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The Amenorrhoeic Patient

by

Y. Salmon, MB, MRCOG.

KANDANG KERBAU HOSPITAL, SINGAPORE.

Amenorrhoea means "without menstruation," and is really a symptom, an important one at that, which brings many a worried mother, trailing her amenorrhoeic daughter to the Gynaecological clinic.

In this enlightened age, where girls marry young, their mothers are naturally anxious when menstruation has not occurred by the age of 16 years upwards. Furthermore, there is a superstition among some secondary amenorrhoeic patients that if they fail to menstruate, they are subject to various ailments, such as the blood going to the head to cause headaches *etc.*

Physiology

Menstruation is dependent on a chain of endocrine interrelationships and an intact genital tract. The details will not be mentioned here. A break in any of the links can cause Amenorrhoea.

Aetiolgy

Two sub-divisions of Amenorrhoea can be made:-

(1) **Physiological** Amenorrhoea—This occurs before puberty, during pregnancy and lactation and after the menopause.

(2) **Pathological** Amenorrhoea

(*a*) **Primary** —failure of the menstruation to appear initially. The Menarche usually occurs at about 13 years of age in Singapore, but it may be delayed, and it is best to postpone detailed investigations until after 18 years of age, except in special cases of amenorrhoea causing undue anxiety to the patient.

(*b*) **Secondary** —cessation of menstruation after the initial menarche.

Pathological Amenorrhoea

With the exception of congenital anomalies, which usually result in primary Amenorrhoea, the same conditions which cause primary can also cause secondary amenorrhoea. They are listed as follows:-

A. PSYCHO-SOMATIC & NEUROGENIC

1. Psychoses

(*a*) Anorexia Nervosa—psychological upset, where the patient veritably starves herself sometimes to death.

(*b*) Pseudocyesis—here a strong desire for pregnancy leads to Amenorrhoea and the other symptoms of pregnancy. Similarly, fear of pregnancy can also cause Amenorrhoea.

(*c*) Emotional shock *e.g.* broken romances, or strain of examinations.

(*d*) Environmental factor *e.g.* change of abode or work or travel.

The Amenorrhoea is the result of the higher centres of the cortex inhibiting the hypothalamus.

2. Organic Brain Disease (Hypothalamic Amenorrhoea).

(*a*) *Frolich's Syndrome* (Dystrophia adiposogenitalis)

(*b*) Laurence-Moon-Biedl Syndrome.

(*c*) Injuries and diseases in the region of the mid-brain.

B. ENDOCRINE

1. **Pituitary**—Disorders of the pituitary per se are rare, and there is usually other evidence of disturbance of pituitary function.

   (*a*) Necrosis—Sheehan's syndrome in which 95% of the anterior pituitary is destroyed, resulting in impairment of all its functions.

   The history of obstetric catastrophe together with investigation of the function of several endocrine glands helps to establish the diagnosis.

   I would like to point out especially that these patients are unable to meet stress, and death under Anaesthesia is common.

   (*b*) Dysfunction, *e.g.* Infantilism of the Lorain type. Sexual and physical development are retarded as the result of diminished growth and gonadotrophic hormone output.

   (*c*) Tumours *e.g.* Basophilic adenoma, resulting in Cushing's syndrome; Acidophilic adenoma resulting in Acromegaly; and chromophobe adenoma resulting in pituitary failure from pressure on the remaining normal pituitary.

2. **Ovaries**

   (*a*) **Dysfunction**—1. Follicular phase defects *e.g.* follicular cysts.

   2. Luteal phase defects *e.g.* luteal cysts.

   3. Hypohormonal *e.g.* surgical excision of the ovaries, destruction of ovaries by radium or X-rays.

   (*b*) **Tumours**— Granulosa cell tumour; arrhenoblastoma; Adrenal rest tumours.

   (*c*) **Polycystic ovaries** of the Stein-Leventhal syndrome resulting in Amenorrhoea, acne, sterility, hirsuites and obesity. Controversy exists about the etiology of this condition—is it primarily ovarian with partial failure of Steroid biosynthesis in the ovary, or is it hypothalamic, pituitary or adrenal?

3. **Thyroid**—Hyperthyroidism with exophthalmos can cause Amenorrhoea.

4. **Pancreas**—Amenorrhoea is often a manifestation of untreated severe Diabetes Mellitus.

5. **Adrenals**

   (*a*) Adrenogenital syndrome—Hyperplasia, adenoma or carcinoma of the adrenal cortex can cause the adrenogenital syndrome. This is characterised by amenorrhoea, hirsuitism, obesity, deepening of voice, enlargement of the clitoris, and atrophy of the genital organs. The congenital type results in the birth of a female pseudohermaphrodite with enlarged clitoris and often a common opening for the urethra and vagina (urogenital sinus) at the base of the phallus.

   (*b*) Addison's disease—Other manifestations of Adrenal insufficiency in addition to amenorrhoea are present.

C. UTERINE AMENORRHOEA

(*a*) Removed at operation;

(*b*) Grossly under developed;

(*c*) Irradiation effect;

(*d*) Infection—tuberculous endometritis;

(*e*) Heavy curettage in the presence of post-abortal infection (Jeffcoate).

(*f*) Refractory uterus—Developmental error of the vascular apparatus?

D. CONGENITAL DEFECTS

(*a*) Imperforate Hymen, leading to Cryptomenorrhoea;

(*b*) Absent or non-canalised vagina;

(*c*) Non-canalised cervix—Occasionally, acquired atresia of the cervix may result from excessive electrocauterisation.

(*d*) Malformed or absent uterus

(*e*) Gonadal Dysgenesis (Turner's Syndrome)· This is characterized by primary amenorrhoea, poorly developed breasts and genitalia, scanty or absent pubic and axillary hair. There may be webbing of the neck, cubitus valgus, coarctation of the aorta; the patients are usually short, but may be of average height, or even tall. The patients may be chromatin, positive or negative. The chromosomal number may be 45 instead of 46 and the chromosomal sex pattern XO. Occasionally, however, mosaic patterns such as XO/XX occur.

(*f*) Testicular Feminising Syndrome— The "women" with this Syndrome are some of the most attractive, but genetically they are males. Many a husband would be incredulous, if told that his wife was really a man. The rudimentary abdominal gonads are testicular tissue. Chromosomal pattern is XY.

E. NUTRITIONAL

(*a*) Malnutrition and serious ill-health durring childhood.

(*b*) Starvation in the adult, or overstrict dieting results in amenorrhoea.

(*c*) Over-eating, on the other hand, can lead to obesity and amenorrhoea. Nature abhors the extremes; the moral is, therefore, to steer the middle course and keep everybody happy.

F. CHRONIC DISEASE

(*a*) Acute illness leads to a short period of amenorrhoea.

(*b*) Chronic illness leads to prolonged suppression of menstruation, *e.g.* Pulmonary Tuberculosis, Nephritis. Can the amenorrhoea in these cases be the result of emotional stress rather than cachexia? Chronic alcocholism may also depress gonadal function.

Investigation

A. HISTORY

This is the first and important step, and details should be obtained of the personal and family history. What was the previous menstrual history, and are there any symptoms of pregnancy? Are there any associated symptoms, *e.g.* cyclical lower abdominal pain in cases of cryptomenorrhoea; weight gain, headaches, visual disturbances or hursuitism; or menopausal symptoms?

B. PHYSICAL EXAMINATION

The height, weight and general build of the patient are noted, as are also axilliary and pubic hair. Any evidence of virilism is looked for—note also enlargement of the clitoris in such cases. Signs of systemic disorder *e.g.* Hyperthyroidism are also noted. Development of the breasts, and especially the nipples, and other secondary sex characters is assessed. These are dependant on Oestrogen production, and if normal, may point to acyclical ovarian function or end organ failure (uterine cause or cryptomenorrhoea); if poorly developed, may point to ovarian failure or anterior pituitary deficiency.

Finally some congenital anomalies like the imperforate hymen and the absent vagina are easily detected.

(C) DIAGNOSTIC PROCEDURES

This is a detailed list, but not all the tests need be done in each case.

Routine	Special		Indications
1. X-ray Exam.			
(*a*) Chest		-	P.T.B.
(*b*) Skull (Sella turcica)		-	Pituitary tumour
	(*a*) I.V.P.	-	Adrenal tumour
		-	Congenital anomaly of genital tract.
	(*b*) Aortogram	-	Adrenal tumour
2. Haematology.			
(*a*) Hb. R.B.C.		-	Anaemia
(*b*) W.B.C. & Diff.	(*a*) B.S.R.	-	Infection
	(*b*) Eosinophilic count	-	Adrenal dysfunction
3. Blood Chemistry.			
(*a*) Serum electrolytes		-	Adrenal dysfunction
(*b*) Fasting blood Sugar	(*a*) G.T.T.	-	Diabetes Mellitus
(*c*) Serum Cholesterol		-	Thyroid dysfunction
4. Urine.			
(*a*) Sugar		-	Diabetes Mellitus
	(*a*) Toad Test	-	Pregnancy
5. Assays.			
(*a*) Urinary 17 keto-Steroids & 17 Ketogenic Steroids		-	Adrenal dysfunction
(*b*) Urinary Oestrogen		-	Follicular Phase defect
(*c*) Urinary Pregnanediol		-	Luteal phase defect
(*d*) Gonadotrophins		-	Pituitary defect
6. Special Tests.			
(*a*) BMR., I^{131} uptake or protein bound serum Iodine.		-	Hyperthyroidism
(*b*) E.U.A. and Endometrial biopsy/D & C		-	Genital tract pathology
(*c*) Culdoscopy		-	Small ovarian tumours & cysts. (Stein-Leventhal Syndrome)
(*d*) Vaginal cytology		-	Hypoestrogenic states
(*e*) Nuclear Sexing		}	Sex aberrations
(*f*) Chromosome Counts			
(*g*) Therapeutic test with Oestrogens.			

A word of caution must be voiced about these special tests and assays. They are, after all, isolated tests and do not give the complete picture of day-to-day variations. However, taken in conjunction with clinical findings, they give useful information.

Now I would like to analyse, along the lines outlined, a few cases of Amenorrhoea, that I have had the privilege of investigating at the Kandang Kerbau Hospital. There were 17 cases of Primary and 20 cases of Secondary Amenorrhoea.

Primary Amenorrhoea

The ages of the patients ranged from 15 to 36 years:-

There was no family history of similar incidence; some gave a history of past illness.

Comparison of the heights showed that 10 patients (59%) were 5' and below. This is not as outstanding as by Western standards, because our "normal" women are about 5' 2" in height. The tallest patient in this series was 5' 6".

FIG. I

Age (yrs.)	15-17	18-20	21-23	24-26	27-29	30-32	33+
Number	4	2	5	4	1	—	1

FIG. II

17 KETOSTEROID ESTIMATION (in mgm.)						
	1—2.9	3—4.9	5—6.9	7—8.9	9—10.9	11—12.9
PRIMARY	8	3	3	—	—	—
SECONDARY	4	4	4	—	2	1

17 HYDROXYCORTICOSTEROID ESTIMATION (in mgm.)						
	up to 4.9	5+	9+	13+	17+	21+	25+
PRIMARY	3	3	2	—	1	—	1
SECONDARY	4	2	2	3	—	—	1

Figure II shows the 17 ketosteroid and 17 Hydroxycorticosteroid estimation in these patients. Eleven cases had low levels below 5 mgm in 24 hours. Could there be an associated adrenal hypofunction as well?

The Nuclear sexing of these patients was female (Chromatin positive) and the chromosome count normal (46).

Fig.III shows the possible causes of these cases of Primary Amenorrhoea. In the group showing deficient Oestrogenic function, it is not possible to determine whether the fault lies primarily in the ovary or is secondary to anterior pituitary hypofunction, because urinary gonadotrophin and Oestrogen estimation cannot be done here at present.

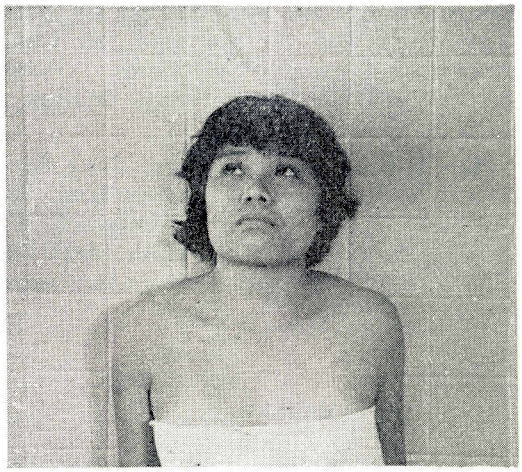
FIG. III

Cause	Nos.
Congenital cervical stenosis	1
Absent vagina	4
? Pituitary Adenoma (? Ovarian dysgenesis)	1
Delayed menarche	1
Ovarian hypofunction (? Pituitary ? Primary Ovarian)	9
Incomplete investigations—defaulted	1

The case of ? Pituitary Adenoma ? Ovarian dysgenesis (Figs.IV & V) is still under investigation. She is aged 25 yrs. 4 '10" tall, shows poor Oestrogen production, but the nuclear sexing is female and the chromosome count is 46. The sella turcica on X-ray appears rather widened, but there are no localising symptoms or signs.

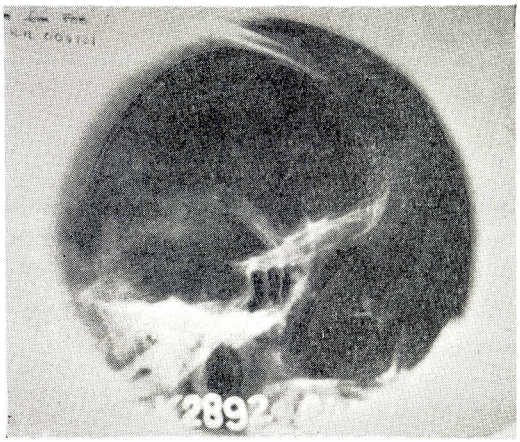
Of the cases with deficient oestrogen production, 5 showed physical and genital under-development and may be pituitary in origin. One girl, especially, was a Pituitary dwarf (Fig. VI; she was too shy to undress). She is aged 21 years, but has the mentality and appearance of a child of about 8 years. She is 4′ 10″ tall, and weighs 70½ lbs. The urinary 17 Ketosteroid estimation was 1.2 mgm. and 17 Hydroxcorticosteroid 2.8 mgm./24 hours, and B.M.R.—39%. The Chromosome count was 46, with a normal female karyotype (46 ××), shown in Fig. VII. She is on treatment with Corticosteroids and Thyroid Extract.

FIG. IV



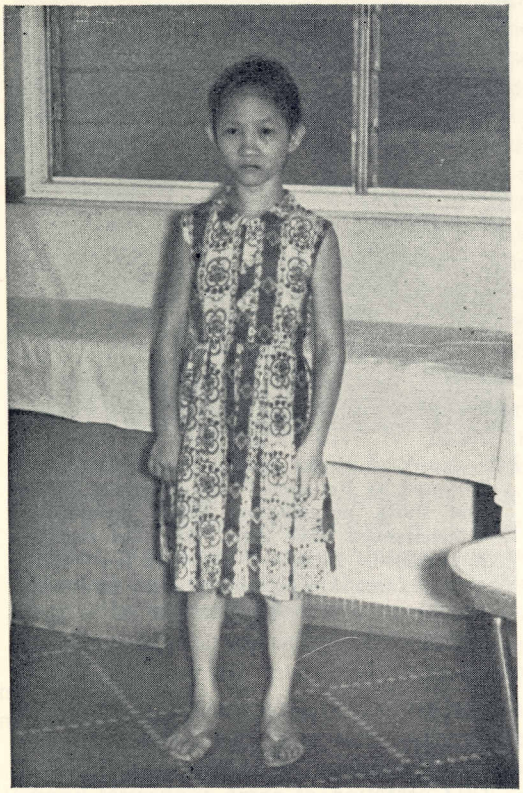
Note webbing of neck.

FIG. V



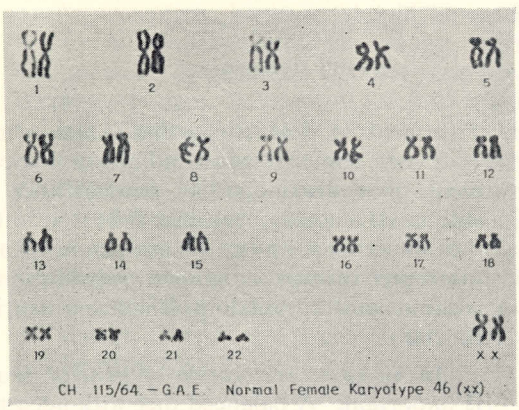
Note wide sella turcica.

FIG. VI



A case of Pituitary Dwarf.

FIG. VII



Karyotype of patient in Fig. 6.

Secondary Amenorrhoea.

Of the 20 cases of Secondary Amenorrhoea 8 cases had urinary 17 Ketosteroid levels below 5 mgm. per 24 hours, and one 17 Hydroxcorticosteroid estimation was above 15 mgm. Their ages ranged from 16 to 37 years. The possible causes are shown in the following figures:-

FIG. VIII

Cause	Nos.
Genital Tuberculosis	2
Psychological causes	3
Obesity	3
Sheehan's Syndrome	2
Severe respiratory infection	1
? Stein-Leventhal Syndrome	1
Unknown ? Pituitary ? Ovarian	3

The psychological causes included patients, who were taking examinations, or who had undertaken uncongenial work, and social cases.

The two patients with Sheehan's Syndrome had typical histories of severe PPH with the last delivery 5 & 9 years ago. The latter (Fig. X) collapsed after a general Anaesthetic for a D & C; We were priviledged to have the diagnosis in her case confirmed by Professor Sheehan himself during his visit here. The former patient, (Fig, IX) aged 35 years, showed a urinary 17 ketosteroid level of 1.1 mgm. and 17 hydroxycorticosteroid level of 0.3 mgm. per 24 hours. The Basal Metabolic Rate was—36%. Dilatation and curettage under local Anaesthesia showed hyperinvolution of the uterus, and no curettings were obtained. This patient also had a severe respiratory infection, which was treated before the investigations were done.

Treatment

Treatment is largely dependant on the cause of the Amenorrhoea.

1. **Specific Medical treatment** will be indicated in Pulmonary Tuberculosis, Diabetes Mellitus, etc.
2. **Specific Surgical Treatment** will be necessary in:-
   (*a*) Adrenal tumours.
   (*b*) Arrhenoblastoma of Ovary.

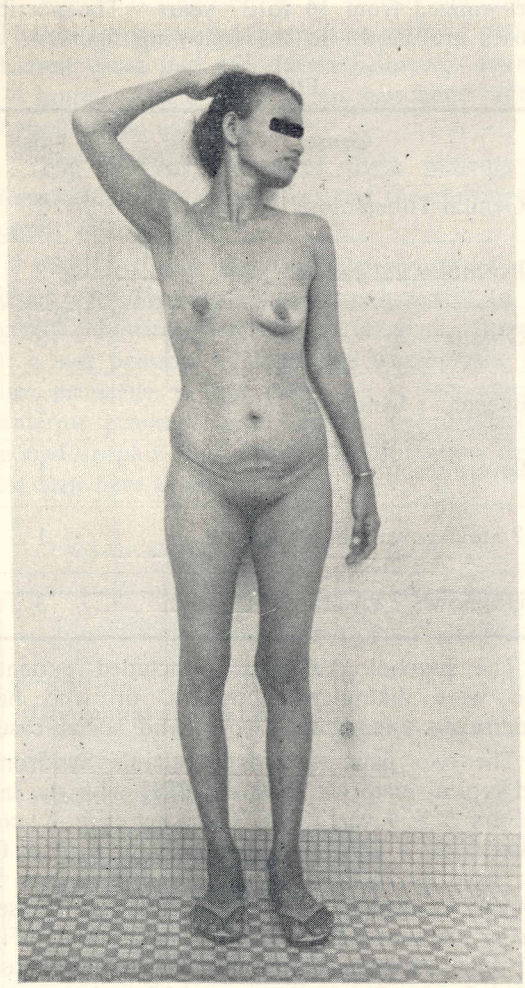


FIG. IX Last delivery 5 yrs. ago, followed by severe P.P.H. Amenorrhoea since then. Aged 35 yrs. Note atrophy of breast tissue and absent axilliary and public hair.

(*c*) Wedge resection of the ovaries in the Stein-Leventhal syndrome. Recently, Jeffcoate, (1963) on a basis of 29 out of 43 cases treated conservatively, states that conservative treatment gives as good results as does ovarian wedge resection and that any beneficial effect of surgery is due to the stress of the operation acting via the pituitary or hypothalamus to correct an underlying error of gonadotrophic or adreno-corticotrophic control of the ovaries. So ovarian resection should not be resorted to as a first line

FIG. X Aged 31 yrs. Last delivery 9 years ago, followed by Retained Placenta, Severe P.P.H., and shock necessitating blood transfusion. Amenorrhoea since then. Pale and puffy in appearance. Increased pigmentation of left side of face; skin coarse and dry. Atrophy of secondary sex organs with absent axilliary and scanty public hair.

of treatment and certainly not until an analysis of the hormone disturbance has been completed.

(*d*) Correction of some congenital anomalies *e.g.*:-

- imperforate hymen
- non-canalised or absent vagina
- cervical stenosis.

3. **Treatment of Endocrinopathic Amenorrhoea**

Every clinician must admit that treatment of endocrinopathic amenorrhoea is still unsatisfactory, because only too often the underlying cause is not known, and oestrogen therapy is at best substitutional, without any stimulating effect on ovarian function.

In all cases *restoration of general health* is important. A balanced diet with adequate amount of proteins, vitamins and iron, sufficient sleep, leisure and exercise and avoidance of any stress are equally necessary. Obese patients should reduce, and this alone may be sufficient. In very thin patients, diet may be supplemented by Nortestosterone compounds, for their nit-

rogen retaining properties (MacGregor). Another point of emphasis is that, not all the patients in this endocrinopathic group call for treatment. To be sure, these patients are anxious to have normal menstruation, and in many cases, it is necessary for their own peace of mind, if not for their confidence in the doctor, to attempt a therapeutic test of uterine reactivity with *intermittent cyclical oestrogen therapy*. Progesterone therapy is more expensive and not more advantageous than oestrogens alone. Stilboestrol 1 mgm. or Ethinyl Oestradiol 0.05 mgm b.d. for 20 days (smaller doses may often suffice) and repeated after an interval of 7 days. Nortestosterone compounds may be added in the second half of the simulated menstrual cycle, if indicated. Three courses are given, and, if the uterus is responsive, withdrawal haemorrhage should occur during one or more of the intervals. If there is no gross endocrine abnormality, this cyclical stimulation of the pituitary is sufficient to restore the normal menstrual cycle again.

If the uterus is refractory or the ovaries do not respond, *e.g.* in an early menopause, then it is unwise to continue artificial stimulation with hormones. The position should be explained to the patient, and she should be reassured.

An exception, however, should be made in hypo-gonadal states in young girls, *e.g.* gonadal dysgenesis. Cyclical oestrogen therapy—1 mgm. Stilboestrol (or 0.05 mgm. Ethinyl Oestradiol) daily for 20 days is continued for several years to promote development of secondary sex characteristics and feminine contours in these patients. It is reported by Escamilla 1956, that Oestrogens strongly stimulate epiphyseal closure and thus cause ultimate shortness of stature—therefore, larger doses should not be employed.

Gonadotrophin therapy may have a place in selected cases. One pattern (Pahlsson; Rydberg) is to give 1500 *i.u.* of Equine Gonadotrophin intramuscularly daily for 5 days followed by three doses of 1500 *i.u.* of Chorionic Gonadotrophin intravenously or intramuscularly every other day; this course is repeated twice on the same dates of successive months. Recently, Crooke, Edwards et al(1963), induced menstruation and even pregnancy after treatment with follicle-stimulating hormone from human pituitary gland in conjunction with chorionic gonadotrophin. This method sounds quite promising in patients with low excretion of urinary gonadotrophins. A word of caution—too prolonged treatment with gonadotrophins may lead to cystic enlargement of the ovaries.

Irradiation of Pituitary & Ovaries

Low dosage to the Pituitary Gland (150 r) and ovaries (100-150 r) as empirical treatment has been advocated, but this is dangerous genetically, and is not widely favoured.

Thyroid is of value in clear cases of Hypothyroidism. Small doses may also help in cases of long standing Amenorrhoea through a stimulating effect on general metabolism.

Neostigmine 1 mgm. 1ml daily for 3 days is often followed by menstruation within one week in cases where menstruation is merely suspended.

Psychotherapy helps in cases of psychogenic Amenorrhoea. We are all familiar with the patient whose periods return once her mental stresses are resolved, and once she has passed her examinations!

Cases with manifestations of *other Endocrine Abnormalities* as well as amenorrhoea, *e.g.* Sheehan's syndrome, Pituitary infantilism and Frolich's syndrome require specialised treatment and will not be touched upon here.

In conclusion, I would like to stress a few points in treatment of amenorrhoea.

1. In young girls, first exclude cryptomenorrhoea, then do not start endocrine therapy too early.

2. Carefully select your cases for endocrine treatment, after first excluding organic lesions; then do not continue treatment too long without appraisal of the effects. Remember that the primary purpose for endocrine therapy of amenorrhoea aims at restoring reproductive function, the only exception being the syndrome of gonadal dysgenesis.

3. Secondary Amenorrhoea is more likely to respond to treatment than primary amenorrhoea.

4. The shorter the duration of amenorrhoea, the more likely is treatment to succeed. In fact, in cases of secondary amenorrhoea of 1-2 years duration, Jeffcoate states that the results of psychotherapy, oestrogen, progesterone, thyroid, irradiation and indeed no treatment at all are identical—60% cure rate.

The results of treatment of the writer's cases were more encouraging in the Secondary than in the Primary amenorrhoeic group.

In the *Primary* group, 7 were given the Oestrogen stimulation test with temporary effect, 2 discontinued treatment as they felt nauseated, 1 (the pituitary dwarf) is having specialised medical treatment and 2 defaulted. Of the congenital anomalies, 1 (cervical stenosis) had a laparotomy with establishment of patency and return of menstruation; the first case of absent or non-canalised vagina refused operation, the second (a married woman of 36 yrs.) was able to have satisfactory marital relationship, and required no further treatment, the third case had an artificial vagina created, while the fourth case is awaiting operation.

In the *Secondary* amenorrhoeic group, 3 cases responded to general measures & reassurance (one passed her examination & was rewarded by the return of her periods, & another changed her work with good effect). Six responded to oestrogen stimulation, while 2 are being treated for genital tuberculosis. Four cases are still under investigation, while a further four defaulted. The patient, with Sheehan's syndrome, who collapsed after a D & C, is being treated with Cortisone and 1-Thyroxine for the last year. Although there has been no return of her menses, and the uterus is half its normal size, her general state of well-being and health has been improved.

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