Case Reports

INTOXICATION BY AMINOPTERIN USED AS AN ABORTIFACIENT*

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TOXIC EFFECTS of folic acid antagonists used therapeutically have been described frequently, but the following is thought to be the first case of poisoning due to unauthorized use of 4-aminopteroylglutamic acid (aminopterin) as an abortifacient. Such use of this drug may now be expected to be fairly widespread, and further cases of similar poisoning may be expected, as at least one lay magazine in the winter of 1955-56 carried an article about "these abortion pills". The article was written in a cautionary tone but at least inferred fairly wide knowledge of the effects of aminopterin.

Knowledge of these abortifacient properties developed from experimental work on animals in 1949[1] and 1950[2] showing toxic effects from folic acid deficient diets on developing fetuses. The same effects were produced by the administration of folic acid antagonists. In 1952 Thiersch[3] applied these findings to humans and studied the use of aminopterin in therapeutic abortion. Twelve cases were studied, in all of which there were definite medical reasons for abortion. Doses of 6-12 mg. over a period of 2-5 days were given to patients in their first trimester. Fetal death followed by spontaneous delivery occurred in 10 of the 12 cases. Doses lethal to the fetus were said to have only transitory effects on the mother.

A 44-year-old white housewife was referred by her family physician to the Emergency Department of the Montreal General Hospital on March 14, 1956. Her principal complaints on arrival at the hospital were of sore throat, redness and swelling of her face, and a burning sensation inside her mouth—all of 24 hours' duration.

The patient, the mother of four grown children, had had her last menstrual period on February 1, 1956. Her menses had always been regular in a 28-day cycle. When her March period did not appear at the expected time, she began to fear that she might be pregnant. By March 10, she had become so anxious that she was willing to try anything to avoid the birth of another child. A female acquaintance arranged for her to purchase 100 tablets of aminopterin (0.5 mg.) from a neighbourhood druggist. Her friend assured her that if she took two of these tablets every five hours, an abortion would be induced, but warned her that she might feel slightly ill afterwards.

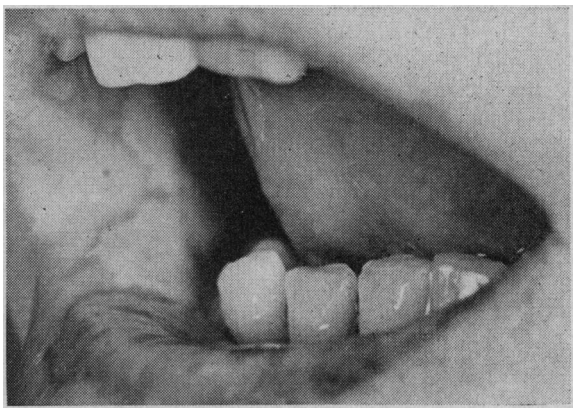

Fig. 1

The patient reported that on March 10 she took eight tablets; on March 11 she took eight and on the evening of March 12 she took an additional four. Thus, according to the history given by the patient, she had ingested a total of 20 tablets or 10 mg. of aminopterin. However, the referring physician stated quite definitely that, when he visited her at home, he counted only 66 tablets remaining in the bottle. There is, then, a strong possibility that she may have taken as much as 17 mg. of aminopterin over a period of 56 hours.

On the morning of March 13, the day following the last ingestion of aminopterin, she first became aware of a sensation of stiffness in the muscles of her face. Later in the day she developed a severe sore throat, and on looking into a mirror noticed that her entire face was swollen and red.

When she was admitted to hospital the next evening, she was in severe discomfort. Her temperature was 98.8° F., pulse rate 100, and blood pressure 125/75 mm. Hg. There was a fiery red, diffuse erythema of the entire face and anterior portion of the neck. Her face was swollen, especially the cheeks and soft tissues around the eyes, giving her a puffy, bloated appearance. This intense erythema was confined to the face; no involvement of the scalp or ears was apparent at this stage. Several small clear vesicles about 0.5 cm. in diameter were present on the chin, cheek and eyelids.

The lips showed a marked mucosal reaction with cracking and peeling of the skin. The gingivæ were pale and covered in most areas by a whitish exudate. The buccal mucosæ and soft palate were an angry red colour, œdematous and covered with large uneven patches of whitish grey exudate (Fig. 1). When this exudate was scraped away, small vesicles, similar to those on the face, were seen, as well as several shallow, irregular, ulcerated areas 1-2 cm. in diameter. Numerous petechial hæmorrhages were found scattered over all the mucous membranes. The faucial pillars and posterior pharyngeal wall were congested and mildly œdematous. The exquisite tenderness of the entire oral cavity caused the patient severe distress. She could not speak above a hoarse whisper and her pain prevented her from swallowing more than a few sips of water. An enlarged tender lymph node was palpated in the left postauricular region. No cervical lymphadenopathy was detected, but there was marked tenderness at the angle of the jaw bilaterally.

A blotchy pink macular eruption, mainly between the breasts, was present on the skin of the anterior chest wall. A few small patches of an eruption similar to the one between the breasts were scattered over the abdomen and flexor surfaces of both arms. On pelvic examination, the uterus was found to be minimally enlarged, the

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cervix closed, and an abundant brown mucous discharge present in the vagina. The remainder of the physical findings were unremarkable.

The hæmogram showed: hæmoglobin level 11.5 g. % (74%); red cell count 4,460,000; white cell count 8450; white cell differential within normal limits; platelets 172,000. Urinalysis: specific gravity 1.023, protein 0, sugar 0, red blood cells 5-10, white blood cells 0, casts 0.

Immediately after admission, the patient was started on the specific antidote, citrovorum factor 0.5 mg. b.i.d., as well as penicillin 400,000 units b.i.d. and streptomycin 0.5 g. b.i.d. Local therapy as suggested by Dr. Roy Forsey of the Department of Dermatology consisted of: hydrogen peroxide mouth washes, 5% aqueous Mercurochrome painted on the eroded areas, cold wet milk and water compresses to the face, and hydrocortisone 0.5% in stearyl cream at intervals between the compresses.

Examination of the larynx and hypopharynx by Dr. E. John Smith, of the Otolaryngology Department, two days after admission, revealed moderate redness of the arytenoids and larynx but no gross œdema. The true cords were also slightly red and covered with scanty mucous threads. Movements of the cords were present but restricted, presumably due to the minimal inflammatory changes seen. Proctoscopic examination failed to show any rectal lesions; there was no tenesmus or occult blood in the stool.

Hæmograms were obtained daily throughout the patient's hospital stay. At no time was there any evidence of suppression of hæmatopoiesis. The white cell count remained between 5000 and 8000 with normal differential counts, and the platelet count between 160,000 and 320,000. The bone marrow was not examined because of the absence of changes in the peripheral blood.

The lesions about the face and mouth remained unchanged for the first three days and then began to improve slowly. Her face became less swollen; the lesions inside the mouth healed slowly with the production of large amounts of exudate. The milk and water compresses gave her great relief from the pain. By the fourth hospital day she had regained her normal voice and was able to swallow a soft diet.

On the other hand, the skin lesions on the chest and abdomen increased in size and number. It was not until the fourth day that they began to subside gradually. The abdominal rash itched intensely, adding greatly to the patient's discomfort.

On the sixth hospital day the patient complained of profuse vaginal bleeding of sudden onset. This hæmorrhage was accompanied by crampy lower abdominal pain and the passage of large clots of blood. On vaginal examination the cervix was open, admitting one finger. The uterus was tender, mobile, slightly soft, and enlarged to the size of four weeks' gestation. A dilatation and curettage under Pentothal and cyclopropane anæsthesia was performed that night by the Department of Gynæcology. On exploration of the uterine cavity, a small amount of decidual tissue was found and removed.

Examination of microscopic sections of the uterine scrapings by Dr. W. H. Mathews, of the Department of Pathology, revealed a marked decidual reaction of the endometrium with a diffuse infiltration of polymorphonuclear leukocytes. No chorionic villi or trophoblastic cells were seen. A fetus was not found in the material submitted for pathological examination.

Following the dilatation and curettage the patient's hæmoglobin level was found to be 10.6 g.%. She was given a transfusion of 1000 c.c. of whole blood on the next day.

The skin and mouth lesions healed rapidly during the next eight days. On the day of discharge, 14 days after admission to hospital, the face and body were completely clear. All that remained of her extensive dermatitis was a few small shallow ulcerations less than 0.5 cm. in diameter on the buccal mucosa. As she was dressing to leave the hospital, she noted for the first time that her hair was falling out. It came away in large handfuls each time she attempted to comb her hair. Although the entire scalp was affected, there was no loss of body hair.

Two weeks after discharge from hospital, she had lost about 75% of the hair on her head. Six weeks after discharge there was evidence of beginning regrowth of hair, and when the patient was last seen, 10 weeks after discharge, her head was covered with fine fuzzy hairs about ½-inch (1.25 cm.) in length.

DISCUSSION

Since Farber introduced the therapeutic use of aminopterin in leukæmias,[4] there have been several descriptions of intoxications in humans.[5-7]

Toxic effects are all typical of folic-acid deficiency and consist chiefly of lesions of the digestive tract and hæmatopoietic system. Lesions of the digestive tract include necrosis of buccal and intestinal mucosa in varying degrees of intensity. Following toxic doses, after an interval of from two days to several months, whitish necrotic areas may appear on hard and soft palate, uvula, buccal mucosa, gums or lips. Usually the lips become cracked and bleed, and occasionally they become infected. The stomal lesions usually heal in 3-14 days. The intestinal lesions may precede or follow the stomal ones. Due to intestinal ulceration, abdominal cramps, diarrhœa and bleeding may occur.

Involvement of the hæmatopoietic system leads to depression of bone marrow activity and may be characterized by leukopenia, thrombocytopenia and anæmia. The clinical features may include petechiæ, bleeding gums and fever. With discontinuation of the toxin and administration of transfusions, these symptoms are usually controlled.

Other toxic effects include sensitivity reactions in which macular rashes are a feature; these respond to antihistamines. Alopecia may develop, even after the drug has been stopped. The hair grows again. Sometimes there is an increased sensitivity to infection, leading to furunculosis.

It has been observed in rat liver slices[8] that synthetic folic acid is converted into folinic acid or "citrovorum factor", so-called because of its utilization for growth by *Leuconostoc citrovorum*. It is in the form of citrovorum factor that folic acid enters into nucleic acid metabolism.[9] The conversion of folic acid to citrovorum factor is prevented by aminopterin.[10] Also aminopterin appears in some way to interfere with the action of citrovorum factor.

From these observations one may conclude that folic acid might prevent toxic effects of aminopterin if given before the antagonist; but

that, after toxic effects have begun, citrovorum factor should be a much more effective antidote. Burchenal and Kingsley-Pillers[11] found that as little as 3 mg. daily intramuscularly of citrovorum factor can prevent the toxic effects of as much as 45-60 mg. daily of Methotrexate (4-amino-N^{10}-methylpteroylglutamic acid) over a three-week period. Schoenbach *et al.*[12] gave 40,000,000 units of synthetic citrovorum factor intramuscularly daily to two patients without discontinuing the antagonist, and yet the toxic effects were reversed. Such an effect was not obtained from 20,000 units daily.

In the present case, the dose of aminopterin (10-17 mg.) was certainly larger than that given to most of the patients in Thiersch's series and probably larger than that given to any of them. Toxic effects began on the third day. There is question whether the slow subsidence of symptoms was due to withdrawal of the drug or was accelerated by the administration of citrovorum factor. However, as the specific antidote, the citrovorum factor may have saved this patient's life and certainly may save the lives of any subsequent patients misguided enough to take an even larger dose of aminopterin for a similar purpose.

SUMMARY

A case is described of intoxication by aminopterin used as an abortifacient. The dose was an amount from 10-17 mg.

Toxic effects appeared three days after the first dose and included skin erythema, macular rash, stomatitis, laryngitis, and temporary loss of hair.

Citrovorum factor was administered and may have hastened recovery.

The authors wish to express their appreciation of the co-operation of Dr. L. H. Battersby, who referred this case to hospital.

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LYMPHANGIOSARCOMA IN LYMPHŒDEMA*

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SINCE STEWART AND TREVES[1] directed attention to lymphangiosarcoma developing in elephantiasis chirurgica, a small number of additional cases have been recorded.[2-7]

This report presents two further cases of lymphangiosarcoma developing in lymphœdema. In the first case the lymphœdema developed after mastectomy while in the second case it was apparently primary in type.

CASE 1.

E.L., a 62-year-old white woman, was admitted to St. Michael's Hospital on July 13, and died on November 1, 1954. On January 7, 1950, she had undergone left radical mastectomy for scirrhous carcinoma of the breast with lymph node metastases. Immediately after mastectomy she received radiation therapy to large anterior and posterior fields covering the supraclavicular and axillary regions. A total of 4000 roentgens was given to each of these two fields in a period of 28 days.

She had been well for three years postoperatively until November 1953, at which time an area of reddening appeared in the left antecubital fossa, associated with swelling of the arm, forearm, and hand. The area of reddening became larger and in the two months prior to admission, pain and marked discomfort of the arm developed.

Physical examination revealed a healed left radical mastectomy scar. The left arm was markedly swollen, warm and indurated from the dorsum of the hand to the axilla. The skin of the axilla was puckered and contracted. Large patchy areas of reddish discoloration were present over the upper arm, infraclavicular area and axilla. On the anterior aspect of the arm a surgical scar was present, adjacent to which there were several tense, purple blebs varying from 0.2 cm. to 1 cm. in diameter. They had smooth, shiny surfaces (Fig. 1). The clinical impression was that she had either interference with the venous or lymphatic return due to postradiation changes, or that the swelling of the arm was due to secondary carcinoma. On three occasions, scar, skin and subcutaneous tissue were removed by plastic procedures designed to establish new lymphatic channels. She withstood the operations well and her progress was satisfactory.

In early October she noticed dyspnœa on exertion which in a few days was also present at rest. Examination revealed tachycardia and evidence of left pleural effusion. Thoracocentesis on five occasions removed a total of 7000 c.c. of fluid which was negative for tumour cells on three examinations. Her course was rapidly downhill, her arm became gangrenous and she died on November 1.

Pathology

(a) Gross.—At autopsy there was extensive gangrene of the left upper arm, which was variegated brownish-black and grey. The skin over the forearm was brownish-grey with several small crusted ulcers. Large areas of purplish discoloration were present in the left axillary

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