They also proposed that alcohol consumption acted as a promoter of carcinoma of the larynx.

It is reasonable to suppose that multiple primary tumours will occur with increasing frequency as the survival rate for cancer continues to improve with advances in diagnostic and therapeutic techniques. In this patient, for example, a complete cure of her skin and laryngeal carcinomas was effected by radiotherapy.

Summary

The case history is described of a woman who died at the age of 71 of a squamous-cell carcinoma of the bronchus after the successful treatment of two other squamous-cell carcinomas, on the face and on a vocal cord, in the last 10 years of her life.

From a review of the literature evidence is presented that suggests there was a systematic predisposition to cancer in this patient.

We acknowledge with thanks the interest and advice of Sir Daniel Davies. The patient had also been under the care of Miss G. Barry, Miss P. Wade, and Mr. J. D. McLaggan, and we are grateful to them for permission to publish this account.

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REPORT OF TWO CASES OF PRECOCIOUS PUBERTY

BY

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Precocious puberty is uncommon enough to warrant reporting. Various authors draw the line of precocity at different ages, but all are agreed that the onset of menstruation below the age of 8 is precocious, and in the two cases reported below menstruation began at the age of 5 and 2 respectively.

Precocity may be of cerebral, adrenal, or gonadal origin. Only where the origin is cerebral does true puberty occur—that is, development of secondary sex characters is accompanied by spermatogenesis or ovulation. Where the cause is adrenal or gonadal the testes or ovaries remain infantile and non-functioning.

Sex interest is uncommon in precocious children, but fertilization is possible in those of cerebral origin; for example, the case reported by Escomel (1939) of the Peruvian girl, Lina Medina, who first menstruated at 8 months, and at 5 years 8 months gave birth to a 6½-lb. (2,950-g.) boy.

Sexual precocity is usually associated with (1) greater physical activity—for example, the child walks early; (2) slight mental retardation with aggressiveness and bad temper—mental precocity is rare; (3) advanced skeletal development, giving an increase in height and weight, and an advance in the bone age with early closing of

the epiphyses—therefore such children are tall in childhood, but short in adult life; (4) undisturbed dentition; and (5) a late menopause.

In "cerebral" precocity the stimulus, which may be functional or organic, is directly on the brain, and is associated with an increase in the pituitary gonadotrophins which stimulate spermatogenesis or ovulation. Where the cerebral precocity is functional or "constitutional," as described by Jolly (1955), the puberty is normal in every way, but occurs many years too early. The normal order of events is maintained—that is, breast development first, then pubic hair, menstruation, axillary hair, and often a white leucorrhoeal discharge some months before the first menstrual period. The cases here reported belong to this group, and it is the most common cause of precocious puberty in girls. Genetic factors may play a part, but there was no hereditary history in these cases. The organic causes of cerebral sexual precocity are due to stimulation of the posterior part of the hypothalamus by tumour, meningitis, or encephalitis, with an intact pituitary, as the eosinophil cells must be free to secrete an excess of gonadotrophins and so stimulate the gonads. Weinberger and Grant (1941) suggest that the lesion of the posterior hypothalamus removes the normal control or inhibitory force exerted over the pars distalis of the anterior lobe of the pituitary, which then releases excess gonadotrophins that stimulate the ovaries or testes to produce oestrin or androgen, which in turn produce the secondary sex characters.

Non-cerebral precocity may be due to (1) adrenal tumours or hyperplasia; these usually produce virilism; or (2) ovarian tumours, the commonest of which is the granulosa-cell tumour, which, however, is very rare in girls under 10. Where it occurs the bleedings are anovular and the other ovary remains infantile, as it is not stimulated by the pituitary, and there are no gonadotrophins present. The tumour is usually large and palpable by the time the genitalia and breasts are affected, and the urinary oestrogens are higher than the normal adult level of 40–600 I.U. Other rare ovarian tumours which occasionally produce precocity are teratomas and chorionepitheliomas.

The following cases fall into the group of functional or constitutional cerebral precocity, and their interest lies in the differential diagnosis and management. The management of such cases after diagnosis should be, in the words of Morse (1897), "complete abstinence of all therapeutic measures, but the psychological treatment is important." The mother should be given a full explanation, and warned of the possibility of pregnancy, and the girl should be encouraged to "think of herself not as different from others, but as capable of growing up faster than her friends" (Jolly, 1955).

Case 1

This child was born by spontaneous delivery at full term on October 3, 1947. Birth weight was 6.12 lb. (2,775 g.). She was breast-fed for four months, and first walked at 11 months. Breast development was first noted at age 3. Three elder sisters were normal in development. No genetic factor was present in the family.

She was first brought to the gynaecological clinic by her mother on July 13, 1953, at the age of 5½ years, having had five days' vaginal bleeding two weeks previously. There was no pain and the child felt well. On examination she was an intelligent co-operative 5-year-old girl, tall for her age. The breast development was that of a 12-year-old

girl. There was no abdominal abnormality. The external genitalia were large for her age. A slight growth of pubic hair was present. It was decided to examine her under anaesthesia to exclude granulosa-cell tumour.

On examination under anaesthesia on August 4 the uterus was 2½ in. (5.7 cm.), and a shred of endometrium was obtained which showed microscopically a normal oestrin-phase picture. No ovarian tumour was palpable. X-ray examination of the skull showed no enlargement of the pituitary fossa, and the 17-ketosteroids were 3.9 mg. a day, which is high for her chronological age of 5 years but normal for her physiological age of 12+ years. Urine analysis in the middle of the cycle showed no free or combined oestrogens at the level of 8 I.U. a day, which ex-

FIG. 1.—Case 1. Patient aged 10 years. First menstruated at 5 years.

FIG. 2.—Case 1. Elbow-joint, showing all epiphyses fused. Therefore bone age of 18+ years, but chronological age 10 years.

52 in.; 132 cm.) and her weight 75 lb. (34 kg.) (normal 65 lb.; 29.5 kg.). Her urinary gonadotrophins were 10 mouse units a day and her total oestrogens 30 I.U. a day. These results are within normal limits for a female within the reproductive era, which is this girl's physiological state, but are high for her chronological age of 10.

cluded a granulosa-cell tumour of the ovary. An intravenous pyelogram showed normal kidney function with no displacement or caliceal abnormality on either side to suggest adrenal enlargement. The bleeding was therefore presumed to be due to functional or "constitutional" precocious puberty. She was seen at regular three-monthly intervals. The bleeding recurred at monthly intervals, regular from the first period; each lasted six days, was free from pain, and did not upset her. Her mother and school teacher were most co-operative, and the child seemed to suffer no psychological upset. The secondary sex characters showed steady development as time progressed, as did her height and weight.

We still see the child at six-monthly intervals, and the periods have continued to be of the type 6/28 days, and painless. The secondary sex characters have not greatly changed in the past year, and at the age of 10 (Fig. 1) she seemed perfectly normal mentally and well adjusted psychologically. She has menstruated regularly for four and a half years. Her skeletal age was 18 or more, with complete fusion of the head of the radius, capitellum, and medial epicondyle in the elbow, and the foot showed the metatarsal and phalangeal epiphyses fused (Figs. 2 and 3). Her height was 54 in. (137 cm.) (normal

Case 2

A girl was admitted to hospital on October 21, 1957, menstruating at the age of 3 years and 1 month. A clear history was difficult to obtain, as her mother was an Italian who spoke poor English and the father had left his wife a year previously. The child had been delivered by

FIG. 3.—Left: Foot of normal child aged 10, showing metatarsal and phalangeal epiphyses. Right: Foot of Case 1, showing fusion of metatarsal and phalangeal epiphyses, and therefore a bone age of 18+.

caesarean section for disproportion, and her birth weight was 8 lb. 3 oz. (3,715 g.). Walking occurred at 11 months. Breast development was noted at about 18 months, and slight pubic hair soon afterwards. She had slight vaginal bleeding at 22 months. The child was said to be quick and to have a good memory. She played well with her own age group. There was no family history of precocity, and the child had had no illnesses and had never complained of headache or abdominal pain. She was inordinately fond of sweets.

On examination she was a pleasant little girl who gave the general appearance of a 6-year-old. Her height was 43 in. (109 cm.) (normal 36 in.; 91.5 cm.) and weight 53 lb. (24 kg.) (normal 32 lb.; 14 kg.). Her breast development (Fig. 4) was that of a 10-12-year-old, there was scanty pubic hair, and menstruation was fairly heavy. There was no palpable abdominal tumour.

On examination under anaesthesia on October 24 the uterus was 2½ in. (6.3 cm.) in length, and some scanty endometrium was obtained which showed normal endometrium with slight luteinization. The cervix dilated easily. There was no tumour of the ovaries palpable. Urine analysis showed a specific gravity of 1020; no glycosuria; no gonadotrophins at the level of 3 mouse units a day; total oestrogens 15 I.U. a day; 17-ketosteroids

FIG. 4.—Case 2, aged 3.

2.3 mg. a day; and 17-ketogenic steroids 7.6 mg. a day. These bio-assays are consistent with a diagnosis of functional precocious puberty. A feminizing tumour of the ovary would give higher oestrin levels, and the 17-ketogenic steroids and 17-ketosteroids, though high for this girl's chronological age, were approximately normal for her physiological age of

12 years. X-ray examination of the elbow showed epiphyseal development of a child of 10 years or over, with all epiphyses present and well formed (Fig. 5). The sella turcica was normal, with no erosion of the clinoid process.

FIG. 5.—Left: Radiograph of elbow (Case 2) at age 3, showing all epiphyses present and well formed—bone age therefore 10+ years. Right: Elbow of normal 3-year-old girl for comparison.

The mother was given a full explanation of the child's condition, and it was stressed that she must not be allowed to think of herself as being in any way abnormal, but just capable of growing up more quickly than other little girls of her age.

Summary

Two cases of constitutional cerebral precocious puberty are described, of girls aged 3 and 5 years. The clinical and biochemical investigations are described and emphasis is placed on the need for accurate diagnosis. In this group of precocious puberty there is no need for endocrine or surgical treatment, but there is a need for explanation and possible psychological treatment.

I thank Dr. W. G. Scott Harden, of the Cumberland Infirmary, for the x-ray films and Dr. J. Steven Faulds for photographs of them and of the children described, and also for his helpful advice. My thanks are also due to Dr. C. D. Paine and Dr. A. Jordan, of Sheffield, for undertaking the biochemical assays, and commenting on them.

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A note on the agricultural and horticultural use of lead arsenate, from the Ministry of Agriculture, Fisheries, and Food, states that this substance should present no hazard to consumers provided there is a minimum interval of six weeks between its last application to crops and harvesting. Nor should it be a hazard to operators provided they observe the following precautions: (1) *Dust and Paste Concentrates (Diluted and Used as a Spray)*.—Wear rubber gloves when using the concentrate and avoid breathing the dust concentrate. Avoid contact with spray mist. Spray across wind when possible. Do not spray in high wind. If the eyes are contaminated with concentrate wash out immediately and thoroughly. If the skin is contaminated with concentrate wash immediately and thoroughly with soap and water. Wash exposed parts of the body before eating, drinking, smoking, and after spraying. (2) *Dust Concentrate (Used Undiluted as a Dusting Powder)*.—Avoid breathing the dust. Wear rubber gloves and an efficient dust mask or other efficient protection for the nose and mouth when using the product. If the eyes or skin become contaminated treat as in (1) above, and again wash after spraying.

Medical Memoranda

Subacute Bacterial Endocarditis Treated with Oral Phenoxymethylpenicillin

While the successful treatment of a wide variety of infections with phenoxymethylpenicillin is now established (Hausmann and Zischinsky, 1953; Sinios, 1954), parenteral therapy is still preferred in such conditions as endocarditis, meningitis, syphilis, and peritonitis, until more data become available. It is therefore worth while reporting this case.

CASE REPORT

A girl of 15 who was known to have a congenital valvular lesion, recognized at the age of 1 year, was admitted to Stobhill General Hospital on May 1, 1956. She complained of malaise, fever, and cough with a mucoid sputum for three weeks; in addition, the sputum had been blood-stained for two days before admission. There was also a history of increasing dyspnoea on exertion.

In 1954 she had been a patient in Glasgow Western Infirmary with erythema nodosum, accompanied by pyrexia, tachycardia, and an increased erythrocyte sedimentation rate. She was assumed to have had a mild attack of rheumatic fever although there were no joint manifestations.

Examination and investigation established the diagnosis of aortic stenosis with subacute bacterial endocarditis due to a penicillin-sensitive strain of *Streptococcus viridans* which was cultured from the patient's blood on four occasions and was found to be highly sensitive to penicillin. The precise degree of sensitivity was not estimated.

Treatment with phenoxymethylpenicillin, 375 mg. (600,000 units) four-hourly, was begun on May 8. The temperature fell to normal on the 10th, but pyrexia recurred on the 21st. The dosage of penicillin was increased to 750 mg. (1,200,000) four-hourly, and the temperature settled on May 24 without recurrence. Treatment was terminated on June 30, a total of 280 mega units of phenoxymethylpenicillin having been given.

Clinical cure was indicated by sterile blood cultures, normal temperature, pulse, and E.S.R., which had all been elevated on admission, and by the disappearance of anaemia of normochromic type which had been present at the beginning of the antibiotic therapy.

The girl reported at the follow-up clinic on September 17, when she was noted to be keeping well and had begun office work. The haemoglobin and E.S.R. were normal and her weight was steady. On October 13 she was readmitted. There had been vomiting for one day and increasing dyspnoea during the previous two weeks. Her condition did not give rise to immediate alarm, but she suddenly collapsed and died about one hour after admission to the ward.

Necropsy.—The heart weighed 400 g. and the left ventricle was greatly hypertrophied. The aortic valve showed considerable distortion, the three cusps being greatly thickened and fused to form a membrane with a very narrow orifice. Numerous calcified nodules, due to healed subacute bacterial endocarditis, were present on the ventricular aspect of the valve cusps. On the mitral valve, along the cusp margins and chordae tendineae, there were slight nodular thickenings more suggestive of rheumatic endocarditis than of subacute bacterial type. Histological examination of the aortic cusps showed the nodules to be composed of fibrosis with patches of recent calcification: deep to the nodules and at their edges were areas of satisfactorily resolving inflammation with no evidence of recent exacerbation or of the presence of organisms. The cusps themselves and the bases of both mitral and aortic valves showed a scattered but denser fibrosis, consistent with valvular damage at the time of the earlier attack of rheumatic fever. The heart muscle also showed the patchy fibrosis of a previous rheumatic attack, but no Aschoff bodies or other recent lesions were found. No other organs showed naked-eye or histological abnormalities.