Canad. M. A. J.
Feb. 1, 1958, vol. 78

Case Reports

FATAL ACUTE HÆMOLYTIC ANÆMIA, THROMBOCYTOPENIC PURPURA, NEPHROSIS AND HEPATITIS RESULTING FROM INGESTION OF A COMPOUND CONTAINING APIOL*

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A CONSIDERABLE NUMBER of reports on apiol poisoning are contained in Dutch, German and French literature between 1931 and 1938. Only an occasional case has been reported in the English literature. The reported cases may be placed in three groups:

1. Those in which polyneuritis was the predominant manifestation; in these patients the polyneuritis was shown to be due to a contaminant, triorthocresylphosphate;
2. A few in which the predominant manifestations were due to an extensive encephalopathy; and
3. Those in which the predominant symptoms and signs were due to an acute nephrosis with uræmia and associated hepatic dysfunction.

In the present case, the patient ingested a preparation containing apiol and subsequently developed acute thrombocytopenic purpura, hepatic dysfunction and an extremely severe acute hæmolytic anæmia associated with methæmalbuminæmia, hæmoglobinæmia and hæmoglobinuria. Subsequently, an acute lower nephron nephrosis with oliguria, and then anuria and uræmia, developed. A septic peritonitis and septicæmia had followed an attempt at mechanical abortion and thus further complicated the findings.

A 28-year-old white woman was admitted as an emergency to the Royal Victoria Hospital by helicopter from Ottawa on November 2, 1956. She had been amenorrhœic for three months. Between October 14 and October 28 she had taken approximately 36 tablets of a proprietary preparation named Apergol. Six of the capsules were taken on October 28. A male companion who travelled with her stated that she had been taking this preparation irregularly and intermittently for some time before October 14. On October 28 a douche nozzle was stated to have been passed by the patient into the os externum of the cervix, and this was followed by severe pain, syncope, considerable vaginal bleeding and incontinence of stools. While at work on October 29, she suffered a severe chill followed by a rise of temperature to 104°F. She was admitted to hospital in Ottawa where a tentative diagnosis of septic abortion and pelvic peritonitis was made. On October 30 she remained febrile and became deeply jaundiced and incoherent; her urinary output was 150 ml. and her non-protein nitrogen (N.P.N.) was found to be 120 mg. %. On October 31, she was transferred to the Ottawa General Hospital. Her fluid output was 175 ml. A blood culture on that day was later reported positive for a non-hæmolytic streptococcus which grew in both anaerobic and aerobic culture and which was sensitive to tetracycline and to a combination of penicillin and streptomycin. Her companion stated that between the night of October 28 and the morning of October 30 her skin became a deep brown. On October 31 she was found to have severe anæmia with a platelet count of 80,000 per c.mm. and a prolonged prothrombin time. Her blood pressure was 100/50 mm. Hg. She was anuric from October 31 until her transfer to the Royal Victoria Hospital on November 2. Her plasma bilirubin was found to be 10 mg. %. She developed clinical purpura with a platelet count of 70,000. A blackish-brown pigment of the skin was noted and a similar pigment was found in the blood plasma. During this period therapy consisted of 300 mg. of hydrocortone, 100 mg. of cortisone acetate every 12 hours, about 500 c.c. of packed red cells about 500 ml. of 20% glucose in water with insulin every 24 hours and 500,000 units of crystalline penicillin every three hours.

Because of the persistent anuria she was transferred to the Royal Victoria Hospital for consideration of the use of the artificial kidney. On admission, she was a well-developed, well-nourished, dehydrated white female with blood pressure of 105/65 mm. Hg, pulse rate of 84 and temperature of 98° F. Her skin and scleræ showed a diffuse dark mahogany brown pigmentation and, in addition, the scleræ appeared icteric. She was confused, incoherent and unco-operative and appeared acutely ill. There were numerous petechial, purpuric and ecchymotic areas over the body, especially over the arms and legs, and a number of petechiæ were present in the mouth. The heart and lungs were normal to examination. There was marked tenderness over the right upper quadrant. The liver was enlarged to percussion and was thought to be palpable, although a definite edge could not be felt. Pelvic examination by Dr. George Maughan revealed a soft cervix and an enlargement of the uterus suggestive of a 2½-month gestation. The cranial nerves, reflexes and motor and sensory systems were normal to examination.

On November 2, the day of her admission, hæmatologic findings were as follows: Hb. 8.4 g. %; packed cell volume 23%; red cell count 2,400,000 per c.mm.; mean corpuscular volume 96 microns; mean corpuscular hæmoglobin 35 micromicrograms; mean corpuscular hæmoglobin concentration 37%; reticulocytes 4.4%; sedimentation rate (Wintrobe) 67 mm. in one hour (uncorrected), 25 mm. (corrected); platelets 14,000; bleeding time (Ivy) longer than 15 minutes; clotting time 16 minutes (normal 20 minutes); prothrombin time 16 seconds (normal 12 seconds), prothrombin complex concentration 45%; vascular fragility (Rumpel-Leede) markedly increased; clot retraction severely impaired; serum prothrombin time 19 seconds (normal 30 seconds or more) indicating diminution of prothrombin consumption; normal plasma fibrinogen concentration; the thromboplastin generation test was impaired because of a defect in the patient's platelets (i.e. the thromboplastin generation was corrected when normal platelets were mixed with the patient's serum and barium sulphate plasma, but was not corrected when normal barium sulphate plasma and normal serum were mixed with the patient's platelets). Total leuko-

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cytes were 50,000 per c.mm. with 35% (17,500) stabs, 52% (26,000) mature neutrophils, 3.5% (1750) monocytes, 8.5% (4250) lymphocytes, 1% (500) metamyelocytes. In the differential smears many typical microcytic spherocytes, a few target cells and some red cells containing Howell-Joly bodies were seen. The anæmia was normochromic and normocytic. In the test of mechanical fragility, 16.8% of the red cells hæmolysed (normal 2.5%). In the test of osmotic fragility anisohæmolysis was demonstrated, a small portion showing increased fragility and a larger portion of the red cells showing increased resistance. The plasma hæmoglobin was 40 mg. % (normal 1-4 mg. %). The direct and indirect Coombs tests were negative.

It was noted that the blood plasma and serum had a deep mahogany appearance which could have been due to the presence of methæmalbumin and/or methæmoglobin. The serum was submitted to spectroscopic examination: a dark absorption band was present at 6200 Angström units and a fainter band was present at 5800. The Schumm test showed that addition of ammonium sulphide caused the band at 6200 to disappear and an intense band appeared at 6530. These findings pointed to the presence of methæmalbumin. The L. E. test was performed and was negative. It was felt that these findings were diagnostic of severe acute hæmolytic anæmia and thrombocytopenic purpura.

On the day of admission N.P.N. was 222 mg. %, total protein 6.29 g. % with 4.05 g. % albumin and 2.12 g. % globulin; total bilirubin was 20 mg. % with 15 mg. % direct reacting bilirubin, D/T 75%, cephalin cholesterol flocculation test was +++, thymol turbidity 6.8 units and thymol flocculation test was negative, CO_2 combining power was 14.1 mEq./l., serum chloride 91.7 mEq./l., serum sodium 134.5 mEq./l., serum potassium 4.25 mEq./l., serum calcium 3.58 mEq./l., serum phosphorus 3.14 mEq./l. and a sugar level in a random blood sample was 135 mg. %. Blood volume determination on November 3 (using RISA) showed a total blood volume of 4756 ml. (anticipated normal 3742 ml.), a red cell volume of 960 c.c. (anticipated normal 1569 c.c.), and a plasma volume of 3716 ml. (anticipated normal 2150 ml.).

During the three days in hospital before her death, her output consisted of a few drops of dark brown urine. Her N.P.N. rose to 266 mg. % and serum creatinine to 11.6 mg. %; her CO_2 combining power remained at about admission level. Her serum potassium did not rise above normal limits and her E.C.G. showed no evidence suggestive of hyperkalæmia. Her serum sodium and chloride remained slightly below normal. The brownish pigmentation of her skin and plasma decreased. Her total red cell volume decreased to 819 c.c. Her purpura and thrombocytopenia persisted although she received three transfusions of fresh whole blood taken in siliconed flasks through plastic tubing. The prothrombin complex concentration improved slightly after blood transfusion and intravenous administration of large amounts of vitamin K_1.

Her abdomen became increasingly distended. She developed inspiratory and expiratory coarse subcrepitant rales throughout both lung fields. Her mental confusion changed to semi-coma and then deep coma. The spleen was never palpable. Her blood pressure varied from 110-134/60-80 mm. Hg throughout her hospitalization. Her fluid intake consisted of a total of 3000 ml. intravenously, including the transfusions of 1500 ml. of blood. She received large amounts of procaine and crystalline penicillin mixed with streptomycin, 50 mg. of cortisone acetate daily, and testosterone propionate, 50 mg. i.m. twice a day. Because of increasing pulmonary œdema on November 3, 1050 ml. of whole blood was removed by phlebotomy while at the same time 400 c.c. of packed red cells was administered.

On November 4 the paper electrophoretic pattern of the serum proteins showed albumin 57.7 %, alpha 1 globulin 8.3%, alpha 2 globulin 11%, beta globulin 8.3% and gamma globulin 14.6%. The only abnormality present was a slight increase of alpha globulins.

On the evening of November 4 she developed severe acute pulmonary œdema and died.

Because of the nature of the case it was necessary to turn the body over to the coroner, whose report of the gross findings is summarized below:

Scalp, skull, brain, heart, stomach, intestines and bladder: no gross change. Lungs: fairly marked congestion, œdema with areas of atelectasis in the dependent portions. Abundant thick secretions in the trachea and bronchi mixed with a reddish serous fluid. Kidneys: right, 235 g.; left, 260 g.; large red kidneys with extensive cortical hæmorrhages. Cortices of the same colour as the medulla. Pelves not remarkable. Liver: weight 2625 g.; increased in size, œdematous and of a beige-brown colour. Uterus: showed a multiparous cervix and measured 10 x 7.4 x 4.3 cm. It was widely patent and contained a mucopurulent secretion. The enlarged uterine cavity showed a brownish mucosa which was thickened, ragged and sanguineous. No trace of significant instrumental trauma was found; only the left ovary was present.

Microscopic sections of certain organs were obtained from the coroner and the pathological examination was reported by Dr. Douglas Waugh. The heart was normal. Sections of the liver showed normal over-all architecture but there were multiple small foci of necrosis with an increased amount of brown pigment, probably bile, in liver cells and canaliculi around the central veins. A few hepatic veins showed small numbers of lymphocytes and polymorphonuclear neutrophils in their walls. In the ovary fragments of the corpus luteum showed early hyalinization; a few follicles and small fragments of normal cortical tissue were present. The sections of the uterus contained masses of fibrinopurulent material and no recognizable tissue. The proximal and distal tubules of the kidneys were extensively occluded by a granular heme pigment and there was associated focal degeneration of epithelium. Inflammatory changes were inconspicuous. The findings were those of an unusually severe hæmoglobinuric nephrosis (Fig. 1).

The pathologic diagnosis was acute nephrosis of hæmoglobinuric type (marked); focal necrosis of liver with bile stasis.

DISCUSSION

Apiol has been widely used and is stated to produce symptomatic relief in menstrual disorders such as amenorrhœa, menorrhagia, hypomenorrhagia, metrorrhagia and dysmenorrhœa. Supposedly, it stimulates the uterine musculature and induces pelvic hyperæmia. It is a camphoraceous material derived from parsley and has the formula 1-allyl-2,5-dimethoxy-3,4-methylene-dioxybenzene.

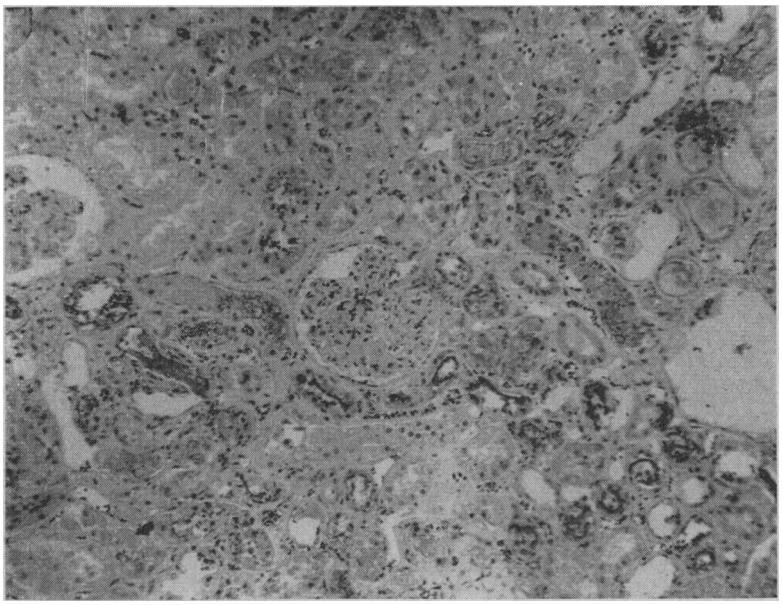

Fig. 1.

There is good evidence to believe that this patient ingested 36 capsules of Apergol over a two-week period preceding the onset of her illness and, probably, she took additional capsules for some time before this. According to the manufacturer, each capsule of Apergol contains 0.3 g. of apiol, 0.008 g. of aloin, 0.065 g. of ergotin, and 0.03 g. of oil of savin and aromatics qs. This formula is identical with that of the preparation ingested by the patient reported in 1938 by Lowenberg.[1] Although the product was prepared by a different manufacturer, his patient ingested only 17 capsules and the clinical manifestations were principally cerebral. He tested his preparation for the presence of triorthocresylphosphate but was unable to confirm its presence. As pointed out by Lowenberg and others, the variable pharmacologic properties of preparations containing apiol may be responsible, at least in part, for the different manifestations of poisoning.

Polyneuritis has been the most commonly reported manifestation of apiol poisoning. It has been shown repeatedly, both experimentally[2] and clinically,[3] that the polyneuritis is due to the presence of triorthocresylphosphate, the substance responsible for the Jamaica ginger polyneuritis which occurred in the United States in 1930.[4–6] This substance is used in apiol preparations because it provides the desired bulk to the capsular contents and because it preserves the appearance and consistency of apiol by preventing its precipitation and by having the same general appearance as yellow apiol. The manufacturer of Apergol does not state in the pamphlet attached to his product whether triorthocresylphosphate is present. At no time did our patient show clinical signs of a polyneuritis.

Administration of apiol to dogs has resulted in toxic damage to the liver, kidneys and heart, as do most volatile oils. A number of European authors have reported nephritis resulting from apiol poisoning.[7, 8] In these patients the symptoms appeared one to eight days after the ingestion of apiol, and were associated with elevation of temperature and pulse, nausea, vomiting and abdominal distress, often with diarrhœa. Erythematous and purpuric eruptions of the skin, gingivitis and œdema of the vulva were not uncommon. At least two authors[7, 8] have noted the brownish pigmentation of the skin and the mahogany or blackish colour of the urine associated with oliguria. One author[7] noted the presence of bilirubin, methæmoglobin and hæmoglobin in the urine; he felt that the renal changes were secondary to these findings.

Except for the above report, the presence and significance of a hæmolytic anæmia does not seem to have been stressed. Our patient had a very severe hæmolytic anæmia associated with a marked thrombocytopenic purpura. This spherocytic anæmia was associated with a marked increase of mechanical and some increase of osmotic fragility; it was not of the auto-immune type. The intense pigmentation of the skin and internal organs and the brown pigment in the urine were probably related to the methæmalbuminæmia which, with the hæmoglobinæmia and hæmoglobinuria, was a manifestation of a very severe hæmolytic process. This intense intravascular hæmolysis resulted in obstruction of the proximal and distal tubules of the kidneys, in the acute nephrosis, the anuria and the uræmia. Many of the clinical and pathological manifestations, and probably the death of the patient, resulted from the severe hæmolytic anæmia. During the patient's stay in the Royal Victoria Hospital she remained afebrile and the clinical findings suggested that any infection present had been localized by previous therapy to the pelvis. It is possible that infection contributed to the hæmolytic anæmia. However, the organism recovered from the blood was not of the type associated with hæmolytic anæmia; evidence of systemic infection was minimal during her stay in the Royal Victoria Hospital, and at autopsy evidence of infection was limited to the uterine cavity. It would seem probable that in many of the reported cases of apiol poisoning with renal involvement there was really a lower nephron nephrosis caused by a similar hæmolytic process.

A few authors have reported death from apiol poisoning as a result of widespread cerebral damage.[1, 10, 11] It is suggested by one author that large doses of the drug cause immediate cerebral damage[11] whereas moderate doses may produce delayed effects upon the peripheral nerves. In the

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instances of cerebral damage it is not clear whether this damage was due to apiol or to the presence of triorthocresylphosphate as a contaminant.

Patients with the nephrotic manifestations may also have central nervous system symptoms and signs, such as confusion, psychosis, convulsions and coma. It is not clear whether these symptoms are due to the associated uræmia or whether they are related to co-existent cerebral damage from the apiol poisoning. Unfortunately, the brain of this patient was not examined microscopically.

It is suggested that poisoning due to compounds containing apiol occurs more frequently than might be anticipated from the number of reports in the English literature. The authors are aware of at least two other cases of such poisoning which have occurred in the Montreal area within the past several years. Preparations containing apiol seem to be used principally in the treatment of amenorrhœa. In view of their potential hazards there would seem to be little or no justification for the continued use of apiol for this purpose.*

SUMMARY AND CONCLUSIONS

A fatal case of severe hæmolytic anæmia, thrombocytopenic purpura, acute lower nephron nephrosis and hepatic dysfunction is reported in a patient who ingested 36 capsules of a compound, each capsule of which contained 0.3 g. of apiol. The patient also suffered from a pelvic peritonitis and probably from septicæmia resulting from septic abortion.

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*The following excerpt is taken from the Transactions of the Ninetieth Annual Meeting of the Canadian Medical Association, held in Edmonton in June 1957.—ED.

"The Committee on Pharmacy had discussed the resolution put forward by the Committee on Maternal Welfare concerning oil of apiol and had reported as follows:

'It is a matter of record that this material has been used as an abortifacient and that illness has resulted not only because of its innate toxicity, but also because of the presence of impurities in it. As far as we are aware, it is not used by the medical profession for any purpose, and its inclusion in any preparation registered under the Patent or Proprietary Medicines Act does not appear to be justified. Its use in preparations marketed under the Food and Drugs Act should also be restricted.

'We are therefore in accord with the sentiments expressed in the resolution, and agree that a recommendation be sent forward to the appropriate Divisions of the Department of National Health and Welfare'." Adopted

ACUTE ERYTHRÆMIC MYELOSIS

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PATIENTS in whom are to be found changes in the peripheral blood, in the bone marrow and in the visceral organs resembling an acute leukæmia but affecting essentially the red cell precursors are rarely encountered. It is therefore considered justifiable to report upon a single case.

The case involved a 57-year-old man admitted to St. Mary's Hospital on January 12, 1955, because of the abrupt onset of severe orthopnœa accompanied by hæmoptysis and melæna. He had experienced progressive weakness with angina of effort in the month before admission. Physical examination showed pallor, engorgement of neck veins, congestion of the lungs, peripheral œdema and cardiomegaly, but otherwise was negative.

There was severe anæmia (hæmoglobin level of 4.8 g.) without characteristic features on the stained smear. Platelets were scanty (about 20,000/c.mm.) There were two late normoblasts per 100 nucleated cells. The white cell count was 4700/c.mm., and a careful differential count, made in retrospect after the marrow had been examined, showed:

Eosinophil polymorphs	< 1%
Neutrophil polymorphs	59
Neutrophil metamyelocytes	2
Neutrophil myelocytes	< 1
Myeloblasts	2
Erythroblasts	4
Undifferentiated "blast" cells	3
Lymphocytes	22
Monocytes	5
Reticulum cells	< 1
Plasma cells	< 1
Unidentifiable	2

Bone marrow was obtained from the sternum, and the specimens were prepared by Davidson's

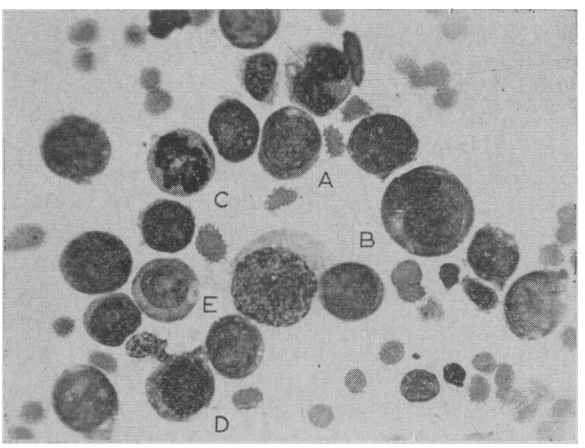

Fig. 1.—Bone marrow smear × 800. A, Erythroblast. B, Binucleate erythroblast. C, Erythroblast in mitosis. D, Megaloblastoid form. E, Large hæmoglobinized cell.

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