

2. Anuria developing after second course of aminopyrine.

this and because the initial period of oliguria closely followed amphotericin B therapy she was again started on aminopyrine Oct 11; dosage was 0.3 gm (5 grains) four times daily. Again there was a drop in urinary output from 850 ml per 24 hours on Oct 11 to 405 ml on Oct 12 and 90 ml on Oct 13, with an eight-hour period of anuria on that day (Fig 2). Aminopyrine was discontinued on Oct 14. Following this last episode of anuria, the patient, whose condition had become progressively worse since admission, became weaker and continued to have a daily rise in BUN despite conservative supportive treatment for acute renal failure. She died on Oct 25. The BUN was 212 mg/100 ml, carbon dioxide, 16 mEq/liter; chloride, 94 mEq/liter; sodium, 133 mEq/liter; and the potassium, 6.8 mEq/liter. Autopsy was refused.

Comment

The occurrence of acute renal failure as a result of drug toxicity is an accepted phenomenon, and the literature on the subject is voluminous. This case presents features that make it highly probable that renal failure was precipitated by aminopyrine. The patient had normal renal function during her previous admissions. Although she did manifest renal damage following the brief course of amphotericin B, a known nephrotoxic agent, there was a dramatic decrease in kidney function coincident with aminopyrine administration. The course was that of a typical renal ischemic episode with partial recovery of renal function following the initial episode. The second episode was long after the amphotericin B treatment, and although the patient still had an elevated BUN there was again a dramatic decrease in renal function coincident with the aminopyrine ingestion. The patient never recovered from this last episode. There is a known element of individual hypersusceptibility in aminopyrine agranulocytosis, which apparently applies to its renal toxic effect as indicated by the low incidence of agranulocytosis and no instance of azotemia in previous reports. This report calls attention to another serious complication of aminopyrine therapy, emphasizing the need for caution in its use, particularly in patients with already inadequate renal function.

Drs. Ralph R. Tompsett and Albert D. Roberts, Jr., made helpful suggestions.

Generic and Trade Names of Drugs

Cyclophosphamide—*Cytotoxan*.
Mannitol—*Mannitol*.
Dexamethasone—*Decadron*, *Deronil*, *Dexameth*, *Gammacorten*, *Hexadrol*.
Methchlorothamine hydrochloride—*Mustargen Hydrochloride*.
Amphotericin B—*Fungizone*.
Sodium methicillin—*Dimocillin-RT*, *Staphcillin*.

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Peutz-Jeghers Syndrome Associated With Functioning Ovarian Tumor

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PEUTZ,¹ in 1921, reported the association of skin pigmentation and small bowel polyps in several members of a family. Jeghers² added two such patients to the literature in 1944 and, in 1949 along with McKusick and Katz,³ he established the syndrome as an entity which appears to be inherited as a mendelian dominant. Since that time additional cases have brought the reported number to somewhat over 100.⁴

An additional patient, a 4½-year-old girl with the rare syndrome of mucocutaneous pigmentation and gastrointestinal polyposis, is presented below because of the associated presence of a granulosa-theca cell tumor of the ovary with resultant precocious puberty. The interest aroused by the coincidence of these two rare disorders has been further stimulated by the isolated reports^{5,6} of two other cases of Peutz-Jeghers syndrome associated granulosa cell tumors.

Report of a Case

A 4½-year-old girl was admitted for evaluation because of a two year history of rapid growth and bilateral enlargement of the breasts. The child, whose birth weight was 4 lb 12 oz (2.14 kg), was the first born of presumed monozygotic twins following an uncomplicated 36 week gestation and normal delivery.

The neonatal period was uneventful. Both physical and mental development were normal up to the age of 2½ years. A snapshot taken at the age of 2½ years reveals definite breast buds in the patient that were not present

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in the twin. At the age of 2½ years the twin sister died elsewhere after a brief illness believed to be salicylate intoxication. When the patient was 2¾ years of age her mother noticed marked enlargement of the breasts and the development of scant pubic and axillary hair. In addition, she rapidly increased in stature going from a size 3 to a size 7 dress.

In May, 1962 (age 3 years), vaginal spotting was noted and this proceeded to heavier bleeding similar to menses. These episodes were said to be regular at 28 to 30 day intervals and to have lasted approximately four days. This more or less cyclical vaginal bleeding continued for six months, but thereafter and up to the present evaluation she has experienced only intermittent, irregular, and scanty spotting.

Family history reveals the father to be in good health and age 32. The mother, 22 years of age, has obvious dark brown pigmentation on the vermilion border of the lips. She gives no history referable to gastrointestinal or reproductive system symptoms. Two siblings, both females, aged 2½ years and 3 weeks, are in good health and neither demonstrate mucocutaneous pigmentation. The mother knows of no relative who has the characteristic pigmentation or any history of gastrointestinal symptomatology, including the deceased "identical" twin.

Physical examination revealed normal vital signs; her weight was 22.3 kg (49.06 lb) (95 percentile) and the height 119 cm (46.41 inches) (greater than 97 percentile). In general, she was large for her stated age, well nourished, and was obviously advanced in sexual development (Fig 1). The head was normocephalic, the ears were unremarkable, and the eyes brown in color. A sty was present on



1. A 4½-year-old girl with granulosa-theca cell tumor of one ovary. Note the marked breast development but only scant pubic hair.

the left lower eyelid. Prominent freckles were present over the bridge of the nose and there was distinct brown pigmentation of the vermilion border of the lips (Fig 2). In addition, there were small areas of brown pigmentation on the gingiva and the buccal mucose.

The thorax was normal. The breasts were symmetrical and of adult contour and size. The heart was normal in size and a soft grade 1/6 functional type murmur was audible at the apex. There was very scant axillary hair. The neurological examination, including electroencephalogram, was normal.

Abdominal examination was negative with no masses or tenderness noticed. Pelvic inspection revealed scant hair over the mons pubis. There was development of the labia minora and the clitoris. Rectal palpation suggested uterine enlargement and a palpably enlarged but normally shaped right ovary. Examination of the left adnexal region suggested the presence of a mass.

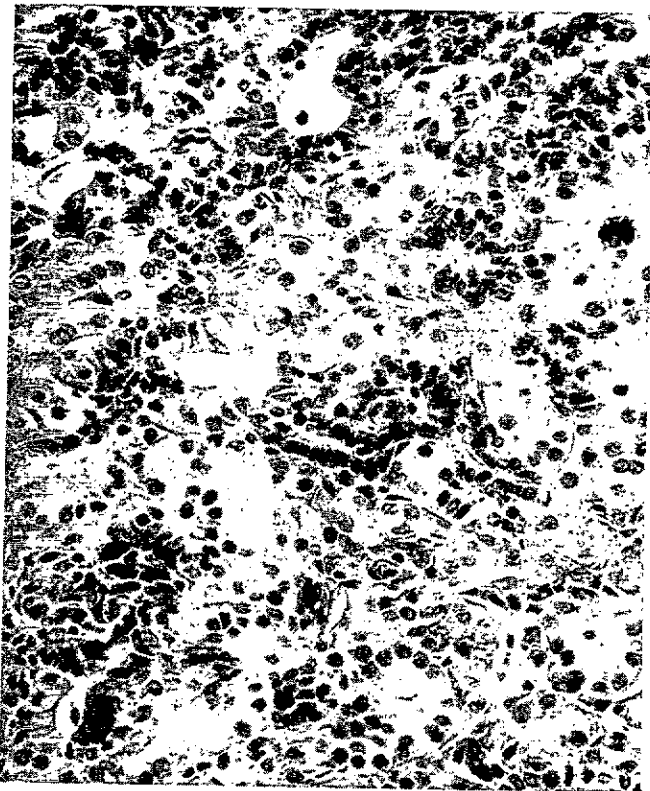
Routine hemogram, urinalysis, and serum electrolytes were normal. A 24 hour urinary output of 640 cc yielded a total estrogen of 9µg (estrone, + 2µg; estradiol, + 1 µg; estriol, + 6µg) (Brown method).^{7,8} Skull, thoracic, and



2. Photograph demonstrating the pigmentation of vermilion border of lips.

abdominal roentgenograms were normal. A bone age study revealed a skeletal maturation of 11 years. An intravenous pyelogram and barium enema were normal. An upper gastrointestinal barium study revealed two large filling defects in the distal third of the lesser curvature of the stomach. In addition, multiple rounded polypoid structures were outlined along the second and third portions of the duodenum.

Examination under anesthesia revealed a 4 cm left adnexal mass. A laparotomy was performed after an endometrial biopsy was obtained. The uterus was two to three times the expected size. The left ovary, enlarged to 4 cm in diameter and well encapsulated, was removed in its entirety. Frozen section revealed a granulosa-theca cell tumor which appeared benign. The right ovary was minimally enlarged for the expected at this age and was bivalved with no evidence of tumor. A bilobed gastric polyp, 3 cm in length, was removed via a gastrotomy incision. The entire gastrointestinal tract from the stomach to the rectum was palpated. The small bowel contained many polypoid masses, estimated to be 2 to 4 mm in diameter, extending from the duodenum to the ileocecal valve. None of these were removed. No lesions were palpated in the colon.



3. Photomicrograph of granulosa-theca cell tumor. (X380)

The postoperative course was uneventful except for scant vaginal bleeding which started some 24 hours after surgery and persisted for a total of 48 hours. A urinary estrogen level determined on the sixth postoperative day revealed a total estrogen of $4\mu\text{g}/24$ hours. A concomitant urinary pregnandiol level (Klopper⁹) was less than $0.1\text{ mg}/24$ hours and the follicle-stimulating hormone (FSH) level was less than 16 mouse uterine units per 24 hours. The child was discharged on the 12th day after her operation.

Pathological evaluation revealed hyperplastic, proliferative endometrium; a $4 \times 2 \times 3.5$ cm, 20 gm left ovarian tumor of the granulosa-theca cell type (Fig 3); and a bilobed gastric mucosal polyp which was benign.

Follow-up examinations at three weeks and three months were negative and revealed no complaints or further vaginal bleeding. There has been distinct reduction in the size of the breasts.

Comment

Sexual precocity secondary to a granulosa-theca cell tumor is in itself rare. Wilkins¹⁰ was able to find only 63 such reported cases. Granulosa-theca cell (feminizing mesenchymal) tumors constitute some 5% of all ovarian tumors. The great majority of these (60+%) are noted in the postmenopausal age group whereas 37% are in the reproductive group, and less than 2% are found in the prepubertal age group.¹¹

In the prepubertal group, small tumors have been in the minority and most have presented as readily palpable abdominal masses. This has contributed to a general impression that a granulosa cell tumor can always be palpated abdominally if it is the

cause of precocious puberty. This case adds to the number of exceptions to this generalization, making it evident that such a tumor may not be excluded by negative abdominal examination. Indeed, if there are no contraindications, every female presenting with sexual precocity should be examined under anesthesia.

Another frequently expressed clinical generalization is that periodic vaginal bleeding reflects only ovulatory cycles and therefore true (constitutional, idiopathic) sexual precocity, and that such bleeding rules out the anovular bleeding of a granulosa-theca cell tumor. Again the history of very regular, menstrual-like bleeding in this case adds an exception to such a generalization.

Dormandy,¹² in his review of the Peutz-Jeghers syndrome, made reference to two isolated case reports of associated granulosa cell tumor, both appearing in the reproductive age group.

The combination of the uncommon granulosa cell tumor and the rare syndrome of mucocutaneous pigmentation and gastrointestinal polyposis would appear to be more than a remarkable coincidence in view of the now reported three cases. In an additional patient with this syndrome, a Brenner tumor of one ovary and a dysgerminoma of the other ovary was reported.¹³

The strong possibility exists that granulosa-theca cell tumors, or other mesenchymomas of the ovary, comprise an addition to the Peutz-Jeghers syndrome and may represent a more complete expression of the hereditary abnormality than pigmentation and polyposis alone.

It is unfortunate that most of the reports of the Peutz-Jeghers syndrome do not mention the pelvic examination or the appearance of the ovaries when a laparotomy was performed. It is hoped that careful pelvic evaluation of such patients may clarify the possible position of ovarian tumors in this syndrome.

Summary

The third known case of Peutz-Jeghers syndrome associated with a granulosa-theca cell tumor of the ovary is apparently the first reported case associated with precocious puberty. The possibility is raised that such tumors or other ovarian tumors represent an addition to the syndrome in certain instances.

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Environmental Influence on Implantable Cardiac Pacemakers

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IMPLANTABLE CARDIAC PACEMAKERS are being used with increasing frequency in the management of patients with symptoms of a complete heart block. Although electromechanical control of heart rate would seem to demand a high level of both knowledge and professional concern regarding interactions between pacemakers and the environment, little information is available in scientific journals. We are, therefore, reporting preliminary observations of the behavior of two brands of pacemakers in several environments which may be encountered by patients.

Material and Methods

Three pacemakers have been used. Two were designed and made by one of us (R. W. S.) and are of the type used in 26 patients treated in this institution.^{1,2} One of these had the long lead wires intact, the other had them removed to ensure that any induction currents or alterations of function which were detected had originated within the pacemaker unit itself. The third pacemaker, a popular, commercially produced brand, was purchased from ordinary stock and studied with its lead wires intact.

All testing in the laboratory was performed by connecting the pacemaker output to an oscilloscope with an attached camera. Tests conducted away from the laboratory were performed in two ways. Qualitative tests of impulse regularity, rate, and

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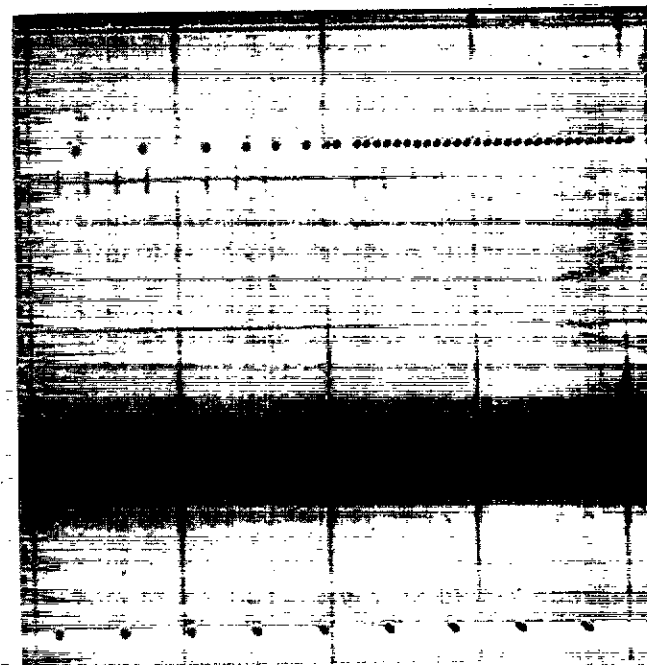
amplitude were made with the pacemaker leads touching the tongue of the investigator. The second method involved the use of a 900-watt, 115-volt, 60-cycle alternator, the oscilloscope and camera, the pacemakers on the end of a long stick, and an observer, all positioned on the tailgate of a station wagon. Each pacemaker was then placed into and systematically moved through the area being tested while the pacemaker output was monitored.

Results

The distributor of a 6-volt automobile electrical system produced acceleration of the pacemaker rate when the pacemaker was brought to within 6 cm of the distributor. An increase in the rate up to 450 impulses per minute occurred when any of the pacemakers was moved to within 1 cm of the distributor (Figure). Upon their withdrawal from the distributor field, however, a difference was noted between the two types of pacemakers; the locally made type produced no impulse for seven to ten seconds, while the commercially available pacemaker promptly resumed the original rate. The distributor of a 12-volt automobile electrical system produced similar alterations in pacemaker performance.

The coils of both automobiles produced occasional, sporadic, premature impulses without a fixed acceleration of rate in either type of pacemaker.

The spark plugs on a gasoline-powered lawnmower and the gasoline-powered alternator were tested. The spark plug of each was shown to alter pacemaker activity when the spark plug-pacemaker separation was less than 8 cm. As demonstrated with the distributor, a progressive acceleration of pace-



Left-to-right sweep of electron beam across oscilloscope face. Lower line shows normal pacemaker activity; upper tracing shows acceleration from 66 to 450 impulses per minute produced by proximity to automobile distributor.