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ETIOLOGICAL FACTORS IN SECONDARY AMENORRHOEA\*

A Study of 100 Cases

by

KUMUD DESHPANDE, M.D., F.C.P.S., D.G.O., D.A.

P. N. SHAH, M.D., F.C.P.S.

and

B. N. PURANDARE, M.D., F.R.C.S., F.C.P.S., F.I.C.S., F.R.C.O.G.

*Introduction*

Secondary amenorrhoea forms one of the commonest problems of menstrual irregularities which confronts a gynaecologist in his everyday practice. It is hardly necessary to emphasise that amenorrhoea is a symptom-complex which reflects some derangement in the hypothalamus-pituitary-ovarian-uterine axis. In the majority of cases the cause is not apparent, and hence every attempt should be made to elucidate the underlying cause or causes before deciding on any line of treatment.

*\*From the Department of Obstetrics & Gynaecology, K. E. M. Hospital and the Department of Endocrinology, Indian Cancer Research Centre, Parel, Bombay 12.*

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The purpose of this paper is to present various etiological factors encountered in our series of cases and to demonstrate the harm that can be done to the patients when short cuts, to produce withdrawal bleeding with hormones, are taken without proper diagnosis.

What exactly constitutes secondary amenorrhoea is not well defined. The minimum duration of cessation of menstruation, after the previous regular period, that is to be considered as secondary amenorrhoea varies according to different authors. Menzer-Benaron (1962) reckon it on the interval of 8 weeks or more in between the menses. Shah (1955), Jones and Nally (1959) apply the term to a woman who complains of amenorrhoea of at least 3 months' duration. Oastler and Sutherland (1953), while

considering 3 months' amenorrhoea as of minimum duration, demarcate the upper age limit of 40 years. We have in this study considered the minimum duration of at least 12 weeks of cessation of menstruation, in a woman otherwise getting regular periods, before accepting her as a case of secondary amenorrhoea for investigations.

#### *Material and Methods*

In all 104 cases of secondary amenorrhoea were referred to the Endocrinology Clinic of the K. E. M. Hospital, Bombay, over a period of two years. Three of these cases (one having pregnancy and two with lactation amenorrhoea) have been exclud-

ketosteroids, gonadotropins from urine or radioiodine studies, were done as and when necessary.

#### *Observations and Discussion*

The patients belonged to the age range of 15 to 36 years. Eighty-three of these patients were married while 17 patients were single. Thirty-six of the 83 married patients had primary involuntary infertility and 9 patients had secondary sterility. On further analysis, since duration of amenorrhoea could be correlated with the final outcome of the treatment given (Table 1), our patients were categorised according to the duration of amenorrhoea, before presenting to the Endocrinology Clinic.

TABLE I  
*Duration of Amenorrhoea in 100 Patients*

3-11 months	1-3 yrs.	4-6 yrs.	7-9 yrs.	10-12 yrs.	13-15 yrs.	Not known	Total
27	33	22	4	8	3	3	100

ed from this series for obvious reasons. Since one more of these patients was not interested in getting investigated, the observations in this presentation are based on the study of 100 cases in all.

Detailed history-taking and a careful general and pelvic examination were made in each case. Serial vaginal smears were taken in patients at weekly intervals for at least 4 to 6 weeks and stained with Papanicolaou's method (1954). Endometrial biopsy with Novak's curette was possible only in 42 cases. Routine investigations like blood, urine, stool, x-ray of the skull and other special investigations like estimation of 17-

Again, it seems that unlike the symptom of excessive uterine bleeding, amenorrhoea does not bother our women sufficiently to consult a physician. This is substantiated by the fact that 77 of our 100 patients had not sought treatment even though the amenorrhoea varied from 4 months to 14 years. This inordinate delay on the part of the patient for not consulting a physician appears to be due to the fact that, besides the lack of hospital facilities outside the cities, our patients were rather reluctant to submit themselves to gynaecological examination.

Thus in a situation such as amenorrhoea, because of patient-delay, there

may exist a long latent period between the onset of amenorrhoea and its definitive diagnosis. The remaining 33 patients, had various combinations of hormonal treatment for amenorrhoea for sometime; of these, 8 patients did not have withdrawal bleeding in spite of taking large doses of estrogens or estrogens and progesterone.

There is no doubt that relevant past history in some patients does help to reveal the etiological pathology. In our series, 24 of the 100 cases appeared to show some correlation between the appearance of amenorrhoea and some past event (Table II). For example, 7 of these patients had their amenorrhoea preceded by post-partum haemorrhage and in 4 more patients amenorrhoea followed the surgical procedure of dilatation and curettage. In another group of 7

features and yet withdrawal hormonal therapy was given to these cases for several years by general practitioners and gynaecologists. All these 3 patients had milky discharge from the breast on examination. In another 3 patients, having apparently normal features, such discharge from the breasts was elicited and one of these had definite evidence of pituitary tumour on skull x-ray, one was suspected of having pituitary tumour and in the remaining one the skull x-ray revealed a normal pituitary fossa. None of these cases, harbouring pituitary tumour, however, had any pressure symptoms. It becomes therefore imperative that breasts should be examined in all patients having amenorrhoea and at least a skull x-ray picture should be taken whenever amenorrhoea is accompanied with breast secretion.

TABLE II  
*Significant Past History in 100 Patients*

Post-partum haemorrhage	Previous curettage	Contact or suffered from tuberculosis	Psychological stress	Non-significant	Total
7	4	7	6	76	100

patients, previous history of tuberculosis, or of having close contact with relatives suffering from proved tuberculosis, was obtained. And finally 6 patients gave history of acute psychological stress before becoming amenorrhoeic. It is necessary to emphasize here that rich harvest may be yielded from detailed history-taking and/or proper medical examination. For example, on general examination 5 patients had severe under-nutrition and debility, 4 were obese. Further, 3 of our patients revealed acromegalic

On bimanual examination whenever the uterus appeared to be unduly small, the length of the cavity was measured. Fourteen patients had uterus smaller than 1.5 inches, which is beyond the range of normal variation. The small size of the uterus in these cases could be due to some derangement in the hormonal production of pituitary-ovarian axis or as a sequela of infection.

Table III shows the distribution of our patients on the basis of their ovarian hormonal status as studied

from the changes in their vaginal smears. In our hands, the vaginal smear method is by far the most practical approach to assess the ovarian function. Ideally speaking multiple daily vaginal smears should be taken for studying the ovarian hormonal status but this schedule was not practicable in our cases, and therefore smears were taken at weekly intervals. The assessment of estrogenic activity from the changes in vaginal cytology occurring in women having cycles of 24-39 days duration, is described "Eutrophic". The abnormal smears are described in the order of decreasing insufficiency in circulating oestrogens.

TABLE III  
*Vaginal Smear Patterns in  
82 Patients*

Smear type	No. of patients	Inference
Eutrophic	24	Good oestrogen effect
Hypotrophic with cyclic changes	4	Minimal oestrogen deficiency
Hypotrophic	45	Moderate oestrogen deficiency
Atrophic	9	Marked oestrogen deficiency

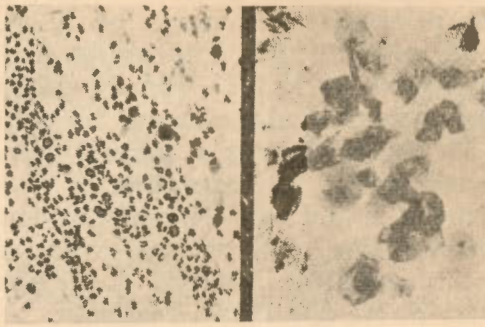
From Table III it is evident that the changes in the vaginal smears in our patients appear to reflect every grade of ovarian activity — from total insufficiency to normal activity. Thus 58 of 82 patients had smears revealing different degrees of hypooestrinism while the remaining 24 patients revealed normal oestrogenic activity. Of these 24 cases, showing normal oestrogenic activity, in only 10 we could study the endometrium and in 5 of these 10 patients we found histo-

logical evidence of tuberculous lesion in the endometrium. It is, therefore, very likely that a few more such cases might have come to light if endometrial biopsies were done in all these 24 cases.

Again, the marked to moderate oestrogen deficiency smears not necessarily indicate the primary defect in the ovarian hormone production. For example, of the total 13 out of 54 cases showing such smears, 2 had hypothalamic amenorrhoea, 10 had pituitary insufficiency due either to tumour or Sheehan's disease and finally the remaining one patient was harbouring an arrhenoblastoma. This last patient revealed smears depicting marked oestrogen deficiency which was probably due to peripheral neutralisation of normal amounts of oestrogen by androgens, since the gonadotropin in this case was present within the normal range. Furthermore, after removal of the tumour, vaginal smear picture changed to one showing good oestrogenic activity and menstruation appeared within one month of the treatment. This patient, three months after operation, became pregnant and delivered a normal baby at full-term. Figure 1 shows the changes in the vaginal cytology before and after treatment in this patient. The detailed report of this patient will be published elsewhere (Shah *et al.*, 1965).

#### *Endometrial Studies*

Endometrial biopsy was not attempted in cases where the vaginal smear consistently revealed marked oestrogen deficiency or where hypothalamic-pituitary lesions were sus-



Pre-treatment

Post-treatment

Fig. 1: Showing changes in vaginal cytology in a case of arrhenoblastoma.

pected. Such a group was constituted by 27 patients. In another 31 patients endometrial biopsy was not possible as they did not attend the Clinic for investigations other than serial vaginal smears. In the remaining 42 patients, in all 78 attempts were made to get the endometrium for histological study. In 36 patients, however, at the first attempt, either no material was obtained or was inadequate for diagnosis. In these cases further attempts were made to get endometrium after hormonal therapy.

Table IV summarises our results on histological examination of the endo-

TABLE IV

Type of endometrium	Number of patients
Atrophic endometrium ..	1
Inactive endometrium ..	1
Proliferative endometrium ..	3 (3)
Secretory endometrium ..	— (6)
Tuberculous endometrium ..	1 (6)
Complete destruction ..	36 (21)
Total .. ..	42

Figures in the brackets are after hormonal therapy.

metrium in 42 patients. The figures in brackets represent repeated biopsies after hormonal therapy. It is evident that endometrial tissue was adequate for histological studies in only 6 out of 42 patients and of these 6 tissues one revealed histological evidence of tuberculous infection.

In the remaining 36 patients, a second attempt to obtain endometrial tissue was made after administration of hormones for 3-4 weeks. Twenty-one of these 36 patients did not yield any material even after administration of hormones, while 6 of the 15 patients responding to hormones revealed histological evidence of tuberculous lesion. In other words, the pathology in these 6 cases, but for the hormonal treatment, would have remained undetected. Thus administration of hormones in patients showing scant tissue can therefore be used profitably to cause growth of the endometrium, facilitating the histological diagnosis of tuberculous endometritis if present.

When the clinical history was carefully reviewed in our patients having tuberculous endometritis it was realised that inadequate investigation only caused further delay in the specific treatment till finally an irreversible process terminated in amenorrhoea. The common practice of inducing withdrawal bleeding with hormonal therapy may be an easy way of getting out of the difficulty, yet its use by gynaecologists, speaking generally, should be highly deprecated. It may well be repeated that unless we study the endometrium in all cases with menstrual irregularities, we are bound to miss this infection in its latent stage. This is tragic,

for the application of specific treatment at the early stage of the disease will make all the difference to many a young woman.

Endometrial biopsy, though a useful investigation, yields very little information on the pathological lesions, especially when amenorrhoea of long duration is associated with scanty endometrial tissue. Difficulty in obtaining the endometrial material arises whenever the uterus is small or when it is almost completely destroyed or atrophied for some reasons. In such situations because of the inavailability of other investigations at present, one is left in the dark. From Table IV it will be evident that such a situation arose very frequently in our series of cases (in 21 of the 42 patients).

Special investigations like measurement of 17-ketosteroids or total gonadotropins from a 24-hour collection of urine is only occasionally helpful for diagnosis. In our series, 17-ketosteroids were indicated only in 2 amenorrhoeic patients having, in addition to amenorrhoea, hirsutism and/or virilisation and, in both, the values were within normal range. Gonadotropins on the other hand when present at elevated levels invariably suggest primary ovarian defect and when absent or present at low levels indicate functional or organic lesions of the hypothalamic-pituitary axis. These total gonadotropin assays were done at the Department of Endocrinology, Indian Cancer Research Centre. The extraction procedure for the gonadotropins was followed as suggested by Butt (1958) and finally the extracts were assayed biologically on Swiss strain

immature female mice according to the procedure laid down by Klinefelter *et al.* (1943). The results were expressed in M.U.U. per 24 hours. The normal values range between 6-30 m.u.u. during a normal menstrual cycle. An excretion of 4 or below 4 m.u.u. per 24 hours is considered low and values over 50 m.u.u. as high (Kothari L. S. and Shah P. N., unpublished data).

TABLE V

Etiology	No. of patients	
Hypothalamic .. ..	6	
Pituitary	19	
(a) Tumour .. ..		6
(b) Sheehan's .. ..		7
Ovarian		
(a) Arrhenoblastoma ..	1	
(b) Precocious menopause ..	1	
Uterine	11	
(a) Amenorrhoea traumatic ..		4
(b) Infection of endometrium ..	7	
Systemic		
(a) Obesity .. ..	4	
(b) Under-nutrition .. ..	5	
(c) Diabetes .. ..	1	
Unknown .. ..	27	
Total .. ..	69	

The etiological factors in 69 cases who could be investigated properly are shown in Table V. It is clear from this table that the causative factors are varied and a large number of amenorrhoeic women (in 27 of 69 women of our series) have no manifestations of any demonstrable

organic disease on physical examination or on routine laboratory investigations.

The causative factors commonly concern three functional levels, viz. (i) hypothalamus or anterior pituitary, (ii) ovary and (iii) uterus. The pivotal role of the hypothalamus in control of ovarian function is no longer debatable, and, therefore, any disturbance in the hypothalamus appears to affect the gonadotropin secretion by interruption in the release of neurohumoral secretion and in turn brings about hypo-ovarianism. In the absence of systemic diseases causing amenorrhoea, investigation of the patient's endocrine system should be carried out. As aforementioned, the dependable investigation for assessing the ovarian function concerns the study of changes in vaginal cytology. Biological assay to determine the level of total gonadotropins in a 24-hour urine sample, on the other hand, seems to be of limited value. In most of the cases having hypothalamic or anterior pituitary dysfunction there was as expected, disappearance of gonadotropins from the urine, or presence of gonadotropins at low level. Trolle *et al.*, (1961) have reported the most striking finding that 79% of 76 cases of secondary amenorrhoea had normal levels of gonadotropins. The majority of these cases of "normogonadotropic" secondary amenorrhoea belonged to the unknown etiology. It can be hoped that refinements in techniques of measurement of gonadotropins from both quantitative and qualitative aspects will, in future, find many more subtle abnormalities in the so-called "normogonadotropic"

group of secondary amenorrhoea.

We would now briefly comment on our cases pertaining to these etiological factors.

#### *Hypothalamic Amenorrhoea*

The recent literature is replete with 'hypothalamic' or psychogenic amenorrhoea.

According to Johnstone (1959) the type of menstrual disorder, that results, depends on the intensity of psychological stress. Sudden overwhelming and concentrated anxiety is likely to produce amenorrhoea while persistent milder attenuated stress is likely to result in menorrhagia and rhythm disturbances.

Reifenstein (1946) described four criteria for establishing the diagnosis of hypothalamic amenorrhoea. According to him there should be:

1. History of psychic trauma just preceding the amenorrhoea.
2. Normal amount of follicular stimulating hormone in the urine.
3. Absence of estrogenic effect on the pelvic tissues.
4. Ability of the endometrium to respond to estrogen withdrawal.

In 6 out of our 100 patients there was history of definite acute psychological stress. One of these patients, an unmarried woman of 32 years, while facing added domestic and financial worries, suddenly became amenorrhoeic. She was the only earning member of the family. She had amenorrhoea of 9 months; her vaginal smears showed changes suggestive of moderate oestrogen deficiency. Endometrial biopsy, however, was done to exclude tuberculous infection. She was told about the etiological factor of her trouble and

was advised general line of treatment for three months, which took care of her other vague symptoms but till date no spontaneous period has occurred.

Another patient of 39 years of age having 9 months of amenorrhoea had a highly strung, extremely nervous personality. She was only lately married. Because of her age, especially when she was eager to have children, she was scared to death lest she may go in for menopause.

In the third patient, in addition to her poverty, the acute stressful situation was created by the admission of her husband to the hospital because of psychological breakdown.

In the fourth patient, aged 17 years, having amenorrhoea of 6 months, the symptom could be traced back to the time when she attempted to commit suicide after a quarrel with her teacher. She was also fed up with the environment at home. On psychic therapy, she is having regular periods.

The fifth patient, aged 23 years, had amenorrhoea for 6 years. She was having regular period from the age of 14 till 16½ when amenorrhoea set in. Amenorrhoea in her case coincided with the incident when her husband took a sudden decision to divorce her without any valid reason.

The last patient had a queer history. Her amenorrhoea started with an incident during one of the religious festivals when she accidentally broke some part of the statue of a deity. She was scared that God would punish her for this act. She had atrophic vaginal smears and endometrial material could not be obtain-

ed on repeated biopsies. She did not co-operate in taking either psychic or hormone therapy.

It is important to stress that in every case one does not succeed in securing a history of psychological stress. While major catastrophies are easily related by the patients, the additive effects of minor psychological trauma cannot easily be evaluated unless efforts are made persistently by the physician throughout the period of observation and investigation.

The results of the therapy in hypothalamic amenorrhoea are equally disappointing. Goldzieher and Goldzieher (1952) have presented two cases of hormone resistant psychogenic amenorrhoea with studies of oestrogen metabolism. In both instances there was excessively rapid destruction of the administered steroid. Jones and Nally (1959) also found that their psychogenic group, amongst 350 cases of secondary amenorrhoea, was remarkably resistant to the therapeutic measures including psychiatric care and sometimes gonadotropin therapy.

#### *Pituitary Causes*

(i) *Tumours.* Of the six patients complaining of amenorrhoea, 3 had definite acromegalic features. Skull x-ray picture showed ballooning of the pituitary fossa with erosion of the floor or dorsum sellae in 4 patients, while in one case the x-ray appearance was suspicious. This latter patient showed no such changes in a similar skull x-ray picture taken one year ago. In the remaining patient the skull x-ray was normal. Both these latter patients are under



observation. One of the four patients, having definite tumour, was quite taken aback to hear that she had a pituitary tumour. One should, therefore, always keep in mind that in patients having pituitary tumours the only presenting complaint may be amenorrhoea for which she would consult a gynaecologist. Amenorrhoea in such cases is due to secondary hypo-ovarianism. In the series reported by Youngusband *et al.*, (1952) amenorrhoea was present in 51% of their cases having pituitary tumour.

The duration of amenorrhoea in our patients varied from 10 months to 5 years. One of these patients was on cyclic therapy for 2 years, while another was receiving symptomatic treatment for headache for more than 2½ years. It may sound ridiculous but both these patients had clinical features of acromegaly.

As for the results, it is very essential that early diagnosis should be made in cases of pituitary tumour, for by the time a symptom like amenorrhoea of long standing develops, the treatment is far from satisfactory as the pituitary gland is almost destroyed by the tumour. The suspicion of pituitary tumour could be strengthened in presence of discharge from the breast. Examination of the breasts therefore should be routinely done in all gynaecological patients.

(ii) *Sheehan's Syndrome*. Contrary to general opinion Sheehan (1954) has shown that this is not an uncommon condition. In our series 4 patients could be categorised under Sheehan's Syndrome. All these patients gave history of postpartum

haemorrhage and absence of lactation during last delivery. According to Sheehan (1939) obstetric history is absolutely characteristic when it is obtained. Vice versa if the delivery can be proved to have been normal the patient's symptoms, however severe they be, cannot be ascribed to postpartum ischemic necrosis. In addition to these, three more patients, although they gave history of postpartum haemorrhage in their last delivery and absence of lactation and amenorrhoea following this episode, did not report for further investigations. We have therefore included these cases under Sheehan's Syndrome. Besides routine investigations, Metopyron test and radioactive uptake of Iodine studies done in these patients revealed gross destruction of the pituitary function since ACTH production was also impaired (Shah and Kothari — Unpublished data).

#### *Ovarian Causes*

The incidence of arrhenoblastoma is quite rare and not all such tumours produce symptoms (Novak and Woodruff, 1962). Our patient harbouring arrhenoblastoma was of 28 years of age and besides amenorrhoea of 2 years, had hirsutism and enlarged clitoris. Repeated measurement of 17-ketosteroids revealed the values within normal range. This confirms the consensus that measurement of 17-ketosteroids, generally speaking, is not of much help in pinpointing the diagnosis (Graber *et al.*, 1961).

#### *Precocious Menopause*

The average age of natural menopause in Indian women is not available but is believed to be 45 years.

Menopause sets in when the ovary is exhausted of all its endowed ova. One of the patients, aged 30 years, having amenorrhoea of 2 years was in menopause, as we could demonstrate presence of gonadotropins at high level in her 24 hour urine. As the facilities for gonadotropin estimation are not available at this hospital, only a few selected patients were subjected to this investigation. Since precocious menopause is not a very rare condition, estimation of total gonadotropins in the rest of the patients might have revealed this condition in a greater number of cases. Trolle *et al.*, (1961) found precocious menopause in 11% of his 76 cases of secondary amenorrhoea; the youngest case reported in the literature, however, was of 16 years (Kettel and Bradbury, 1964).

#### *Uterine Causes*

Four patients gave history of amenorrhoea following the surgical procedure of dilatation and curettage. This procedure in none of these cases was carried out on puerperal or post-abortal uterus. In one patient it was done for menorrhagia. In the remaining 3 patients curettage was done for diagnostic purposes. In one of these 3 patients there were only two scanty periods following curettage. Vigorous curettage of the uterus not only removed the superficial, but also the basal layer of the endometrium, from which regeneration of the whole endometrium occurs.

#### *Infection of Endometrium*

Seven patients, out of 42, in whom endometrium could be studied, showed tuberculous granuloma. Of these,

3 patients aged 16, 20 and 25 years were unmarried. We agree with Shah *et al.*, (1961) that every effort should be made to diagnose this condition as early as possible in these young patients even to save their menstrual function for psychological reasons. In such cases there is a clear indication for curettage under general anaesthesia, all other considerations apart. On the other hand it may sound ridiculous but five of the 7 cases were treated by others with hormone preparations to bring about withdrawal bleeding without diagnostic curettage. The duration of amenorrhoea varied from 2 to 12 years. In view of the above findings, suspicion of tuberculous infection was aroused whenever the patient was found to be healthy in other respects and the vaginal smears revealed eutrophic changes. In such cases serial vaginal smears have revealed cyclic changes depicting good oestrogenic and progestational effect (Shah, 1955).

As already mentioned 21 of the 36 patients did not have any endometrial tissue even after hormonal stimulation, administered to exclude tuberculous lesion. When presented with such a situation many a time one is left with a feeling of defeatism in the absence of any other method to exclude this possibility. Not infrequently when one finds such young women who have otherwise no future as far as childbearing or spontaneously occurring menstruation is concerned, one seriously thinks of giving a therapeutic trial with antituberculous drugs for a short period to start with. One such patient of 2½ years' amenorrhoea, having inadequate endo-

metrium for diagnosis and gritty uterine walls but still responding to hormones in producing withdrawal bleeding, was advised streptomycin and P.A.S. for 3 months. Surprisingly, after 10 injections of streptomycin this patient reported with the first spontaneous period after 2 years of amenorrhoea. This patient is under close follow up. According to some authors (Jedberg, 1950; Stallworthy, 1952), amenorrhoea is a rare symptom associated with tuberculous endometritis while Malkani (1962) has reported the incidence of 40.8% in her series of 186 patients of tuberculous endometritis. The varying incidence of amenorrhoea in tuberculous endometritis, as reported by different authors, may be dependent upon the time, when the patient presents herself. Thus higher incidence of amenorrhoea is expected in patients who present at an advanced stage of the disease, when almost all the endometrium is destroyed.

#### *Systemic Causes*

(i) Undernutrition most probably affects the menstrual cycle through hypothalamic-pituitary-ovarian axis. Nutritional deficiency particularly the absence of proteins over a period of time may inhibit gonadotropin production. The vaginal smears were hypotrophic in all the 5 patients of our study. On general lines of treatment, 2 patients started spontaneous menstruation and are having menstrual periods at regular intervals during the last one year of follow-up.

One certainly envisages the possibility of interlocking etiological factors in one and the same patient. For example, one of these patients,

aged 19 years, having amenorrhoea of 4 years did not produce any endometrial material for diagnosis even after increasing dosage of hormones; the uterine wall in this patient was gritty. It is quite possible that total destruction of the endometrium in this particular case had taken place because of some infection, probably tuberculosis, but the pathology remains undetected because of paucity of endometrial material.

#### (ii) *Obesity*

Four patients were extremely obese, their weight ranging from 165 to 210 lbs. The obesity was of alimentary type and specific endocrinopathy could be excluded from the history as well as physical examination. X-ray of the skull was non-contributory. The vaginal smears in all these cases revealed changes suggestive of moderate oestrogen deficiency. One of these four patients, after weight reduction of 15 lbs., has started spontaneous menstrual cycle and is having regular periods for the last 6 months. Oastler and Sutherland (1953), however, have reported greater incidence of obesity (29 out of 149 cases) in their patients complaining of secondary amenorrhoea, and have also reported success in some of their cases after weight reduction.

#### (iii) *Diabetes Mellitus*

There was one patient who, in addition to diabetes mellitus, had 5 months of amenorrhoea. She was 30 years old. Brennan *et al.*, (1956) have reported widespread destruction of the pituitary with a frequency of 1:50 in diabetics versus 1:550 in con-

trols from their findings in 7326 routine autopsies. Necrosis of the pituitary is due to the small infarcts resulting from tiny thrombi from the vessels supplying the pituitary.

Generally speaking the outcome of the treatment in secondary amenorrhoea is not very encouraging. Out of 69 patients that were followed, only 12 patients had re-established their spontaneous menstrual cycles. One of the reasons for the poor outcome in our cases may be that our patients had, comparatively, amenorrhoea of long duration before serious attempts were made to search the etiological pathology. From the present series it becomes evident that all the patients who started spontaneous menstruation belonged to the groups having amenorrhoea of less than 3 years' duration. Besides duration of amenorrhoea, the prognosis in each patient would depend upon the nature of the etiological pathology, how early the etiological factor was detected and how good is the treatment available at present for the pathological lesion found.

#### Summary

(1) The study comprises our observations on 100 consecutive cases of secondary amenorrhoea and discusses the difficulties encountered in the basic investigations to ascertain etiological factors.

(2) Of the 69 patients adequately investigated, hypothalamic or pituitary factors could be incriminated in 15 patients; systemic causes again acting through the hypothalamic-pituitary system were present in another 10 patients, while 11 of the re-

maining 44 patients revealed uterine causes contributing to the development of amenorrhoea. In 27 of 69 patients, however, the etiological factor remained undetected.

(3) The underlying pathological lesions such as pituitary tumour and tuberculous endometritis may remain undetected unless one anticipates and makes a thorough search for them.

(4) The harm that could be done to the patient by inadvertent hormonal treatment without diagnosing the etiology of amenorrhoea is emphasised.

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