In so far as major endocrine disorders, particularly those of hyperfunction, are frequently familial and genetically determined, and in so far as many major endocrine disorders have their representation, but with less intensity, in accepted normality, observations in regard to the association of major endocrine disorders with characteristic behaviour patterns are relevant to a consideration of the varieties of normal behaviour pattern among normal individuals.

Classifications of physical build, as used by anthropologists, bear some relationship to classifications of endocrine constitution, and the evidence put forward suggests an endocrine basis for two of the anthropological groups, the muscular mesomorphs and the adipose endomorphs, thus giving further support to the previous two conclusions.

I qualify my conclusions by an unqualified admission of the importance of non-endocrine factors in determining behaviour patterns, and even more so in the case of the psychoneuroses and psychoses, the majority of the latter of which are not due to endocrine disorders.

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The hospital waiting-list for cases of tuberculosis in Northern Ireland virtually disappeared in 1956, according to the eleventh Annual Report of the Northern Ireland Tuberculosis Authority. In consequence, when the Waringfield Chest Hospital becomes available for the reception of patients, the chest hospitals at Armagh and Downpatrick will be used for other types of cases. The number of people given B.C.G. vaccination was 32,669. The number of patients examined by the mass radiography service was 124,459; of 10,622 people referred by general practitioners in Belfast, 438 were diagnosed tuberculous.

ENDOCRINE ACTIVITY IN PSYCHIATRIC PATIENTS WITH MENSTRUAL DISORDERS

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Though psychiatric literature is full of references to the relationship of mental illness and disorders of the sexual and reproductive systems, few studies have been carried out of gonadal activity in mental disorders. This is partly due to the great difficulties encountered in its proper assessment. The methods available are laborious and time-consuming. This applies both to bioassays and to chemical methods, especially serial investigations.

The need for such studies arises, firstly, because of the high incidence of menstrual abnormality in mental illness (Hause, 1923; Allen and Henry, 1933; Strachan and Skottowe, 1933; Ripley and Papanicolaou, 1942); secondly, because psychological changes are observed during the cycle and certain periodic syndromes and events occur at specific times during the cycle (Cooke, 1945; Reifenstein, 1946; Kroger and Freed, 1951; Mackinnon and Mackinnon, 1956); and, thirdly, because of the complexity of the psycho-physiological processes which produce normal and abnormal cycles (Kroger and Freed, 1951).

The Experiment

An experiment was designed to obtain information primarily with regard to gonadal activity in psychiatric patients with menstrual disorders. Information was also obtained with regard to gonadotrophic, thyroid, and adrenal activity.

Material.—Patients were chosen from amongst the in-patient population of the hospital. They suffered from: (1) amenorrhoea (below age 45); (2) irregular periods; (3) menstrual disturbances (above age 45); (4) puerperal amenorrhoea. The only other factor affecting the choice of patients was the willingness to show sufficient co-operation in the collection of biological specimens—for example, urine and vaginal smears.

Definitions.—Arey (1939) has summarized the results of 10 different investigations and has found for the length of the cycle a mean of 28 days, with a standard variation of 4.92. This was adopted as a measure of the normal cycle. Any variation of more than twice the standard deviation each way but less than twice the normal cycle was defined as an irregular cycle. Amenorrhoea was taken to be present when a full cycle had been missed—that is, twice the length of a cycle.

Methods Used for Hormonal Estimations.—(*a*) Gonadal activity was assessed by the vaginal-smear method (de Allende and Orias, 1950; Pundel, 1952; Wachtel, 1954). Smears can be repeated over a long period of time, and the information obtained from such a procedure is fairly extensive. Oestrogenic activity can be measured quantitatively by the cornification index count, and indications of ovulation and pro-

gesteronic activity are also available. Some information about pituitary activity is implied in the fact that the pituitary must be active if gonadal activity is present, whilst the reverse is not true. Smears were made in duplicate and a count of cornified cells was done on both smears. (*b*) Thyroid activity was assessed by the radioactive iodine urinary excretion method (Fraser *et al.*, 1953). (*c*) Follicular stimulating hormone (F.S.H.) was estimated by the Gorbman (1945) ultrafiltration method. (*d*) 17-Ketosteroids were estimated by the method recommended by the Medical Research Council (1951).

Information Sought.—(1) *Gonads:* Serial examinations of vaginal cytology were carried on for detecting (*a*) fluctuations in the cornification index; (*b*) presence of ovulation; (*c*) signs of progesterone activity; and (*d*) other characteristics such as general appearance of smears, signs of atrophy, presence of basal cells, leucocytes, etc. (2) The daily morning temperature taken by mouth was recorded in all cases. (3) Estimations of thyroid activity, 17-ketosteroids, and urinary gonadotrophin were done to investigate (*a*) the marked deviations from the normal; and (*b*) if within normal limits, whether the values obtained tended towards the upper or lower end of the scale.

Gonadal Activity

The 67 patients investigated for their vaginal cytology have been grouped according to menstrual status (Table I) and according to diagnosis (Table II).

TABLE I

Menstrual Status	No. of Cases
Secondary amenorrhoea (below age 45)	22
Amenorrhoea (puerperal)	20
Secondary amenorrhoea and irregular bleeding (above age 45)	8
Irregular bleeding (below age 45)	8
Regular bleeding	9

TABLE II

Diagnosis	No. of Cases	Diagnosis	No. of Cases
Anorexia nervosa	6	Schizophrenia	8
Anxiety hysteria	7	Temporal lobe epilepsy	3
Reactive depression	10	Climacteric	8
Manic-depressive	5	Puerperal psychoses	20

Table III shows the length of time during which gonadal activity was studied and the frequency with which smears were taken.

TABLE III.—*Duration of Study of Gonadal Activity*

No. of Cases	No. of Days	Frequency of Smears
20	30	Daily
16	60	,,
5	90	,,
2	120	,,
2	150	,,
1	360	,,
1	540	,,
20	60–120	Every 3rd day approx.

Vaginal Smears Findings (see Charts 1–18 on Figs. 1–4)

Secondary Amenorrhoea (Below Age 45).—(*a*) In all cases there was absence of ovulation and absence of clearly defined progesterone activity. (*b*) There were marked differences from patient to patient with regard to oestrogenic activity as reflected in the cornification index (C.I.). The only patients in whom low levels persisted (1–10%) unchanged for any length of time were those suffering from anorexia nervosa. But even these patients after a time showed variations in the C.I., especially when some improvement in the mental and physical states took place. In all other patients a varying degree of oestrogenic activity was present (Figs. 5 and 6). The common feature was the slow and delayed character of the rise in the C.I., the failure to

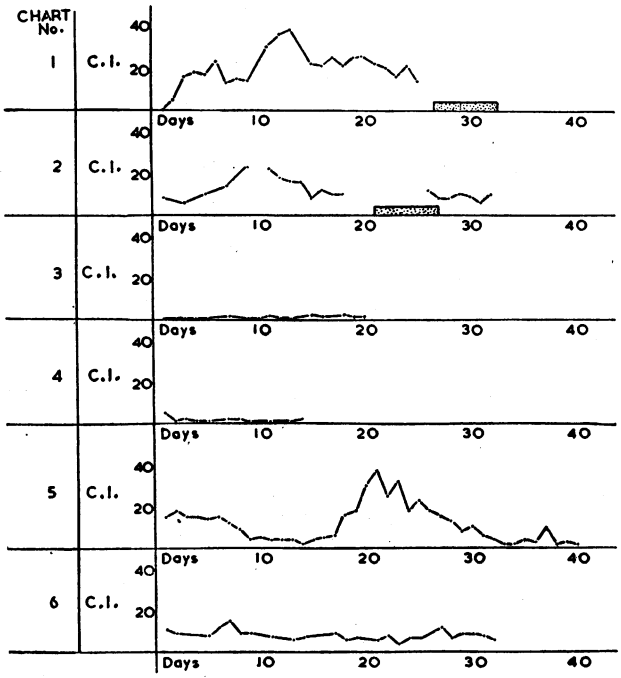

FIG. 1.—Cornification indices: Charts 1–6 (see text). Legends to Charts 1–18 appear on pp. 849–50.

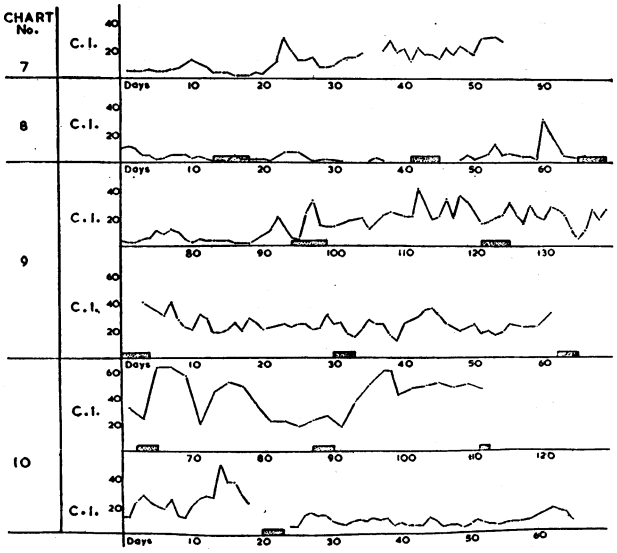

FIG. 2.—C.I.: Charts 7–10 (see text).

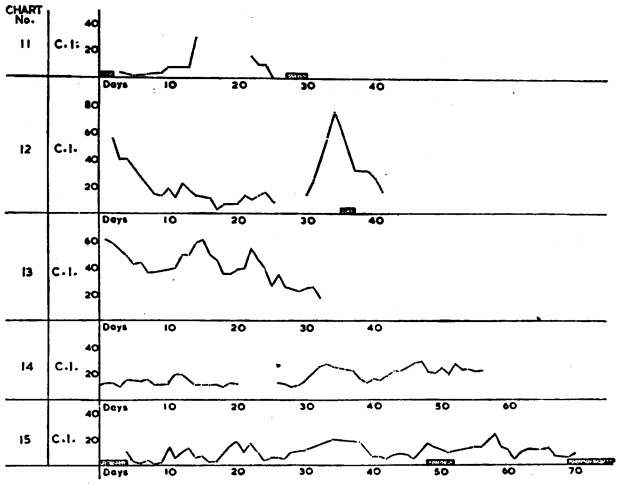

FIG. 3.—C.I.: Charts 11–15 (see text).

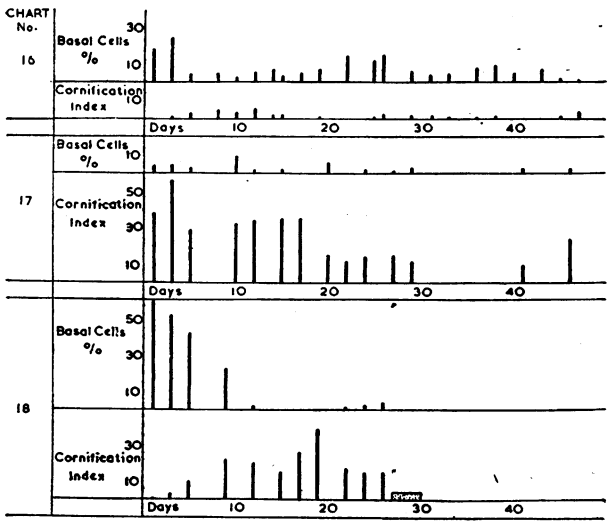

FIG. 4.—C.I. and percentage of basal cells in three cases (see text).

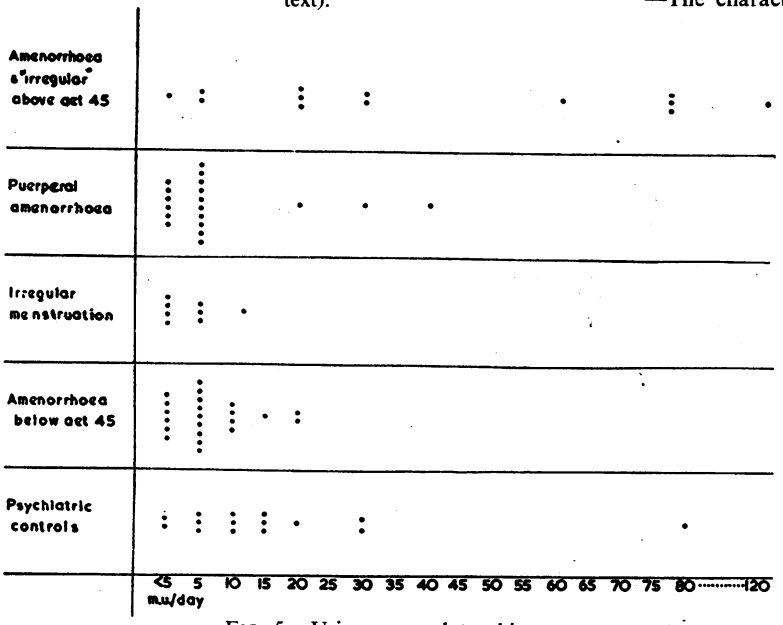

FIG. 5.—Urinary gonadotrophins.

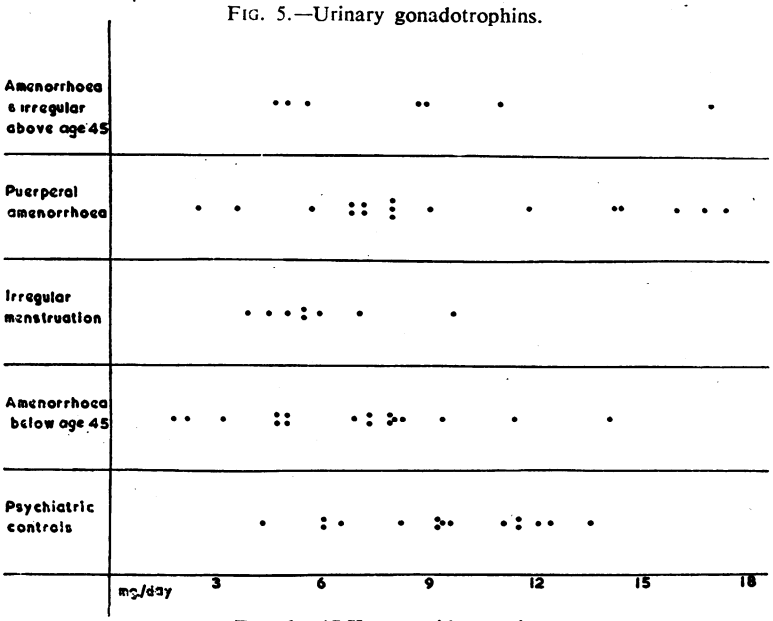

FIG. 6.—17-Ketosteroid excretion.

maintain higher levels of cornification and to pass to ovulation and progesterone production as judged by the constant absence from the smears of any characteristic of such activity. (*c*) Basal cells were present at levels varying between 5 and 10% in the cases of anorexia nervosa, and were also found in the patients with a very low C.I., seldom above 3–4%. (*d*) The general picture of the smears depended on the level of the C.I.: the lower the C.I. the more "dirty" was the appearance of the smear, showing the presence of small cells, broken cells, and leucocytes. The smears of the patients seldom look like those of healthy patients during the first half of the cycle. There is an absence of large well-developed cells with a clear protoplasm, characteristic of that stage of the cycle.

Irregular Menstruation (Below Age 45).—The main findings are delayed rise of the C.I., delayed or absent ovulation, and lack of well-established progesterone effect. There was also a lack of a definite pattern of rise and fall of the C.I. during these cycles. Thus, apart from the delayed reaction mentioned above, sometimes great daily fluctuations in the C.I. were observed.

Amenorrhoea and Irregular Menstruation (Above Age 45).—The characteristics of the smears seem to depend on the stage reached. In the long-standing cases the usual atrophic smear is found. But in the early stages two types of activity can be seen. Either a low and ill-sustained level of the cornification index and no progesterone activity, or a fairly high C.I. level well maintained but no progesterone activity.

Puerperal Psychoses.—Of the 20 patients studied, all had stopped lactation when the investigation was started. In three cases menstruation was resumed during the first month of the investigation. One patient started with a relatively high C.I., reaching levels of 60 and 70%. The remaining 16 patients had a low C.I. varying between 3 to 4% and 10 to 20%. In some cases it was possible to observe cyclical activity in the course of the investigation. However, after basic data had been obtained for a period of no less than a month these patients were submitted to leptazol treatment or electroplexy, which may have interfered with later findings. (The group of puerperal psychoses will be reported upon separately later on as it forms part of another study.) Basal cells were present in 14 patients. In two cases levels up to 50% were reached and in 12 they were not constantly present, the levels fluctuating between 0 and 10% approximately and at times showing an inverse relationship to the C.I. The smears were generally of the "dirty" type; with smaller cells than normal, broken cells, debris, and leucocytes.

Temperature Curves.—Daily temperature curves failed to show the patterns associated with regular ovular cycles.

Urinary Gonadotrophin (Fig. 5)

Urinary gonadotrophin was estimated in 62 patients with menstrual disorder and 15 psychiatric control patients. In 29 cases repeated estimations were made at intervals varying from 2 to 12 assays. For the sake of comparison between groups the first estimation made in each of the four abnormal groups was compared with estimations made between the 7th and the 15th day of the cycle in a control group of psychiatric patients approximately matched for diagnosis and age.

The relationship between age and gonadotrophin levels within the groups was investigated statistically and no correlation was found (Table IV).

TABLE IV.—*Mean Age and Gonadotrophin Levels for the Groups*

Menstrual Disorder	No. of Cases	Age	Gonadotrophin m.u.
Amenorrhoea	22	26	5·9
"Irregular"	8	28	3·8
Puerperal	19	29	7·6
Amenorrhoea and irregular above 45	13	52	40·4
Psychiatric controls ..	15	29	16·3

The gonadotrophin values for each group were submitted to an analysis of variance. The statistical test is only a rough one, as the groups are not homogeneous in their variance. No significant difference was found between the amenorrhoea, "irregular," and puerperal groups. But these as a group differed significantly from the "above age 45" group and the psychiatric control group. The variance ratio between groups is 4.95, and this is significant at the 1% level. Further, a comparison was made between the combined "below age 45" groups and the psychiatric controls by means of the χ^2 test, all values of 5 units or less being counted as low against all values 10 units and above. It was found that there was a significantly greater number of patients in the low levels in the combined "below age 45" groups than in the psychiatric controls at the 1% level.

The conclusion is that by comparison with a group of patients tested during the period of expected full activity the group of menstrual disorder below the age 45 shows when tested at random a lower level of gonadotrophin excretion.

It must be pointed out that at lower levels testing is affected by the toxicity of the gonadotrophin extract, which increases at higher concentrations. It must also be mentioned that in spite of all precautions the collection of urine in the puerperal group is less reliable than in the other groups, as these patients are well known to be difficult.

Repeated estimations have shown fluctuations in urinary gonadotrophin excretion, and maximum values similar to those found in the psychiatric controls have been recorded. However, when the gonadotrophin activity is compared with the level of C.I. in the same patient at different times, higher levels in the one tended to correspond to higher levels in the other. The only exceptions were found in the cases of puerperal psychoses, when two gonadotrophin values of 30 and 40 m.u. respectively did not show a corresponding tendency to a proportionate rise in the C.I. The absence of compensating high levels of gonadotrophin excretion, as in castrates or menopausal women, is very striking.

17-Ketosteroid Excretion (Fig. 6)

For the sake of comparison between groups whenever repeated estimations were available—that is, in 35 of the abnormal cases—the first estimation made at random was chosen.

No significant correlation was found between age and steroid excretion within groups (Table V). An analysis of variance for differences in 17-ketosteroid excretion showed that the variance between the groups appears to be significant at the 0.05 level. The main difference is the one between the amenorrhoea and "irregular" groups and the rest. The variance ratio is 9.71 and the difference is significant at the 1% level.

TABLE V.—*Mean Age and 17-Ketosteroids for the Groups*

Menstrual Disorder	No. of Cases	Age	17-Ketosteroids mg./24 hrs.
Amenorrhoea	17	25·8	6·8
"Irregular"	8	29·9	5·9
Puerperal	17	28·8	9·5
Amenorrhoea and irregular above 45	7	46·3	8·7
Psychiatric controls ..	15	29·3	9·4

These results show a significant tendency for the 17-ketosteroid excretion for the amenorrhoea and "irregular" groups to fluctuate towards the low side of normal. Thus in the two combined groups excretion for 21 out of 25 cases was below 9.4 mg./24 hours, the mean for the control group, whilst in the puerperal and psychiatric control groups the distribution is about equal around the mean.

The low values found in some cases cannot be accounted for solely by the factor of undernutrition, for, apart from cases of anorexia nervosa, none of the patients showed undernutrition. In some cases of anorexia in spite of defective food intake and loss of weight the 17-ketosteroid levels were well maintained—for example, 9.4 and 7.3 mg./24 hours. Patients in other diagnostic categories had low values—for example, 3.2, 1.8, 4.7, 3.9, and 4.5 mg./24 hours—which cannot be clinically accounted for by undernutrition.

Thyroid Activity

All patients with abnormal menstruation were grouped together, and their thyroid function was compared with that of a group of psychiatric patients approximately matched for age and diagnosis. Fig. 7 shows the distribution for the percentage excretion of the initial dose of ^{131}I for periods of 0 to 48 hours and 8 to 24 hours, and the factor T (Fraser *et al.*, 1953). An analysis of variance indicates that there was no significant difference between the group with abnormal menstruation and the psychiatric control group. The mean values for the two groups compare well with the findings of Fraser *et al.* (Table VI). However, the iodine excretion varies significantly more widely among the abnormal cases than among the controls for both the 0 to 48 hour and the 8 to 24 hour readings. There is no difference with regards to the factor T.

TABLE VI.—*Mean Thyroid Activity for the Groups*

Menstruation	No. of Cases	% Excretion 0–48 hrs.	S.D.	% Excretion 0–24 hrs.	S.D.	T	S.D.
Abnormal ..	30	50·1	16·55	16·1	6·11	4·7	2·68
Psychiatric controls ..	24	52·7	12·82	14·7	4·28	5·2	2·74
Normal (Fraser *et al.*, 1953)	32	55·8	8·7	13·6	3·7	5·2	

It can be seen in Fig. 7 that one reading for T falls in the high uptake range for the abnormal group. This is in a case of anorexia nervosa, and the probable explanation is that this finding is due to retention of iodine because of dietary iodine deficiency. One reading is also found in the high uptake range for T in the psychiatric control group. It is almost certainly due to defective urine collection of the 8 to 24 hour sample (8 to 24 hours being 5.6%, with a total of 40.6% excretion).

The scattergram for T in Fig. 7 seems to indicate that a greater number of cases are found in the low levels of thyroid function in the group with abnormal periods than in the psychiatric controls. This observation was submitted to statistical analysis by arbitrarily choosing a level of T=3.5 as a dividing line suggested by the distribution in the scattergram, and applying the χ^2 test. The result shows that there is a significant tendency beyond the 2% level for lower T values to be found in the abnormal group. For the control group there are 21 cases above and 3 below 3.5, as against 17 above and 13 below in the abnormal group.

Discussion

One finding that seems common to all the cases with menstrual abnormalities investigated in this study is the absence of progesterone production. This is connected with absence of ovulation, or, if ovulation has taken place, at any rate there is a defective progesterone production. Further, serial study of the C.I. shows that various levels of oestrogen production could be observed and that considerable variations existed between amenorrhoeic patients

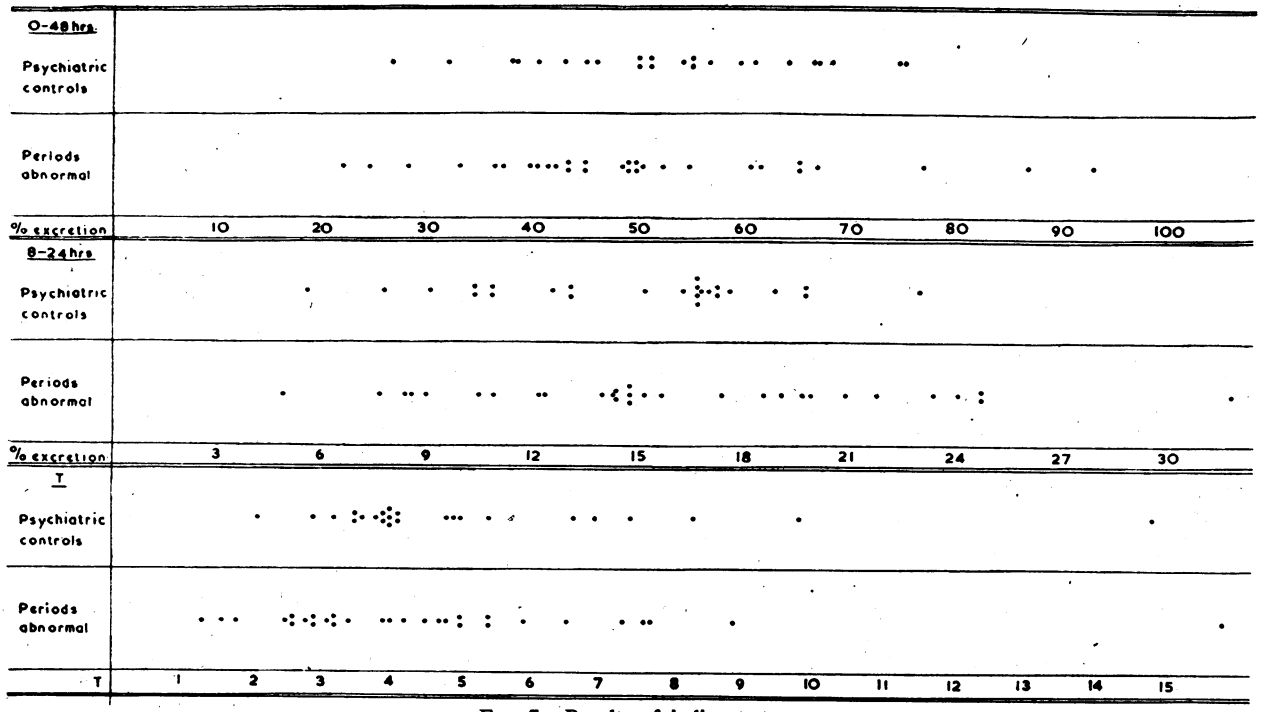

FIG. 7.—Results of iodine test.

or, in time, in the same patient. The tendency is towards a protracted low level of cornification. It must be pointed out that these findings are based on studies of vaginal smears and not on direct estimation of urinary pregnandiol or oestrogens. However, the close agreement of C.I. and urinary excretion of oestrogens has been confirmed by Young *et al.* (1957). Uterine biopsies were done on 10 patients suffering from puerperal psychosis and confirmed the absence of luteal activity. Bleeding in the course of amenorrhoeic spells is no indication that the normal cycle has been resumed, as it has been possible to observe numerous examples of bleeding on withdrawal of oestrogen. This is also true of patients with irregular cycles who show prolonged follicular phases, or anovular cycles, or defective progesterone effects. It has been mentioned that in many instances, even when the C.I. indicated a fair level of oestrogenic activity, the general aspect of the smear was different from what is found for a corresponding level of activity in the normal cycle. This is suggestive that the lack of some other factor than oestrogen may contribute to this picture.

The daily temperature readings have also confirmed the absence of the usual rise expected with ovulation and progesterone production. However, in some of these patients gross daily fluctuations have been observed, especially in cases where equally marked daily fluctuations in the cornification were found. These findings in vaginal cytology in psychiatric patients agree very closely with the findings reported by de Allende and Orias (1950), who classify the amenorrhoeas (in non-psychiatric patients) on the basis of vaginal smears into four groups: (1) the atrophic smears of the "dirty" type; (2) the hypotrophic curves with unvarying cornification; (3) the hypotrophic curves with variable cornification almost never exceeding 20%; and (4) amenorrhoea with persistently high vaginal cornification, which appears to be very rare.

With regard to psychiatric patients, Ripley and Papanicolaou (1942) made a study with vaginal smears of the menstrual cycle in 31 patients suffering from schizophrenia, depression, and elation, and they state that the smears were taken usually at daily intervals. They found only five patients who showed entirely normal cycles. Another 12 showed at times normal and at times irregular cycles. The patients who had normal menstrual cycles had well-expressed follicular reactions. In most cases the follicular reaction was not entirely typical. A frequent finding was the occurrence of a delayed follicular phase. This is said to be atypical in that cornified cells and basal cells were present at the same time, indicative of a subnormal oestrogenic production. Other abnormalities such as atrophic smears are also reported. Improvement in the appearance of smears coincided with improvement in the mental condition, as was found in eight patients in whom this occurred during the period of observation. In no case did increased abnormality of the vaginal smear occur when improvement in the mental state took place.

From the evidence of their statistical data on menstrual irregularities and from that derived from the studies of vaginal smears, the authors conclude that there is evidence of a mild and temporary disturbance in the normal development and maturation of the follicle, resulting in delayed ovulation and in prolonged menstrual cycle. A stronger reaction would result in amenorrhoea. They state that they have no direct information regarding the factors responsible for the suppressive action upon the ovaries except for a positive relationship between severity of illness and degree of ovarian dysfunction. Also the fact that only 5 out of the 31 subjects showed any appreciable degree of undernutrition is not in favour of this factor being very important.

With regard to the origin of the suppressive factor, Reifenstein (1946) has suggested that a deficiency of luteinizing hormone (L.H.) could result in what he has called "hypothalamic amenorrhoea." The conditions to be fulfilled in that syndrome are: a history of psychic trauma preceding the amenorrhoea, a normal F.S.H. production, absence of oestrogenic effect on the endometrium and vaginal mucosa, failure of bleeding after adequate progesterone stimulation, and ability of the endometrium to respond to oestrogen withdrawal with bleeding. It is not clear whether Reifenstein did serial investigation of F.S.H. excretion and thus decide if normal values recorded by him were not of a transient nature and insufficiently sustained. Two cases are quoted in his study as examples, and only one estimation is reported in each case.

Gonadotrophin Production and Excretion

What constitutes normal gonadotrophin production is a very complex problem. Fortunately two excellent reviews of the subject are now available by Albert (1956) and by

Loraine (1956). For a long time it was believed, chiefly following the work of D'Amour (1943), that there was a peak of gonadotrophin production at the time of ovulation. Heller (1941) and Heller *et al.* (1944) showed that no such peak could be demonstrated and that in some cycles positive values could be obtained every day while in others gonadotrophin was absent altogether for several days. Albert (1956), using improved methods of bioassay, found positive values in 87% of the estimations carried out throughout the cycle in four young women. Positive values were found at any time, although negative findings occurred with least frequency at mid-cycle but were equally distributed between the follicular and the luteal phase. The same pattern separated itself from subject to subject. Reviewing the findings up to date, Loraine (1956) states: "It is obvious that much work is still required with improved methods of extraction and more accurate bioassay techniques before the pattern of excretion of gonadotrophin during the normal menstrual cycle can be established." The increased gonadotrophin excretion at the menopause is well established, but Albert (1956) has further demonstrated in post-menopausal women that production takes place at rhythmic intervals of three to five days.

A number of studies are available about gonadotrophin excretion in the amenorrhoeas. One of the most extensive is that of Pedersen-Bjergaard and Tonnesen (1951). They examined 221 women suffering from secondary amenorrhoea, 145 with hypo-oligo-amenorrhoea, 77 with other menstrual abnormalities, and 110 with primary amenorrhoea. They estimated gonadotrophin and oestrogen urinary excretions by doing bioassays. Of the 221 women with secondary amenorrhoea, 34% had a normal gonadotrophin and oestrogen excretion, 16% had an increased gonadotrophin excretion, and 50% a non-increased and reduced oestrogen production. In none of them was there an increased oestrogen production. Unfortunately it is not possible from the authors' data to assess the incidence of reduced gonadotrophin production. They used a dividing-line for the upper limits of normal for their gonadotrophin estimations, so that they have two groups, increased and non-increased levels. Of the 50% of cases with non-increased gonadotrophin and reduced oestrogen excretion they say that they may represent cases with ovarian function not so greatly affected that it did call for compensatory gonadotrophin excretion, but "these effects may of course be due to a primary reduced hypophysial function."

The percentages of normal gonadotrophin and oestrogen excretion in the hypo-oligo-amenorrhoea and the other menstrual anomalies were 67 and 81 respectively, and the diminished oestrogen production 28 and 14 respectively. The authors also lay great stress on the day-to-day fluctuations of gonadotrophin and oestrogen excretion. They have used single determinations, but have followed a few cases serially. Two patients with secondary amenorrhoea showed excretion curves similar to those of normally menstruating women.

Frank *et al.* (1937) examined 21 cases of secondary and six cases of primary amenorrhoea. They showed amongst the 21 cases of secondary amenorrhoea that all levels of oestrogen excretion could be found—low, subnormal, normal, and above normal. They did serial examinations over long periods and compared their findings with those from normally menstruating women. They also investigated the gonadotrophin excretion serially in six cases of secondary amenorrhoea and found abnormally high levels in four and no activity in two. They also state that all levels of oestrogen production could be found whatever were the gonadotrophin values.

In 29 cases in the present series repeated gonadotrophin estimations were done and fluctuations in excretion were found. These fluctuations also usually corresponded with fluctuation in the cornification index. The possibility therefore cannot be discarded that added to the postulated absence of L.H. there is a tendency towards diminished production of F.S.H. as well. It has been suggested by Hubble (1955) that in cases of functional hypopituitarism there is a definite hierarchy in the dissolution of function of pituitary trophic hormones, the reproductive system being the most sensitive and the first to disappear. It may well be that L.H. may be the most sensitive hormone or the only one to disappear in some cases—for example, hypothalamic amenorrhoea—but that F.S.H. may also follow suit if the process becomes deeper. Such is undoubtedly the case in anorexia nervosa as reported by various authors (Emanuel, 1956), and it appears to be so in the present series in other diagnostic groups as well.

The demonstration of the role of the lutein-stimulating hormone has been a very difficult problem, as no practical and satisfactory method of estimation is available. McArthur *et al.* (1955) have used the weight of the ventral prostate in hypophysectomized male rats. They found qualitatively and quantitatively different patterns of excretion of L.H. from the normal in patients suffering from a number of gynaecological disorders, including psychic amenorrhoea.

Similar difficulties have existed with regard to pregnandiol estimations. Brown (1956) has shown, by using the much more precise method of Klopper *et al.* (1955), that the luteal phase in a menstruating woman could be of a very short and evanescent nature and may thus be easily missed.

17-Ketosteroid Excretion

The results obtained with regard to 17-ketosteroid excretion and thyroid activity seem to indicate that the disturbance may involve other endocrine glands, possibly also via a more general hypopituitarism. The 17-ketosteroid excretion was significantly lower in the amenorrhoeic (non-puerperal) and "irregular" groups than in the psychiatric controls and on the low side of accepted normal values for the age groups. This does not apply to the group of puerperal psychoses.

Reifenstein (1946) states that the 17-ketosteroids are usually below normal in "hypothalamic amenorrhoea." Hubble (1952) suggests that this may be due to the absent stimulation of the adrenals by L.H. according to Albright's hypothesis but that there is no decrease in corticotrophin production. The question of the participation of the ovaries in the production of androgens is therefore of great interest. Some observations made during these studies are given here as they seem relevant to the problem, but they are not thought definite enough to be reported in detail. It has been observed that in some patients there was an increase in 17-ketosteroid excretion as the cornification index rose. Also fluctuations in 17-ketosteroid excretion were found during the cycles, the level rising towards mid-cycle. In one case a chromatographic examination done at the beginning and one done at mid-cycle showed a marked increase in the androsterone and etiocholanolone fractions in the latter chromatogram.

Dingemanse and Huis in't Veld (1951) and Huis in't Veld and Dingemanse (1952) have demonstrated a difference in the excretion pattern of castrated women, who show an increase in the β-fraction and a decrease in the androsterone and etiocholanolone excretion. Migeon (1955) has shown a fluctuation in the blood dehydroisoandrosterone levels during the menstrual cycle. The question of the relative part played by the adrenals and the ovaries during the menstrual cycle, normal and abnormal, needs further elaboration. Hyperadrenalism as a cause of disturbance in the reproductive system has come much to the fore with the work of Wilkins *et al.* (1955), of Jones (1955), etc. It is now well known that certain forms of mental illnesses in their acute phase can be accompanied by increased adrenal activity both of corticoids and of 17-ketosteroids. Altschule (1953) has suggested that some of the disturbances of the menstrual cycle in psychiatric patients could be due to that cause. In two patients in the present series with a consistently high excretion such a mechanism could have been at work: they both suffered from hirsuties.

The normal, low normal, and low values found in this series do not suggest that this mechanism applies on a large

scale unless the stage of adrenal hyperactivity was missed, or that most patients with menstrual disorders have been investigated in a later phase when hypofunction has followed hyperfunction. Hubble (1952), in his cases, reports normal values for all aspects of adrenal function. In another study in progress a number of patients showed fluctuations in excretion of 17-ketosteroids and corticosteroids during the menstrual cycle, sometimes to abnormally high levels, and the first stage of interference could be suppression of the more sensitive gonadotrophin component—that is, the lutein stimulating hormone. However, it must also be remembered that the reverse process may also be true and that the absence of lutein stimulation and progesterone production could call for adrenal compensation in the face of unbalanced oestrogen activity. The role of the adrenals must wait for further experimental work.

With regard to the part played by undernutrition, this factor was pronounced only in the cases of anorexia nervosa. However, the consensus of opinion is that the menstrual disturbance often precedes the anorexia. But it is probable that the undernutrition increases and maintains the endocrine hypofunction, and improvement in weight is always associated with improvement in other spheres. It is only in the severe cases of anorexia nervosa that near complete absence of gonadal activity was found in the present study.

The problem of undernutrition and 17-ketosteroid excretion in this series has already been dealt with. Clinically there seemed to be a difference between the patients with well-preserved 17-ketosteroid excretion and those with low levels in the anorexia group. The former appear to be much more active and lively than the latter.

The question of the correlation of the mental state to the endocrine changes and the menstrual abnormalities will be considered in another study because of the complicated relationship involved. The subject of the influence of emotions on disturbances of the menstrual cycle has been dealt with by Kroger and Freed (1951); but the remarks of Ripley and Papanicolaou (1942), that in no case did increased abnormality of the vaginal smear occur when improvement in the mental state took place, can be confirmed. Further, the observation of Reifenstein (1946) with regard to his cases of "hypothalamic amenorrhoea," that in many patients the discussion of their psychological problems and superficial psychotherapy can effect a recovery, has also been noted, though in certain patients the disturbance seems to be much more persistent. The literature on the hypothalamic control of the pituitary has been well summed up by Harris (1955).

Conclusion

It is thought that the findings of the hypotrophic type of smear, the low cornification index, the absence of progesterone activity in the smear, the tendency to lowered F.S.H. production, and a possible tendency to low normal 17-ketosteroid excretion and low normal thyroid uptake point to a functional lowering of pituitary activity in the patients of this group.

The disturbance seems to vary in the degree to which the pituitary functions are affected, the gonadotrophin being the most sensitive. When function returns the follicular activity appears before any progesterone activity, and this may last for long periods or anovular cycles may be observed. This is in agreement with the hypothesis of a hierarchy of pituitary function during phases of dissolution and reconstruction.

The association with mental disturbance also indicates that a brain pituitary mechanism is involved. A possible pathway is suggested by the hypothalamic control of pituitary activity, with special reference to the reproductive functions.

Summary

Fifty-eight patients with menstrual disorders and nine with normal periods were investigated. Serial vaginal smears were taken over periods varying from 30 to 540 days. Gonadotrophic and thyroid activity and 17-ketosteroid excretion were also assessed and compared with similar measurements in psychiatric control groups. Repeated estimations showed fluctuation in the factors measured.

Gonadotrophin estimations in the amenorrhoeic patients were significantly lower than the values recorded for the control group between the eighth and the fourteenth day of the cycle. Highest values selected from repeated estimations did not differ.

17-Ketosteroid excretion in the amenorrhoeic and "irregular" groups, but not in the puerperal group, was slightly lower than, and differed significantly from, the psychiatric control group.

Thyroid activity did not differ significantly between groups, but showed a significantly greater spread of values in the group with menstrual disorder.

Serial vaginal smears showed that complete absence of gonadal activity is rare, and that great variations in cornification index values exist between patients and in the same patient over a period of time. Protracted phases of low oestrogen activity is a common finding; ovulation and progesterone effects were never detected in the patients with amenorrhoea.

Uterine biopsies done on 10 patients with puerperal psychoses confirmed the absence of the luteal phase.

The general hormonal picture is one which indicates that the main type of amenorrhoea met with in psychiatric patients is one of lowering of pituitary function; gonadal activity is abnormal, the luteal function being the one most constantly altered, combined with protracted low oestrogen levels. Gonadotrophin production can also be diminished, and the tendency of the 17-ketosteroid excretion is to vary from normal to the low side of normal. The thyroid also shows variations from the normal distribution.

The relationship to mental illness and the fluctuations observed in the hormonal balance suggest interference at the brain–pituitary level.

LEGENDS TO CHARTS (Figs. 1–4)

Chart 1.—Represents a normal cycle in an unmarried woman aged 20. There is a gradual rise and fall of the C.I.; no marked daily fluctuations. The highest level reached for the C.I. is in the region of 40%.

Chart 2.—Represents a cycle in a woman aged 25. It also shows a gradual rise and fall of the C.I., but the general level of cornification is below that of the cycle shown in Chart 1.

Chart 3.—From an unmarried woman aged 23 who has suffered from anorexia nervosa and amenorrhoea for three years. The curve shows that there is practically no oestrogenic activity. The C.I. fluctuates between 0 and 3%. The smears show characteristics of atrophic smears and the basal cells are in sufficient number for a count to be made.

Chart 4.—From a woman aged 32 who has been suffering from anorexia and amenorrhoea for 14 years. The curve shows the absence of hormonal stimulation; the C.I. fluctuates between 0 and 3%. The smears show the characteristics of atrophy and the presence of basal cells.

Chart 5.—From the same patient as Chart 4, but taken later on when the patient had been improving. It will be noticed that the C.I. shows great fluctuations but that the normal rhythm of the menstrual cycle is not established, so that this woman is submitted here to a fluctuating stimulation by oestrogens but not to the physiological process of menstruation.

Chart 6.—From a girl aged 20 suffering from feelings of depression and lack of drive interfering with her studies. For some time previous to admission she had suffered from anorexia and loss of weight down to 7 st. 4 lb. (3.3 kg.), and amenorrhoea. However, on admission her weight was 9 st. 1 lb. (4.1 kg.). The C.I. curve shows the low level of oestrogenic activity with fluctuations but no indications of any cycle.

Chart 7.—From an unmarried woman of 24 suffering from temporal lobe epilepsy and with a hysterical personality. Her periods have always been irregular and painful since they started at the age of 13. The C.I. curve shows a gradual rise with fluctuations of the C.I. after a period of months. Once more there is here no regular menstrual cycle. When bleeding occurs it is scanty and does not last more than two or three days.

Chart 8.—From a woman aged 38 suffering from attacks of agitated depression and occasional mania. This curve illustrates a number of points in relationship to the menstrual cycle. In the first two cycles there is extremely little ovarian activity though bleeding still takes place. There is no sign of ovulation or progestational activity in these two cycles, and here one must quite clearly distinguish between periodic bleeding and bleeding in relationship to the normal well-defined physiological process of menstruation. In the third cycle the C.I. is at a somewhat higher level and there is a premenstrual peak just before the bleeding. Nearly 18 cycles were studied in this woman, and they all showed this premenstrual peak and sometimes a menstrual peak. In the following cycle once more the level of the C.I. is somewhat higher than in the previous cycle, and clearly defined premenstrual and menstrual peaks can be seen. Again in these two cycles there is no evidence of ovulation or progestational activity. The next cycle shows a still higher level of activity, premenstrual peak, and marked fluctuations but no progestational activity. The various cycles studied are abnormal in that they show low levels of gonadal activity, no ovulation, and no progestin activity. Nevertheless, bleeding takes place at fairly regular intervals and is presumably due to oestrogen withdrawal. Further, a characteristic of the cycles appears to be the premenstrual rise and fall followed by the bleeding. But perhaps the most interesting fact here is the observation that there is a gradual step-up level of gonadal activity from cycle to cycle, though in the present study not yet leading to a normal cycle. This case has been extensively studied over a long period of time and will be reported separately.

Chart 9.—From a woman of 30 suffering from a schizo-affective disorder. She has had pain associated with her periods, and has related some of her symptoms to phases of the menstrual cycle. In this case it can be seen, in the first cycle studied, that the level of hormones is maintained throughout the cycle at a C.I. between 20 and 30 with daily fluctuations. The second cycle shows the beginning of a rise and fall of the C.I., with the latter being constantly maintained above a level of 20–25 C.I. In these two cycles a premenstrual peak is also present. In the third cycle the picture has altered and two well-defined periods of rise and fall can be observed, with the general level of the C.I. above that of the previous cycle. It was not possible in that cycle to detect any signs of progestational activity. However, the general shape of the curve does suggest that it is possible that ovulation has taken place, but if there has been corpus luteum formation progesterone production was very defective. The last cycle resembles the previous one. The level of the C.I. is at a higher one generally than in the previous cycle, otherwise the same remarks apply. In this woman the cycles studied can be compared with interest to the previous case (Chart 8). In both cases the step-up activity can be observed very clearly, though in Case 9 the general level at the time the study was started was higher than that in the previous case. It also illustrates the differences between the normal physiological cycle and periodic bleeding.

Chart 10.—From an unmarried woman of 25 suffering from periods of depression and elation. The first part of the chart shows a rising and falling C.I., followed by bleeding. As the whole cycle was not studied, it is not possible to make further comments on this part of the curve, but it can be seen that, following the bleeding, the normal cycle was not resumed, and for a period extending over weeks the gonadal activity remained very low. The curve is shown to illustrate a protracted first phase of the cycle. She entered menarche at 15 with periods grossly irregular and often associated with marked mood swings. She was capable of ovulation, as she had had an illegitimate child 18 months before the study.

Chart 11.—From an unmarried woman of 19 who had been suffering from a recurrent mood of depression with a tendency to stuporous and bizarre behaviour. The first cycle shown demonstrates the character of the oestrogen rise occurring very suddenly after a period of low gonadal activity in the first half of the cycle. The patient went into the depression and stupor-like state at this point and refused co-operation. The last bit of the curve in that cycle represents the time when it was possible to resume the cytological studies.

Chart 12.—From an unmarried girl of 19 suffering from manic-depressive swings. The chart shows the sudden and sharp rise and fall of the oestrogen and the abnormal cycle as the rise and fall precedes the bleeding and the sudden change in mood.

Chart 13.—From a married woman aged 47 suffering from a menopausal illness with paranoid ideas and disturbing sexual impulses. Her menstruation had become irregular for some time. It can be seen that during the phase studied here she was constantly under oestrogen stimulation at a fairly high level with no normal cyclical change and no progestational activity.

Chart 14.—From a woman of 47 entering into menopause and showing paraphrenic symptoms. In this case it can be seen that the cycle has also become abnormal and irregular, but, in contrast to the previous case, the level of gonadal activity is quite low, ill-sustained, and unbalanced, for progestational activity is lacking.

Chart 15.—From a woman just entering menopause with paranoid symptoms. There is constant oestrogen stimulation, but no cycle.

Chart 16.—A woman aged 34 who developed a schizophrenic-like illness seven days after giving birth. The investigation started 30 days after the baby was born. The chart shows the very low level of cornification and the presence of basal cells. There are no signs that the gonads are showing any tendency to fluctuating activity. After shock treatment she improved and her periods returned.

Chart 17.—A woman aged 24 who developed a schizophrenic-like illness after delivery of her first child. The investigation started 83 days after the baby was born. The chart shows a much higher level of cornification and fewer basal cells than the previous patient (No. 16) and serves to illustrate the various levels of oestrogenic activity that can be observed during amenorrhoeic periods.

Chart 18.—A woman aged 27 who became depressed during her fifth pregnancy and was admitted to hospital during her sixth month of pregnancy. She settled down fairly well, had her baby, and is chosen as a comparison with the two previous cases (Nos. 16 and 17) suffering from serious illnesses. The investigation was started shortly after birth. The chart shows what appears to be an amenorrhoeic cycle—the first one—and also shows very clearly the inverse relationship of the C.I. and the percentage of basal cells.

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