the end of July, and throughout it there were no toxic signs or symptoms, except a slight pruritus following the third injection. The urine was regularly tested for albumin, and the test was as regularly negative. She was seen again as an out-patient on August 10, and at that time mentioned some bruising she had on her arms. Ten days later she came into hospital.

On examination she was still losing heavily per vaginam, and in addition there were many fresh bruises and purpuric spots on her limbs, and some bleeding from the gum margins. A blood count showed: haemoglobin, 48%; white cells 3,200 per c.mm. (48% polymorphonuclears); blood platelets 2,000 per c.mm.

A transfusion of 2 pints (1,140 ml.) of fresh blood was given, raising the haemoglobin to 68%, stopping the bleeding from the gums, and diminishing the loss per vaginam.

It was considered an unlikely coincidence that she should develop an idiopathic thrombocytopenic purpura so soon after the administration of a drug known to have toxic effects on the bone marrow, and the illness was assumed to be due to gold poisoning. Two further facts supported this assumption: first, the examination of the peripheral blood (and later of the bone marrow) showed that all cellular blood elements had been affected, not only the platelets; and, secondly, the only drug that the patient had taken, apart from the gold, was aspirin—one which, although it may prolong the bleeding-time when taken in excessive doses, has never been shown to have any poisonous effect on the bone marrow. An attempt was therefore made to increase the excretion of the gold remaining in the body by using dimercaprol. A first injection of 400 mg. was given on the day after admission, and the drug was continued in a decreasing dosage for five days thereafter. The urine was tested for gold on the third and fifth days of this treatment, but none was found; and no evidence was ever obtained that dimercaprol had any effect, either at this time or when a second course was given between August 29 and September 2.

In addition to the dimercaprol and the blood transfusions she was given A.C.T.H. in a dose of 25 mg. six-hourly between August 25 and September 2. The object in giving her the hormone was only in part to relieve her arthritis, although this was achieved within the first three days of treatment, and her hands continued to improve throughout the course; it was also hoped that the A.C.T.H. might have a stimulating effect on the bone marrow. In the three or four days immediately following the first administration of A.C.T.H. there was some increase in the number of lymphocytes in the peripheral blood, but the number of polymorphonuclears showed a steady decline until the end. In view of this severe and increasing granulopenia, penicillin was given as a prophylactic measure throughout.

The patient was also given pentnucleotide, but there was no noticeable effect in the peripheral blood consequent upon it. In spite of blood transfusions she died on September 4.

At necropsy an enormous intraperitoneal haemorrhage was found which had originated from a normal ruptured ovarian follicle. This had obviously been the final event which caused her death, although haemorrhages were also present in the pelvis of the left kidney, in both pleural cavities, on the pericardium, and on the surface of the brain. Histological examination of the femoral marrow revealed merely a fatty marrow with scanty haemopoiesis, and that mainly erythroblastic.

A report on the sternal marrow, a sample of which was taken and examined on August 22, stated: "A few flecks of a very hypoplastic marrow were obtained. No megakaryocytes were seen. Erythropoiesis is normoblastic, but there is hypoplasia of the erythropoietic and myeloid tissue. There is no maturation arrest of the myeloid tissue."

Reviewing this case after an interval of time, it seems that two failures contributed to the outcome: (1) failure to appreciate the significance of the evanescent pruritus after the third injection of gold; and (2) a failure to foresee the possible danger from ovulation, which could readily have been avoided by timely administration of oestrogen.

Mild toxic symptoms of intolerance to gold occur in nearly half the patients to whom the salts are given, but it must always be remembered that these mild reactions may be the only warnings of more severe ones to come. In regard to the second failure, if ovulation had been suppressed artificially death would have been delayed at least some days, though whether this would have affected the final outcome can never be known.

I should like to thank Dr. A. L. Jacobs for permission to publish this case and for his advice during the writing of this report.

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