CASE REPORT

APLASTIC ANEMIA

Secondary to Gold Therapy

By William J. FitzPatrick, M.D., and Steven O. Schwartz, M.D.

GOLD has become widely used as a therapeutic agent.[3,7] Its greatest accepted field of effectiveness is in the treatment of rheumatoid arthritis. It has also been employed therapeutically for lupus erythematosis and, for many years, especially in France, for all types of tuberculosis. Toxic effects are frequent in large series of gold treated cases. Hartfall et al.[7] reported 41.9 per cent incidence of toxic reactions in the treatment of 900 cases. Of these reactions 6 per cent were severe, with 7 deaths: 3 from hemorrhagic purpura, 1 from agranulocytosis, 2 from liver necrosis, and 1 from exfoliative dermatitis. There were adverse hematologic reactions in 10 cases in all. In 1942 Cecil et al.[3] reported on 245 cases treated with gold. Of these, 105 had toxic manifestations (42 per cent): 4 cases were hematologic, and included 3 hemorrhagic purpuras and 1 agranulocytosis. A recent report by Lockie et al.[9] mentions toxic reactions in 20 per cent. Whether these toxic manifestations are due directly to the drug or to individual sensitivity is as yet unknown. Clinical evidence favors individual sensitivity, since there is often little correlation between the amount administered and the severity of adverse effects. Experimental evidence also favors hypersensitivity,[8] since toxic symptoms, at least of the hematologic type, could not consistently be reproduced in animals. Hematologic manifestations of toxicity, though relatively rare, are among the most serious. Of these, thrombocytopenia is the most common with agranulocytosis next in frequency and aplastic anemia the rarest and most serious.

Dameshek[5] reviewed the literature in 1934, and found 6 cases of aplastic anemia due to gold therapy. To these he added a case. In 1939 Wintrobe et al.[13] collected 6 more cases and added still another. Four more cases have appeared in the literature since that time. Giraud[6] mentioned a case presenting 750,000 red blood cells, 1,800 white blood cells and a granulopenia of 30 per cent following gold therapy. Pergola[10] reported the case of a 35 year old dancer who developed aplastic anemia following her second course of gold in which a total of 1 Gm. of gold salt was given. This case had the classic triad of anemia, granulopenia, and thrombopenia, and in addition a fatty marrow, 80 per cent of whose cells were lymphocytes. She recovered after a period of 8 months. Armas Cruz and coworkers[1] described a case of aplastic anemia which occurred after a total of only 3 ampules of "Salganol" in-

From the Hematology Laboratory and the Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Illinois.

Aided by a grant from the Wilson Laboratories.

tramuscularly and 2 injections of 0.25 and 0.50 gr. of gold chloride intravenously. Sternal marrow revealed marked fibrosis. The patient was being treated for lupus erythematosis. Aubert[2] in 1946 published the case report of a 36 year old female who received a total of 2.1 Gm. of "Salganol" and who, 5 months later, developed classic signs and symptoms of aplastic anemia.

Altogether 18 cases of aplastic anemia following gold therapy have been reported, with 4 recoveries. We are describing 2 more cases, both terminating fatally, bringing the total to 20. The cases reported fulfill the diagnostic criteria of gold therapy followed by a syndrome of anemia, leucopenia, granulopenia, thrombocytopenia and hypoplasia or aplasia of the marrow.

Case Reports

Case 1 was a 32 year old white married female who presented herself on July 23, 1946 because of bleeding from the gums, vagina and "under the skin" for 3 weeks.

At the age of 5 she had had uncomplicated measles and chickenpox. At 12 she began to menstruate, the periods occurring every 21 to 28 days and lasting 2 days. Three years later she had a tonsillectomy which seemed to interrupt a series of moderately severe sore throats. At the age of 20 she had a trichomonas vaginitis and at this time noted that certain areas on her body, especially the arms, were losing their normal pigmentation. This depigmentation was not accompanied by pain, pruritus or local irritation. She married at this time and for the next 4 years tried unsuccessfully to become pregnant. At the age of 25 she began to complain of joint pains. At first the shoulders were involved and after aching for several days the pain passed to the elbows, wrists, knees and small joints of the fingers. These joints subsequently became hot, tender, and swollen. She visited various clinics seeking relief of her joint pains but received little benefit. At about this same time it was found that her uterus was slightly deviated to the left and the right fallopian tube was occluded. By the time she was 27 her joint pains had become more severe, and pain and soreness were present most of the time. She now began to receive "shots" for her arthritis and after a year seemed to feel much better. At 28 and again at 31 she had exacerbations of her joint symptoms. The "shots" for the arthritis were discontinued in January 1946. In the fall of 1945 she became aware of the fact that a spot on the top of her head, which had been present for about 8 years and had never bothered her, began to appear inflamed. Her physician prescribed an ointment which had little effect. At the same time she noticed a purplish red rash on both cheeks and the bridge of the nose. However this too had been present, "more or less," for 4 years. The rash never caused pain or itching, was always dry, and was darker in color at the time of the menstrual periods. A dermatologist diagnosed the lesion as "lupus." She was advised to keep out of the sun and in November 1945 began to receive injections of gold: 50 mg. per injection every 5 days. These were continued until July 1946, with progressive improvement in the rash.

At the time of her admission to the hospital she stated that she had begun to bleed about 14 days previously. She had no pain but noted that she was weaker than normally and tired more easily. The vaginal bleeding, present for 12 days, and at first consisting only of thin blood, now contained clots. She had been given a "shot" to stop the vaginal bleeding without effect. One week before admission she developed a fever (which went as high as 102.8°F.) and 2 days later her throat became sore. She was given another "shot" to stop the bleeding and "sulfa pills" for the sore throat. The sore throat improved but the vaginal bleeding continued, as did the bleeding from the gums. Slight trauma caused the appearance of large "black and blue" spots on the skin. The only other symptoms of significance were a weight loss of 5 pounds in the preceding 2 weeks and headaches for the preceding 5 days.

On examination she was found to be pale but did not appear seriously ill. There was a nickle sized area of alopecia at the vertex of the skull. The skin was both pigmented and depigmented in various places on both cheeks. Over the bridge of the nose she had a so called "butterfly" distribution and was more red over the nose than elsewhere. The sclerae were clear, the conjunctivae pale, and funduscopic examination revealed no hemorrhages or abnormal findings. There was a hemorrhagic area on the right buccal mucosa. The gums were soft, friable, and bled upon slight pressure. There were palpable nontender cervical, and

tender submental lymph nodes. The blood pressure was 118/60. The apex of the heart was 8 cm. from the mid-sternum in the fifth interspace, and a systolic murmur was heard at the apex and base. There were no palpable organs or masses in the abdomen but there was slight tenderness on deep and superficial palpation in the epigastrium and right lower quadrant. Many bluish ecchymotic areas were seen on all extremities. Many of the small joints of the hands were collared with small hard nodules which seemed to be outgrowths from underlying bone. There were depigmented areas on both arms and legs. The reflexes were normal. Vaginal examination disclosed tenderness in the right cul-de-sac and retroversion of the uterus.

On July 24, 1946 the red cell count was 1.73 million, the hemoglobin 20 per cent (3.1 Gm.), and the white cell count was 1,750. There were 2 polys, 95 lymphs, 1 monocyte, 2 eosinophils. Toxicity was 2 plus and poikilocytosis 3 plus. The reticulocyte count was 0.1 per cent and the platelet count was zero. Bleeding time was in excess of 20 minutes while coagulation time was 3 minutes. Total plasma protein was 6.3 grams per 100 cc., carbon dioxide combining power was 29 volumes per cent, chlorides 630 mg. of NaCl per 100 cc., and Kahn test was negative. The electrocardiogram showed a sinus tachycardia of 110 with an abnormal, though nondiagnostic, configuration. The urine was alkaline in reaction with a specific gravity of 1.020, 2 plus albumin, 3 plus occult blood, and no sugar, acetone or bile. The marrow obtained from the sternum was, for the most part, replaced by fibrous tissue. Only an occasional normal marrow cell was present. The cellular elements which constituted what remained of the marrow were lymphocytes and plasma cells. The findings were typical of "aplastic anemia" with fibrosis of the marrow.

The day after admission she was started on 20,000 units of penicillin every 3 hours and the following day she was given 1,000 cc. of whole blood. The vaginal bleeding continued and she vomited small amounts of blood. Ten per cent "BAL" was started in quantities of 2 cc. every 4 hours on July 26. In spite of these measures the patient began to bleed profusely from the nose and bilateral nasal packs were required to control the bleeding. Eight cc. of 10 per cent "BAL" was given that day supplemented by 500 cc. of blood. The "BAL" and penicillin were continued, intravenous glucose, saline, and oxygen were given, and alcohol sponge baths and cold enemas were used, but in spite of these measures the temperature rose to 105.6°F. 2 days later.

On July 30, 1946 the patient's condition appeared to be terminal. She was dyspneic and extremely weak. Pulse was weak and heart sounds resembled embryocardia. She expired the same day. Permission for postmortem examination was denied.

Case 2 was a 59 year old white married female who, on her first admission to the hospital on May 2, 1944, complained of nose bleeds for 4 weeks and the appearance of "black and blue" spots for 2 weeks. Her history dated back to 1928 when, at the age of 43, she first began to notice pain and swelling in the joints of the index finger of the right hand. In 1932 she had a tonsillectomy following which the arthritis spread to all the fingers of the right hand and to the toes of the right foot. In 1936 her teeth were removed, but still no relief was obtained from her joint symptoms. By this time the small joints of the left hand were also involved. She continued to have pain interspaced with occasional spontaneous remissions and exacerbations until April 1944. At that time she again presented herself for treatment to her physician. She was given liver, iron, concentrated yellow bone marrow, a bland diet, local heat and injections of gold. The exact dose of the gold is not known but she was given about 8 injections in all.

Her past history revealed no serious illnesses or operations. She had 5 pregnancies of which only 2 were carried to term. As a child she had chickenpox, measles and mumps. Menopause occurred at 41. Menstrual flow was always copious. She could not eat fish, strawberries, cherries or ice cream as these foods caused hives. Her mother and father died of pneumonia, otherwise the family history was noncontributory. She had taken cathartics and Anacin for many years.

The present illness began about 4 weeks before admission to the hospital with the sudden onset of a severe nose bleed, provoked by a rapid change of position from lying to standing. Bleeding continued for several hours and "the blood came in gushes." One week later she had a recurrence of bleeding. In both instances the bleeding was principally from the right nostril. About this time she also began to have some dyspnea on exertion and a "pounding sensation" in her head and ears whenever she changed position rapidly or became excited. These symptoms progressed and 1 week before admission to the hospital she began to have ankle edema which accumulated during the day and disappeared at night. Coincidentally with the onset of the nose bleeds, clusters of small "reddish points," principally on her

chest, made their appearance. These spots appeared suddenly and disappeared in about 3 days. At times these spots became confluent. About 2 weeks later, larger purplish "black and blue" spots began to appear, especially on the upper arms. These were not the results of trauma. Several days later, pain in the right eye, shoulder, hip and thigh appeared. The pain was described as a feeling of soreness, was intermittent in character and at times became severe enough to restrict motion. In addition to the above complaints she noted a gradually increasing fatigueability.

On admission to the hospital on May 2, 1944 she was found to be obese and pale. A small ulcer was seen on the soft palate and another in the right tonsillar fossa. The pharynx was injected. The heart was not enlarged, rhythm was regular, and a soft systolic murmur was heard at the apex. No organs or masses were felt in the abdomen. Multiple petechiae and ecchymoses were seen everywhere on the skin.

Laboratory examination. R.B.C. 1.79 million, Hgb. 30 per cent, W.B.C. 5,000. Differential: 8 polys, 3 eosinophils, 1 basophil, and 88 lymphocytes. The nonprotein nitrogen was 41 mg. per cent and the blood sugar was 148 mg. per cent. The urine had a specific gravity of 1.014 and was negative for albumin and sugar. The bleeding time was 8 minutes and the coagulation time 4 minutes, 40 seconds. The platelet count by the direct method was 190,000. Stools were negative for occult blood and the Kahn test was negative.

A diagnosis of hypoplasia of the marrow was made. Sternal puncture revealed a moderately cellular marrow. Megakaryocytes were rare. Erythroid development was normoblastic with evidence of great regenerative activity. Granulocyte development was moderately depressed, but adequate numbers of late granulocytes were present to justify the expectation that the granulopenia was a transient phenomenon. Many primitive cells were encountered. The findings were interpreted as compatible with the clinical impression of hypoplasia of the marrow, in a regenerative phase.

She received several transfusions while in the hospital and following her discharge continued to receive about one transfusion every month. In spite of this she persisted in having an anemia, granulopenia and thrombopenia. She began to have rather frequent febrile reactions following transfusions of whole blood and, because of this, red cell transfusions were often given instead.

By the end of 1945, she had received about 18 transfusions, but her condition was essentially unchanged. She was pale and weak and there were pigmented blotches on her zygoma and over the lips. There were bony deformities and partial ankylosis of the distal and interphalangeal joints of the hands. Her R.B.C. was 2.30, Hgb. 55 per cent, W.B.C. 5,400.

On March 30, 1946 she was again admitted to the hospital for study, complaining of weakness and "black and blue spots." By this time she had received 33 transfusions. Physical examination was essentially negative except for obesity, pallor, petechiae, and ecchymoses. Laboratory examination revealed the following: icterus index 6, cholesterol 230 mg. per cent with 60 per cent esters, total protein 6 Gm. with an albumin of 3.7 Gm. and globulin of 2.3 Gm. The fasting blood sugar was 104 mg. per cent and the nonprotein nitrogen was 38 mg. per cent. Urinalysis revealed nothing except a faint trace of albumin. The stool cultures were negative and the basal metabolic rate was −10. She received 7 blood transfusions and a blood count taken before the last transfusion revealed an R.B.C. of 4.5, Hgb. 81 per cent, W.B.C. 4,500 with a differential of 30 per cent polys and 61 per cent lymphs. Sternal marrow was now quite cellular but with retarded liberation of mature nucleated red cells and paucity of megakaryocytes. Following this admission she received a therapeutic trial with folic acid (15 mg.) and thyroid (130 mg. daily).

On September 10, 1946 she was again hospitalized for transfusions, by this time having received 52. Her admission hemogram was: R.B.C. 1.94, Hgb. 38 per cent, W.B.C. 1,500 with a differential of polys 23 per cent, bands 6 per cent, lymphs 54 per cent, monocytes 17 per cent, platelets 30,000.

The patient was last seen on January 17, 1947. Soon afterwards she became ill at home and died suddenly. No postmortem examination was performed.

Discussion

The treatment of toxic reactions secondary to heavy metal therapy had been largely symptomatic until World War II, in spite of the fact that much investigative work was carried out in an attempt to discover effective antidotes for heavy

metal intoxication. Following the introduction of BAL (British Anti-Lewisite, 2,3,—dimercaptopropanol) as an antidote for lewisite gas it became effectively used in the treatment of arsenical reactions occurring in the course of antiluetic therapy. These results stimulated the investigation of its effectiveness in the treatment of poisoning with other heavy metals and the drug was subsequently found to be similarly effective in counteracting reactions due to mercury, zinc and copper. Several publications have appeared of late reporting excellent results with BAL treatment of gold reactions. Before administering BAL to man Ragan and Boots[11] gave gold and BAL injections to rats to determine if the newly formed compound of BAL plus gold was toxic. They were prompted to do this by the report of Waters and Stock[12] that the compound of cadmium and BAL was toxic. Ragan and Boots were not able to demonstrate a similar toxicity. Of their 5 cases of dermatitis due to gold there was rapid recovery in 4 following the exhibition of BAL. It is of interest to note that the urinary excretion of gold was increased following the administration of BAL in all 5 cases. The damage in the fifth case was apparently irreversible. Cohen et al.[4] also reported 5 cases of gold toxicity with dermatologic manifestations treated with BAL. They felt that the results were good in all cases. Lockie et al.[9] reported 2 cases of hematologic reactions due to gold, one a thrombocytopenic purpura and one a granulocytopenia, in both of which BAL was successfully used.

There have been no previous cases of aplastic anemia due to gold reported in which BAL was used. The failure of the drug to help in Case 1 above does not imply a condemnation. Aplastic anemia in itself has an extremely high mortality. Besides this over 25 days had elapsed since the last gold injection had been given and the patient was hardly alive long enough to test the drug's efficacy. BAL should certainly be given an adequate therapeutic trial when another case of aplastic anemia due to gold presents itself.

Summary

Two cases of aplastic anemia following gold therapy are presented, bringing the total number of reported cases to 20. In one of the cases BAL was unsuccessfully used therapeutically.

REFERENCES

[1] Armas Cruz, R., Ducach, G., Goyenecke, A., and Wainstein, A.: Panmieloptisis secundaria a sales de oro, Rev. med. de Chile *68:* 1153, 1940.

[2] Aubert, A.: Panmyelopathy (panmyelophthisis), Acta, med. Scandinav. *123:* 377, 1946.

[3] Cecil, R. L., Kammerer, W. H. and dePhume, F. J.: Gold salts in treatment of rheumatoid arthritis: study of 245 cases. Ann. Int. Med. *16:* 811, 1942.

[4] Cohen, A., Goldman, J., and Dubbs, A.: The treatment of acute gold and arsenic poisoning. J. A. M. A. *133:* 749, 1947.

[5] Dameshek, W.: Aplastic anemia following treatment of lupus erythematosus with gold sodium thiosulphate; with review of literature of hematological reactions following gold therapy. New England J. Med. *210:* 687, 1934.

[6] Giraud, G.: Effect of bone marrow administration in course of hypoplastic anemia following treatment with gold. Montpellier méd. *447:* 19, 1941.

[7] HARTFALL, S. J., GARLAND, H. G. AND GOLDIE, W.: Gold treatment of arthritis; review of 900 cases. Lancet *2:* 838, 1937.

[8] KAETHER, H.: Das Verhalten der Thrombocyten nach Injektionen von Solganal Boleosum und Neo-Solganal. Klin. Wchnschr. *20:* 99, 1941.

[9] LOCKIE, L. M., NORCROSS, B. M., AND GEORGE, C. W.: Treatment of two reactions due to gold. J. A. M. A. *133:* 754, 1947.

[10] PERGOLA, A.: Severe agranulocytic aleukia hemorrhagica following treatment with gold. Sang *16:* 37, 1944.

[11] RAGAN, C., AND BOOTS, R. H.: The treatment of gold dermatitides, J. A. M. A. *133:* 752, 1947.

[12] WATERS, L. L. AND STOCK, C.: BAL (British Anti-Lewisite). Science *102:* 601, 1945.

[13] WINTROBE, M. M., STOWELL, A. S. AND ROLL, R. M.: Report of case of aplastic anemia following gold injections in which recovery occurred. Am. J. M. Sc. *197:* 698, 1939.