

AN INVESTIGATION INTO THE
CAUSES OF DELAYED
MENSTRUATION, AND ITS TREATMENT
IN THE
WOMEN'S AUXILIARY AIR FORCE.

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The prevalence of amenorrhoea without any obvious pathology in the uterus or adnexa or in any of the other body systems is well known in the Women's Services. The incidence of this type of amenorrhoea in the Women's Auxiliary Air Force prompted me to investigate this interesting condition. In the majority of cases, the onset of symptoms coincides with entry into, or occurs shortly after entry to service. That the condition, however, does not only occur in service personnel is a fact well recognised. Many nurses on first commencing their career in hospital have amenorrhoea for some months and the Matron of a large teaching hospital in Glasgow states that about one out of every eighty probationers have this condition. (Personal communication from Matron Lang, Western Infirmary, Glasgow.) It is a well known malady in girls who take up factory work, or who go into domestic service, or in young girls entering boarding school for the first time. It is not uncommon on going away for a holiday or returning from a holiday, nor is it unusual in those who for a variety of reasons fear the onset of pregnancy or in those in whom the desire for pregnancy is so strong that it produces the clinical syndrome of pseudocyesis. Some patients relate the cessation of the menstrual period to acting as a blood donor or following a gynaecological examination. It can occur in a host of other states but the common precipitating factor in all is a complete change of environment, recreation and work or a period of mental and

emotional stress.

CLASSIFICATION AND TERMINOLOGY.

The classification of true amenorrhoea into primary and secondary, is generally considered to be inaccurate and unsatisfactory, considering the number of factors now known to control the menstrual cycle. I can see little advantage in this division either from the clinical or therapeutic stand-point. While amenorrhoea may be primary in the sense that the menstrual flow has never appeared, this may be secondary to disease in some organ of the body other than the uterus, or ovaries. Similarly, while secondary amenorrhoea is regarded as the cessation of the menstrual period, after it has been established for some time, this may be regarded as primary in the pathological sense, due to disease or removal of the ovaries or uterus. I see very little, therefore, in support of the arbitrary division of amenorrhoea into those who have menstruated and those who have never experienced the menstrual function. While I hesitate to introduce the new classification and thus make a complex subject more complicated, I feel that a modification of the classification would not be out of place. If the amenorrhoeas were to be regarded from the clinico-pathological aspect rather than from the time of onset of the amenorrhoea, I think that actual simplification would occur. Thus I would define primary amenorrhoea as that type of amenorrhoea which is due

directly to disease in the uterus or adnexa whether the period was absent ab initio or had been present normally for some time, similarly secondary amenorrhoea can be defined as that type of amenorrhoea resulting from disease in some other body system besides the genital system, whether the menstrual period has never been present or had been established normally for some time, thus the modified classification of the true amenorrhoeas would be as follows :-

PRIMARY.

1. Ovarian.

- (a) Congenital absence of both ovaries (rare).
- (b) Extirpation of ovaries.
- (c) X-Ray therapy.
- (d) Bilateral ovarian tumours.
- (e) Tuberculous and gonococcal affections.

2. Uterine.

- (a) Rudimentary and foetal types.
- (b) Superinvolution.
- (c) Surgical removal of uterus.
- (d) Tuberculous and gonococcal affections.

SECONDARY.

1. Endocrine Dysfunction.

- (a) Pituitary - dystrophia adiposo - genitalis,
Cushing's Syndrome, Simmond's disease.
- (b) Thyroid - cretinism, myxoedema, hyperthyroidism

(c) Suprarenal - Addison's disease, hypernephromata involving the suprarenal glands.

2. Chronic debilitating diseases - tuberculosis, diabetes, chronic nephritis, malignant disease, severe anaemia.
3. Chronic poisoning - lead and opium.
4. General diseases, acute specific fevers, and debility following prolonged illness.

(This classification has excluded concealed menstruation or cryptomenorrhoea as it is not a true form of amenorrhoea).

As will be seen the type of amenorrhoea which is the subject of this paper has been excluded from the above classification as I choose to consider it separately. This condition can be defined as that symptom complex, characterised by the sudden cessation of the menstrual period in an otherwise healthy subject, without any demonstrable lesion in the uterus or adnexa and its equally sudden return in a few days to eight months, rarely longer. The condition was well known in Great War 1, when it was called Kriegsamorrhöe by German authors. But it is obvious that the condition might well be called peace amenorrhoea or factory amenorrhoea, or hospital amenorrhoea as it is not peculiar to war alone. Nor is there anything in favour of the ^{ap}pellation "functional amenorrhoea" as the word functional merely masks our unfortunate ignorance of the subject. More recently the term "delayed menstruation" has been used by American authors.

This term is more appropriate as it indicates that the menstrual function inevitably returns. In the following pages therefore the term delayed menstruation will be used to describe the specific symptom complex as has been defined above.

HISTORICAL.

The comparative absence of any important work on the subject of delayed menstruation in the English language up till about 1939, is to be wondered at. Most of the early literature is from German sources written towards the end of the last war. It is highly improbable that the condition was not recognised in this country at that time. A certain amount of difficulty and confusion may have arisen by misinterpreting the symptoms of delayed menstruation for chlorosis and the natural onset of the menstrual flow was attributed to the use of iron preparation administered for the anaemia.

One of the earliest references to delayed menstruation was by Bernhard Schweitzer¹ (1917). Writing of *Kriegsamorrhöe*, as it was then called, as it occurred in Polish women, he believed that undernutrition was the most important aetiological factor. Hard work and emotional stress such as the calling up of a husband or the wounding of a near relative, etc., were contributory factors. In most cases the amenorrhoea lasted 4 - 6 months. In peacetime

Schweitzer found that this type of amenorrhoea was rarely above 1% of all cases examined, but this rose to 5.6% in the last quarter of 1916. The following figures in this respect are rather interesting. In the year 1911-1912, 1,984 consultations took place and of these only 17 cases of delayed menstruation occurred giving a percentage of .8 of the total. In 1910-1911 out of 1,893 consultations only .7% of cases had this type of amenorrhoea and this rose sharply to 4% of all cases (2,016 consultations) in the 1916-1917 period. The majority of the women were between 26 and 30 years of age. Commenting on the occupations of these women Schweitzer noted that the greatest number occurred in munition workers (50%) while servants (17%) and salesgirls (10%) were next in frequency. He also pointed out that one patient who had amenorrhoea for 18 months became pregnant. This is a rather interesting sidelight, as many patients with delayed menstruation fear that they are sterile also. Recent investigation however indicates that this is unlikely and although the menstrual flow may be absent ovulation probably occurs. As will be seen the 1916-17 figures compare closely with my own but unfortunately no figures are available of the condition prior to 1940.

The importance of the nutritional factor is again emphasised by Graefe². He attributes Kriegsamorrhöe to a lack of meat and fat probably as a result of strengthening of the British blockade of Germany in 1917. He also recognised

that violent psychic disturbances are able to produce a premature climacteric. Certain symptoms were found frequently in these patients such as anaemia, headache, giddiness and abdominal and sacral pains. Graefe's figures are similar to those of Schweitzer. In 1914 only 1.5% of all gynaecological cases examined had delayed menstruation and this rose to 2.85% in 1916 and 5% in the first quarter of 1917. Walter Hannes (1917)³ working in the Poliklinik of Breslau, on the other hand, did not think that the psychic functions were of any importance. Lack of food is again held to blame for the production of the symptom complex.

Hannes³ figures for comparison are .56% of cases in 1913 and in April-June 1917 out of 484 patients examined 4.3% were suffering from Kriegsamorrhöe. The latter figure however also includes a number of cases of chlorosis. He also records the case of one woman 25 years old who conceived after an absence of the menstrual flow for 10 months.

Grünebaum⁴ in an article "Zur Frage der Entstehung von Kriegsamorrhöe" is probably nearer the truth when he states that he does not believe that malnutrition is an important aetiological factor. He reported on a group of patients who were evacuated to a village in France in 1917. Of 11 of the evacuees who consulted him 3 suffered from amenorrhoea while 16 of the original population who consulted him had no symptoms of Kriegsamorrhöe. The evacuees were fed by the Spanish-Dutch Committee formed at this time to relieve

distressed populations in the area. There was no evidence therefore of malnutrition in these 3 cases. The precipitating factor was obviously their evacuation and the psychical disturbance associated with it.

That a lack of essential food plays no part in the production of *Kriegsamenorrhöe* is further emphasised by Siegel⁵ who reported 20 cases between the ages of 20-40. He attributes the condition as the previous German authors do to harder physical and mental strain. It is also significant that pregnancy occurred in 3 cases.

Eckstein's⁶ figures for *Kriegsamenorrhöe* is as follows : Of 354 clinical examinations 9.3% (133) had amenorrhoea of which 36% (12 of the 133) had negative gynaecological findings. Thus 3.4% of all cases had amenorrhoea without any pathology in the genito-urinary system.

At a gynaecological meeting in 1917 Stickel⁷ maintained the view that the three main factors in the production of the amenorrhoea were (1) malnutrition (2) hard work (3) psychic disturbance.

In an attempt to find some pathological basis for *Kriegsamenorrhöe*, Köhler⁸ examined the ovaries of 4 cases between the ages of 24-35 in whom amenorrhoea had been present for 9 weeks to 6 months. He states that excision of the ovaries was necessary for prolapse or retroflexion so that it is evident that some gynaecological condition besides the amenorrhoea was present. One is inclined to think that the

following description of ovarian pathology is complicated by organic disease in the uterus or ovaries. In 3 of the cases there was cystic degeneration of the ovaries and atrophy of the uterus. Ripe and degenerating Graafian follicles were present. In a case of amenorrhoea lasting 1-1½ years he found hyaline degeneration in the ovaries. It would be interesting to discover whether any permanent pathological changes occur in the ovaries, the endometrium or uterus proper, as a result of prolonged menstrual delay. This type of investigation would require frequent biopsies of the uterine epithelium. Köhler unlike his contemporaries does not lay much stress on psychical disturbances as an aetiological factor, in the condition. He maintains that malnutrition is the most important cause and the lack of sexual intercourse as a subsidiary cause. In treating these cases Köhler recommends yohimbin in tablet form giving .005 gm. 3 times per day. This of course acts by dilating the genital and uterine capillaries. Although he states that success can be expected in women who have had amenorrhoea up to 6 months, he does not give any definite figures and it is unlikely this treatment is very efficacious.

Hirsch⁹ (1917) recommends the combined intramuscular and oral administration of ovarian extracts and arsenicals. This is probably one of the earliest references to the use of ovarian preparations in the treatment of amenorrhoea.

Franziska Cordes¹⁰ writing from a large experience in

private practice introduced a new aetiological factor. As the evidence of amenorrhoea appeared to be greater in the winter than in the summer, it is probable that cold and dampness may be a precipitating factor, in the production of the condition. She also, besides agreeing with the previous authors, lays somewhat greater stress on the enforced celibacy in women whose husbands were at the front. In the treatment of the condition she recommends increasing the diet where possible and uterine massage.

Adda Nillson¹¹ working in Stockholm also found a great increase in the number of cases of amenorrhoea in 1917. As is well known at that time there was a deficiency of fats and carbohydrates in Sweden and especially of Vitamin A. But as Nillson states the amenorrhoea began before the lack of fats and in addition the carbohydrate was rationed so that relatively the proteins were increased.

In a most comprehensive review of the whole subject covering the war years and the 10 year post-war period, Georg Teebken¹² in 1928 gave the following figures. In 1914 the number of cases of delayed menstruation was only .19% of the total examined, this gradually rose to 0.31% in 1915 and to 0.57% in 1916. His figure of 5.11% in 1917 out of a total of 2,896 consultations is in close agreement with those of Schweitzer and Ekstein and the corresponding figures for 1918 and 1919 are 2.5% and 1.18% respectively. The number of cases then rose from .48% in 1920 to .71% in 1923 and fell

again to 0.06% in 1926. The greatest number of cases at all periods occurred in the 18-24 age group. The duration of the amenorrhoea was 2-24 months and one case lasted 48 months.

In attempting to relate the incidence of amenorrhoea with occupation, Teebken found that 33% occurred amongst servant girls and 7.5% cases were amongst factory workers. This does not agree with Schweitzer's figures who found that by far the greatest number occurred in factory girls, while servants and maids were relatively low in the list.

Teebken also described a number of symptoms such as weakness, tiredness and abdominal pain and swelling of the breasts at the time of the expected period.

The actual number of cases described is 518 between 1914 and 1926 and as others have previously reported, Teebken also found that pregnancy occurred in 47 of these cases. In giving these figures, Teebken excludes amenorrhoea resulting from aplasia and hypoplasia of the uterus, organic disease of the ovaries and fallopian tubes, also general diseases such as tuberculosis, chlorosis, anaemia, acute and chronic nephritis, hyperthyroidism, myxoedema and Addison's disease. The resultant cases, he concludes, are purely functional.

Discussing the aetiological factors governing Kriegsamorrhöe, Teebken is in full agreement with Stickel and Köhler in that the probable causes in the order of their importance are (1) change of food (2) psychic disturbances (3) increased work. He also recognises that the absence of

sexual intercourse when the husband is away from home or illicit intercourse between married and unmarried people are frequent causes of amenorrhoea. One finds it rather difficult to understand what is meant by a "change" of food. Is it to be taken as an absence of essential food factors such as first class proteins and Vitamins or is it merely a change in the type of food without any nutritional deficiency? As Teebken, however, states somewhat later in his paper that a lack of protein is an important aetiological factor - presumably that is what is meant by a "change" of food. Referring to the work of Fischer who contended that chronic poisoning with mütterkorn (ergot) through poor grinding of the corn and mixing it with rye was a probable cause of Kriegsamorrhöe, Teebken states that this is highly unlikely as more general signs of ergot poisoning would have been noted in the population at large.

A detailed account of the food situation in Germany during the 1916-17 period then follows and Teebken asserts that the rapid deterioration in the quality and quantity of food was due to the blockade by the British Navy. Thus our sailors were held responsible for the amenorrhoea in female population of Germany at that time.

In June 1915 (28th) rationing first appeared in Germany and in August of that year each adult was allowed to obtain 200 gm. meal per day. This contained about 10% potato flour and was soon increased to 20%. In July 1916 the average

calorie value of the food per person daily was 1,980 calories and consisted of 350 grammes carbohydrate, 65 grammes protein and 40 grammes fat. From this time malnutrition began to appear in the country and towards the end of 1916 the average person received about 1,558 calories daily. The number of cases was inversely proportional to the calorie value of the diet. In February 1917 even potatoes were unobtainable and ersatz potatoes were used. In July 1917, Teebken reckoned that the average German had to be satisfied with 1,466 calories, the diet consisting of 53 grammes protein, 32 grammes fat and 230 grammes carbohydrate. During September and October 1917 the daily calorie value of the diet increased and there was a coincident reduction in the number of cases of amenorrhoea. This was due to the fact that in the second half of September 1917 an addition of 10 lbs. potatoes was made to the ration, per week, and this was increased to 20 lbs. per week. The most important change in the food, states Teebken, took place between January-March 1917 when swedes replaced potatoes as a staple article of diet and a coincident rise in the number of cases of amenorrhoea occurred. On the other hand, in 1919 no single case was reported. This again is attributed to the increase in the calorie content of the diet due to the importation of peas, beans, wheat and bacon from this country and America to relieve the food situation in Germany. So that Teebken concludes quite emphatically that the chief cause of amenorrhoea

is food rationing. However it can be stated just as emphatically that a lack of food and essential food factors per se can play a very little part in the production of delayed menstruation, as the condition occurs with great frequency even when the diet is sufficient in total calorie value, protein, essential salts and Vitamins (vide infra).

Teebken then attempts to deduce the essential food responsible for the production of the amenorrhoea. That the carbohydrate is blameless in this respect was due to the fact that carbohydrates were distributed to the population in the form of bread, sugar and potatoes. Neither does he think that a lack of fat had anything to do with the condition as fat and carbohydrate can replace one another in metabolism. So that by a process of elimination he concludes that protein is the responsible factor. Supporting this contention he states that when meat rationing was introduced the number of cases of amenorrhoea increased but when the importation of meat and bacon began the number of cases dwindled. Up till August 1917 there was only 200 grammes meat daily per person which however included 150 grammes sausage meat. Further, the milling of wheat must be taken into account, which was 82% at the beginning of the war and 94% in February 1917 and in addition potato flour was added (10% in "K" bread and 10-20% in "KK" bread). Teebken believed therefore that the most important single factor in the production of amenorrhoea was a lack of first class protein and the lack of fat only

plays a minor part, while the wartime monotony of the diet acted as a contributory factor.

The weakness in this argument is apparent. For instance the question of a vitamin deficiency could not be completely ruled out. And although our knowledge concerning these accessory food factors, as they were originally called, was limited, Vitamin A and Vitamin B1 were already known, the former discovered in 1912 by McCollum, Osborne and Mendel simultaneously and the latter in 1897 by Eijkman. By 1928 both Vitamins C and D were discovered. So that it was not impossible for an unknown essential food factor to have caused amenorrhoea. If protein deficiency was an important factor in the production of amenorrhoea, it is difficult to explain why some women developed amenorrhoea and others did not, when presumably all women were subjected to the same dietary deficiency. Further experimental evidence by reducing the protein consumption of normal women to a level far below 100 gm. daily and determining whether this produced amenorrhoea, would have been necessary to prove Teebken's contention. Thus in actual fact there is very little evidence to support the theory that a protein deficiency can cause amenorrhoea and an attempt will be made to show this more satisfactorily in a later stage of the investigation.

The increase in the number of cases of amenorrhoea during the period of inflation in 1922-23 cannot be explained

satisfactorily on the basis of a lack of protein in the diet, continues Teebken. Because although at that time the purchase of a small quantity of food meant the expenditure of possibly millions of marks, the situation was relieved to some extent by the philanthropic work of the Quakers, who indeed saved the poorer classes of the population from almost complete starvation. When stabilisation of the mark occurred in 1924, the number of cases again sank to their pre-war level. It is far more likely that the greater mental and emotional strain which burdens women even heavier than men in periods of economic depression played a far greater part than the absence of protein.

In an article which takes the form of a reply to Teebken, Erwin Graff and Joseph Nowak¹³ fully endorse the statements made by Teebken, that the main aetiological factors in the production of amenorrhoea in wartime are (1) under-nutrition (2) increased work and (3) psychic|trauma. The writers do not add anything now to the subject and merely substantiate the remarks of the previous authors. They rather significantly believe that psychic|trauma plays a very small part in the production of the syndrome and support this statement with the fact that although in the earlier stages of the 1914-18 conflict women were subjected to far greater emotional crises than in the later part of the war, the number of cases of amenorrhoea was far greater in the 1917-18 period when there was a great shortage of food.

The authors maintain that increased work was not an important aetiological factor as amenorrhoea occurred in women whose work was no harder than it was in peacetime. They also disagree with the "mutterkorn" theory of Fischer, and believe that sexual abstinence was a possible causative factor. They dismiss the possible effects from absence of salts and vitamins by the brief statement, "We cannot find any proof that a lack of salts or vitamins causes amenorrhoea so that we come to the conclusion that the chief cause is a lack of protein in the war food". The fallacy in the logic is apparent.

Summarising the work of the German authors on the subject of delayed menstruation up till 1929 the following appear to be the facts of importance. Amenorrhoea in the absence of organic disease was not a common condition in Germany before the last war when the incidence rose from 0.199% in 1914 to 5.11% in 1917. The incidence then gradually fell to its pre war level but there was another increase in the number of cases in 1922-23 corresponding with the period of inflation. The condition appeared to have been more common among maids and factory workers than among housewives and the commonest age group was 18-24 years.

Most of the German authors are in general agreement that the main factors in the production of the syndrome are :
(1) malnutrition (2) increased work (3) psychical and emotional stress (4) cold and damp (Cordes). However a

difference of opinion exists as to the relative importance of each of these factors in the production of the condition. That undernutrition is the most important single factor in the aetiology is stressed by Schweitzer, Graefe, Köhler and Teebken. The latter attributes this to an insufficiency of protein during the blockade years, i.e. 1917-18. However Hannes and Grünbaum believe that the psychical factors are of the greatest importance. Fischer's view on poisoning by ergot is discredited by most German authors. (It will be shown later in this investigation that malnutrition can have little if anything to do with the production of delayed menstruation.)

The possibility of a vitamin or salt deficiency could not, as has already been pointed out, be ruled out completely. The evidence in favour of a protein deficiency is inconclusive. Further Teebken contradicts himself when, on recognising the sudden rise in cases of amenorrhoea during the inflation period, states that there was no protein deficiency at that time. Was the condition then due to increased work? - this hypothesis does not stand close scrutiny, because as Graff and Nowak have pointed out amenorrhoea occurred in women whose work was no harder than in peace time. Further, what then is the explanation of the occurrence of amenorrhoea in pseudocyesis and following blood transfusions where the conditions are not necessarily associated with an increase in physical effort? Finally the evidence in favour of

amenorrhoea having any association with climatic variations is manifestly weak. What then is the factor common to all these states which produces the amenorrhoea - obviously psychological stress, emotional upset, fear and anxiety. And these states can occur under so many different circumstances that it is impossible to tabulate them all.

As for symptoms, low back and sacral pains were described by Graefe. Both he and Teebken also mention headaches, giddiness, tiredness and weakness. All the German authors do not give definite figures as to the length of the amenorrhoea but it appears to be on the average about 2-4 months and in one case 48 months. 51 cases of pregnancy during the amenorrhoeic period are described by Hannes, Grünbaum and Teebken.

Yohimbin, ovarian extracts, arsenicals and abdominal massage are all recommended as therapeutic measures.

With the above facts in mind it was realised that a unique opportunity presented itself to pursue further investigation on delayed menstruation in members of the Women's Auxiliary Air Force, in whom its occurrence was by no means infrequent. An attempt was therefore made to investigate (1) the incidence of delayed menstruation in W.A.A.F. personnel (2) the relationship if any between delayed menstruation and occupation (3) the relationship, if any, to the quantity of protein in the diet (4) other symptoms besides amenorrhoea (5) differential diagnosis

and choice of case (6) a form of therapy (7) possible mechanism of production of amenorrhoea.

The following pages are therefore devoted to the above questions and include all the literature incidental to the investigation. The period covered is from about May 1943. The investigation would have been far more rapid but for the difficulties of obtaining the requisite permission and clinical facilities to investigate the cases. The cessation of recruitment of women into the forces further reduced the possible number of cases which would have arisen.

1. Incidence of delayed menstruation in W.A.A.F. personnel.

The incidence of amenorrhoea was investigated in nine R.A.F. Stations and the total number of W.A.A.F. involved was 2,312. The girls were questioned during what is known as an F.F.I. examination (i.e. free from infection) which is done as routine with frequent regularity in a W.A.A.F.'s career to exclude the presence of pediculi and the ordinary skin infection such as scabies and tinea. They were specifically questioned with regard to (a) regularity or otherwise of the menstrual cycle (b) a history of amenorrhoea on entry to service (c) the presence of dysmenorrhoea and (d) menorrhagia. Those with cycles more or less than 28 days but still perfectly regular were classified, for the sake of convenience, and in order to avoid confusion, as regular. It was sometimes extremely difficult to decide whether a W.A.A.F. had true dysmenorrhoea

or merely suffering from symptoms present in most normal women at the menstrual period and collectively described as the menstrual molimen. Few women are completely free from menstrual discomfort and this may amount to actual pain in the sacral region or lower abdomen and is sometimes associated with headaches, depression and sickness. Cases were only classified as dysmenorrhoea when pain, sickness or headaches were so severe as to completely incapacitate them for one or two days during the menstrual period or when they frequently required treatment for their symptoms.

The following table is a summary of the results obtained :-

TABLE 1.

Year	Normal and Regular	Amenorrhoea on entry to Service	Dysmenorrhoea	Menorrhagia	Completely irregular	Total
1939	5	-	-	-	-	5
1940	186 84.54%	6 2.73%	11 5%	2 0.91%	15 6.82%	220
1941	689 83.01%	52 6.19%	31 3.73%	14 1.69%	44 5.30%	830
1942	753 82.3%	59 6.45%	33 3.60%	18 1.97%	52 5.66%	915
1943	285 83.33%	22 6.43%	13 3.80%	1 .29%	21 6.14%	342

It will be noted that all cases are correlated with their year of entry to service. Thus we have for comparison the number and percentage of cases who had the symptoms indicated in the table for each year from 1939-1943.

As will be seen from the table 2.73% of all girls entering

the W.A.A.F. in 1940 could expect to have amenorrhoea. This rose to more than double this figure in 1941 (6.19%) and rose slightly to 6.45% in 1942 and remained relatively stationary at 6.43% in 1943. These figures are slightly higher than those obtained by Schweitzer and Teebken in 1916-17 period. It must also be remembered that they compare their amenorrhoeas with the total number of gynaecological consultations while my own figures are compared with the total number of girls entering the service normal or otherwise gynaecologically. So that since the standards of comparison differ, it is obvious that the number of cases of delayed menstruation in this country during the present conflict is greater than in Germany during the last war.

It is significant that the number of cases of amenorrhoea are only equalled by the number of irregular cases and the former thus constitutes one of the greatest gynaecological abnormalities in service personnel.

I cannot offer any reasonable explanation for the sudden rise in the number of cases of amenorrhoea from 2.73% in 1940 to 6.19% in 1941. The aetiology of delayed menstruation will be discussed as a whole at a later stage, but if I might offer a suggestion at this juncture, I would say that the rise in the number of cases of amenorrhoea is roughly parallel to the military and economic situation existing in the country at that time. It is probable also that the great stepping up of recruitment into the W.A.A.F. from 1940

to the middle of 1943 was largely responsible for the great increase of cases of delayed menstruation during these years. This is evidenced by the fact that only 208 girls in the series entered the service in 1940 as compared with 830 in 1941 and 915 in 1942.

The number of cases of dysmenorrhoea varied between 5% in 1940 to 3.80% in 1943. Very few conclusions can be drawn from these figures.

Cases of menorrhagia also varied somewhat. The lowest figure recorded was .29% in 1943 and highest at 2.23% in 1942. The figures for 1940 and 1941 were .91% and 1.69% respectively.

The number of cases of irregular menstruation remains practically constant between 5.3% and 6.82%.

2. Relationship between Delayed Menstruation and occupation.

The total number of cases of amenorrhoea in the present series was 139 between the years 1940-1943. This however excludes the4 cases to be described separately at a further stage in the investigation.

Of the 139 cases of delayed menstruation 52 (37.41%) were clerks, 20 (14.39%) were cooks, 16 (11.53%) were M.T. drivers, and 9 (6.47%) were ACH/G.D., i.e. employed on general unskilled duties, such as cleaning, acting as runners, and serving in the mess, etc. Telephone operators numbered 9 (6.47%), 8 (5.75%) were equipment assistants and 7 (5.03%) were batwomen, while only 4 (2.88%) were flight mechanics.

Waitresses numbered 3 (2.16%). Only 2 cases (1.44%) occurred in each of the following trades : administrative staff, safety equipment workers, wireless operators, tailors and instrument repairer. Finally 1 (.72%) was a sparking plug tester.

These results are in direct contradiction to those of Schweitzer, who found that the greatest proportion of his cases of amenorrhoea (50%) occurred in those working in the heavy industries, e.g. munition workers, while a further 17% occurred in servant girls. Almost all the German authors attribute one of the causes of delayed menstruation to increased work. However, I am not at all convinced that that is the case and in the Service at any rate the greatest incidence of delayed menstruation falls within the class of sedentary workers. Thus it will be noted the incidence of amenorrhoea in clerks is more than twice as great as that in cooks and 13 times as great as in flight mechanics, whose work involves the expenditure of a great amount of physical energy, climbing up and down aircraft, removing heavy engine parts, and in fact do a job which was previously only restricted to men. M.T. drivers and telephone operators, whose work also involves little expenditure of energy, are also relatively high in the list with 11.53% and 6.47% respectively.

In the present series, therefore, it can be seen that the greatest number of cases of amenorrhoea occur in the sedentary

occupations such as clerks, M.T. drivers and telephone operators, while those whose duties are of a heavier nature such as waitresses, batwomen, flight mechanics and safety equipment workers, do not suffer from amenorrhoea to the same extent.

Length of the Menstrual delay.

The length of the menstrual delay is reckoned from the time of the first missed period. For instance if a patient's last period was 2.3.43 then the next period would normally be expected on 30.3.43. If this period does not appear then the delay is reckoned from 30.3.43. So that if the patient is examined on 11.4.43 then the menstrual delay at that time is 12 days.

The menstrual delay in the 139 cases of amenorrhoea was therefore calculated in this manner. Some had a delay of less than 1 month, but as this was between 20-30 days in all these cases, it was reckoned as one month for simplicity. In the others the delay was calculated to the nearest month.

The following results were obtained :-

Menstrual Delay in Months	No. of Cases	Percentage
1	9	6.47
2	29	20.86
3	62	44.64
4	16	11.51
5	5	3.59
6	15	10.79
7	3	2.15

TABLE 2. Menstrual Delay in 2,312 Airwomen.

It will be noticed that the greater number, 62 (44.64%) had a delay of 3 months while the next in frequency, 20 (86%) had a delay of about 2 months, and the least number 2.15% had a delay of 7 months.

3. The Relationship Between Delayed Menstruation and the Protein Content of the Diet.

The very detailed investigation by Teebken on the quantity and quality of the German diet during the years 1916-18, and his eventual conclusion that a deficiency of protein was the most important factor in the production of amenorrhoea prompted me to pursue this matter further. As a result, the diets of a number of Royal Air Force Stations in which cases of amenorrhoea had occurred were investigated and the total daily calorie values and the total weight in grammes of carbohydrate, protein and fat respectively were calculated.

It might be advisable to give a resumé of the quantity and type of foodstuff which may be drawn for airmen and airwomen.

The maximum daily quantity of foodstuff which may be drawn for personnel in messes is as follows :-

Women - (Eating in W.A.A.F. Mess) (14)

Bread or Flour	9.2/3	ounces	
Meat	5	"	(bone in)
Bacon	1.1/7	"	
Butter	$\frac{1}{2}$	"	
Margarine	4/7	"	
Cheese	2/7	"	
Sugar	2	"	
Salmon, herring, pilchards or canned sardines	2/7	"	

Jam			1.9/14	ounces
Milk (fresh)			1/5	"
Evaporated Milk			2	"
Powdered Milk			2/7	"
Biscuits)				
or)	12 ounces	= Bread	16	"
Flour)				
Meat - Boneless)	4 $\frac{1}{2}$	"		
or)		= Meat in Bone	6	"
Preserved Meat)	4	"		
Bacon, canned	2 $\frac{1}{2}$	"	= Bacon, Mild canned	3 "

In some Stations however where there is a large W.A.A.F. personnel, the airwomen are allowed to eat in the airmen's mess and thus their rations are the same as the men's.

The following is therefore the official allowance for airmen :-

<u>Airmen's Ration</u>	<u>Ounces Daily</u>
Bread or Flour equivalent to	12.1/3
Meat (Bone in)	6
Bacon	1.2/7
Butter	$\frac{1}{2}$
Margarine	1
Cheese	6/7
Tea	2/7
Sugar	2
Tinned Fish (e.g. Salmon)	3/7
Jam	1.1/7
1 egg when available	
Porridge	1
Potato	8
Cabbage	8
Peas	1
Haricot Beans	6/7
Liver	4 (per fortnight)
Fish (wet)	6 (per week)
Spam	3 (per week)
Cooking Fat	$\frac{1}{2}$ (daily)
Rice	1 (daily)

The following additional allowances are made :

Beetroot, rhubarb, prunes, apricots, dried apple, sultanas or pears are drawn as 4 ounces weekly per individual.

Sausages which are a relatively frequent article of diet are not limited officially but rarely exceed 4 ounces per meal.

Condensed whole unsweetened milk (U.S.A.) = 3 ounces daily
(615 calories
per pound)

Milk Powder Skimmed = 2/7 ounces daily
(1500 calories
per pound)

1 ounce Biscuits = 1.1/3 ounces bread.

It will be noted that bread, flour and biscuits are interchangeable but 1 ounce of flour or biscuits is equivalent to 1.1/3 ounces bread. Similarly boneless meat, preserved meat and meat and vegetables are interchangeable with meat "bone in" in the proportions of $4\frac{1}{2}:4:12:6$ respectively.

It will be seen that although many articles of diet are given as a daily quantity some foods such as fish, liver, dried fruits are only issued in small quantities weekly. It was found extremely difficult, therefore, to make a total calorie check on the tables supplied above. Specimen menus were therefore obtained from the different Stations and the calorie values, protein, carbohydrate and fat contents were thus calculated from the diets.

Only three specimen menus will be quoted in full, drawn at random from the Stations under investigation. See TABLES - 3, 4 and 5.

Menu	Weight in ounces	Calories per ounce	Carbo-	Protein	Fat	Total Calories
			hydrate	IN GRAMMES		
Porridge	1	108	18	4.6	2	108
Bacon	1.2/7	153	0	9.2	17.6	196.7
Egg	2	37	0	7.6	4.8	74
Bread	8	69	114.4	16	3.2	552
Butter	1 1/4	225	0	0	12.5	112.5
Milk	1 1/4	19	6	4	4	76
BREAKFAST			138.4	41.4	44.1	1118.3
Brown Stew	6	65	0	48	22.2	390
Potatoes (boiled)	8	21	42	0	0	168
Brussel Sprouts	8	3	6	0	0	24
Peas	1	21	5.25	0	0	21
Stewed Apple	4	15	15	0	0	60
DINNER			68.25	48	22.2	663
Sausage	4	80	?	?	?	320
Biscuits	2	92	38	5.3	1.06	184
TEA			38	5.3	1.06	504
Spaghetti	4	98	100.8	6.4	.4	392
Cheese	6/7	123	1.1	7.52	7.9	105.4
Tea, Coffee, etc.						
SUPPER			101.9	13.92	8.3	497.4
Jam	1.1/7	81	22.5	.23	0	92.5
Sugar	2	120	60	0	0	240
Cooking Fat	1 1/2	253	0	0	14.2	126
Margarine	1	226				226
Condensed whole) Unsweetened Milk)	3	38.5	?	?	?	115.5
Flour	1.2/3	92	31.8	4.4	.9	153.3
Milk Powder	2/7	93.7	?	?	?	26.8
Dried whole Egg	3/7	144.6	?	?	?	63.4
EXTRAS			114.3	4.63	15.1	1043.5
TOTAL.						
Breakfast			138.4	41.4	44.1	1118.3
Dinner			68.25	48	22.2	663
Tea			38	5.3	1.06	504
Supper			101.9	13.9	8.3	497.4
Extras			114.3	4.63	15.1	1043.5
TOTAL			461	113.23	80.76	3826.2

TABLE No. 3 (26, 27, 28).

Menu	Weight in ounces	Calories per ounce	Carbo-	Protein	Fat	Total Calories
			hydrate	IN GRAMMES		
Cornflakes	1	108	18	4.6	2	108
Cold Ham	1.2/7	153	0	9.2	17.6	196.7
Sausage (cold)	4	80	?	?	?	320
Bread	8	69	114.4	16	3.2	552
Butter	$\frac{1}{2}$	225	0	0	12.5	112.5
Milk	4	19	6	4	4	76
BREAKFAST			138.4	33.8	39.3	1365.2
Cold Roast	6	65	0	48	22.2	390
Cream Potatoes	8	21	42	0	0	168
Lettuce	4	3	3	0	0	12
Peas	1	21	5.25	0	0	21
Stewed Rhubarb	5	3	3.7	0	0	15
DINNER			53.95	48	22.2	606
Salmon (tinned)	3	40	0	17.7	5.4	120
Lettuce	4	3	3	0	0	12
Beetroot	4	9	9	0	0	36
Cakes	2	92	38	5.3	1.06	184
TEA			50	23	6.46	352
Meat Paste	2	54	?	?	?	108
Cheese	6/7	123	1.1	7.5	7.9	105
SUPPER			1.1	7.5	7.9	213
TOTAL.						
Breakfast			138.4	33.8	39.3	1365
Dinner			53.95	48	22.2	606
Tea			50	23	6.46	352
Supper			1.1	7.5	7.9	213
Extras from Table 3			114.3	4.63	15.1	1043
TOTAL			367.75	116.93	90.96	3580

TABLE No. 4 (Cold Menu).

Menu	Weight in ounces	Calories per ounce	Carbo-	Protein	Fat	Total Calories
			hydrate	IN GRAMMES		
Shredded Wheat	1	108	18	4.6	2	108
Kidney Bread	4 8	58 69	0 114.4	36.6 16	10.8 3.2	232 552
Butter	$\frac{1}{2}$	225	0	0	12.5	112.5
Milk	4	19	6	4	4	76
Tea, etc.						
BREAKFAST			138.4	58.2	32.5	1080.5
Roast Beef	6	65	0	48	22.2	390
Potatoes	8	21	42	0	0	168
Carrots	8	3	6	0	0	24
Apple	4	15	15	0	0	60
DINNER			63	48	22.2	642
Meat Pie	4	80	?	?	?	320
Cake and Biscuits	2	92	38	5.3	1.06	184
Tea, Coffee, etc.						
TEA			38	5.3	1.06	504
Cod (fried)	5.6	24	0	30.2	1.7	134.4
Peas	1	21	5.25	0	0	21
Cheese	6/7	123	1.1	7.5	7.9	105.4
SUPPER			6.35	37.7	9.6	260.8
<u>TOTAL.</u>						
Breakfast			138.4	58.2	32.5	1080.5
Dinner			63	48	22.2	642
Tea			38	5.3	1.06	504
Supper			63.5	37.7	9.6	260.8
Extras (from Table 3)			114.3	4.63	15.1	1043.5
TOTAL			360.05	153.83	79.46	3530.8

TABLE No. 5.

A similar investigation of other menus which will not be quoted in full yielded the following results :-

Diet	Carbohydrate IN GRAMMES	Protein	Fat	Total Calories
1	442.8	102.2	84.7	3645.5
2	332.05	116.3	92	3574.78
3	297.38	142	91	3523.3

TABLE 6. Calorie value and carbohydrate, protein and fat content of 3 further menus.

The above values are for airwomen who eat in the air-men's mess, but as has already been said, on some stations where W.A.A.F. strength is small, the airwomen eat in a separate mess of their own and thus as will be seen from a previous table certain differences arise in the following commodities.

Foodstuff	Airwomen	Airmen	Difference
Bread	9.2/3 ounces	12.1/3 ounces	- 2.2/3 ounces
Beef	5 ounces	6 ounces	- 1 ounce
Jam	4 1/4 ounces	1.1/7 ounces	+ 1 1/2 ounces
Bacon	1.1/7 ounces	1.2/7 ounces	- 1/7 ounce

TABLE 7. Differences between airmen's and airwomen's rations.

Thus if we compute the values of the above foodstuffs in the difference column in the terms of calories the following will be obtained :-

Foodstuff	Weight in ounces	Calories per ounce	Carbo-	Protein	Fat	Total Calories
			hydrate	IN GRAMMES		
Bread	- 2.2/3	69	38.1	5.3	1.1	184
Beef	- 1	65	0	8	3.7	65
Bacon	- 1/7	153	0	1	2	21.8
			38.1	14.3	6.8	270.8
Jam	+ 1/2	81	2.8	.23		40.5
			35.3	14.07	6.8	230.3

TABLE 8. Amounts of carbohydrate, protein and fat, to be subtracted to obtain airwomen's ration allowance.

Thus if 35.3 grammes carbohydrate, 14.07 grammes protein, and 6.8 grammes are deducted from the diets in tables 3 - 5 we will obtain the weights of these substances when the airwomen eat in their own mess, similarly to obtain the calories value of the diet, deduct 230.3 calories from the above total calorie value of the menus as shown in the above tables.

Certain difficulties in constructing an accurate table of calorie values must be pointed out. The difference between airwomen messing alone and in the communal airmen's mess has already been pointed out. One question which arose was - what was the content of a sausage or a meat pie in terms of protein, carbohydrate and fat. No amount of interrogation could elicit a satisfactory result from the various catering officers concerned. I was informed that sausages varied depending on whether they were made from food left over from other meals or obtained direct from the Navy, Army and Air Force Institutes. The same applied to

the mysterious pork-pie. So the enigma of the sausage and the pork-pie remained unsolved and their content of protein, carbohydrate and fat were merely indicated by a question mark. The calorie value was taken as 80 calories per ounce. Question marks in various parts of tables 3 - 5 also indicated that the weights of carbohydrate, protein and fat of certain foods were not known although their calorie value was to a greater or lesser extent definitely established. As a result therefore the true total weights of carbohydrate, protein and fat is slightly greater than that shown in the tables.

Further, a number of articles in the diet have been omitted from the tables although present in the menu, e.g. custard, tea, jam rolls, welsh rarebit, puddings, etc., either due to the fact that their calorie value was too small for inclusion or that they are compounded from jam, flour, bread and cheese each of which is already accounted for in the diet.

Variations in the diet are found to occur from time to time in the same station and certainly on different stations depending on supply and demand and ease with which certain commodities can be obtained locally.

The full ration of potatoes is considered to be taken at dinner time although they may also be present at other meals, similarly, the full ration of bread, butter and milk is considered to have been taken at breakfast time. It must be

pointed out that only airwomen are allowed 1/5th pint fresh milk daily in addition to the normal diet.

From the tables, therefore, it can be seen in no case does the calorie value of the diet fall below 3,500 calories per day and in most cases it is 100-300 calories more than this. Such a diet can be considered as adequate for the normal person of average weight, performing heavy labour even after deducting 230.3 calories per day when airwomen are in their own mess. This conforms to the standard of requirements as laid down by Air Ministry (18), which is a minimum of 3,500 calories per day for male personnel and 3,200 calories per day for female personnel.

With regard to the protein content of the diet, a glance at tables 3 - 5 will show that the weight of protein is rarely less than 100 gm. and in many cases more. Taking 1 gramme of protein per kilo as adequate, it will be seen that 100 grammes of protein daily is sufficient for the needs of most individuals.

Thus it can be shown that Teebken's contention that a deficiency of protein is an essential factor in the production of delayed menstruation has little foundation in the production of the syndrome as applied to airwomen. Indeed it can be stated more dogmatically that if any single factor is to blame for the production of the amenorrhoea it is certainly not a deficiency of protein as the condition occurs with the frequency shown in the earlier part of this work in the

presence of an adequate protein intake.

Although no conclusion can be reached as to the vitamin and salt content of the diet we can assume that if the menu is well composed and varied and contains the allotted quantities of butter, milk, eggs and fruit, the vitamin content will be sufficient for normal needs. It cannot be denied that there is a possibility of a "subclinical" deficiency of vitamin B, which has been overcome to a certain extent by the consumption of "war-time" bread or "National Wheatmeal" bread which contains 85% wheat grain, bran part excluded. A deficiency of vitamin C is also a possibility to be considered, as it is not always possible to obtain fresh fruit. However there is no evidence to show that this vitamin is responsible for amenorrhoea. It is a fact however that deficiencies if present can easily be made good by supplying the synthetic vitamin, and most Station Sick Quarters are stocked with adequate quantities of ascorbic acid. In addition to the food which the airmen and airwomen obtain from the mess, such articles as chocolate, cakes, fruit and many other unrationed articles of food may be obtained from the Navy, Army and Air Force Institutes and it is unusual for personnel not to obtain another 200-300 extra calories in this manner.

From what has already been said it can be seen that no nutritional deficiency exists in the stations investigated and that the protein content of the diet is adequate for

normal needs. Yet in spite of this delayed menstruation occurs in 2-6% of all female personnel. It can therefore be emphatically stated that a lack of food and particularly a deficiency of protein has little if anything to do with the production of the symptom complex.

4. Other Symptoms Besides Amenorrhoea.

The symptoms of delayed menstruation apart from the absence of the menstrual period are few. Perhaps the two most prominent are - an increase in weight (this being really a sign) and debility. It may be agreed that an increase in weight is a common occurrence in girls entering the service. But it will be shown later that provided the amenorrhoea is present for some months that the increase in weight is greater than would be expected in normal girls by comparison. The debility manifests itself as weakness, tiredness and inability to concentrate. This debility is probably the result, rather than the cause of the amenorrhoea, as each of the patients felt perfectly well before the onset of the symptom complex. In some cases, especially those in which the amenorrhoea persists for 6 months or more, headaches, dizziness and fainting attacks are common. On the other hand there is no doubt that some patients regard the absence of the menstrual period with a measure of relief rather than anxiety as it removes the concomitant discomfort associated with bleeding and in fact apart from an undue increase in weight feel perfectly healthy. The delay in the menstrual

period lasts from a few days to 6 months. In one of my cases the delay was 20 months. But in every case the periodic bleeding returned as suddenly as it had ceased, generally after 3 months while the airwoman is at home on her first leave. In one case only was there any history of low back pain and a suggestion of the menstrual molimen was experienced.

Significance of obesity in Amenorrhoea Patients.

One of the most prominent signs in cases of delayed menstruation is great increase in weight. But it is a well known fact that many girls on entry to service increase in weight whether they have amenorrhoea or not, thus it was extremely difficult to decide whether the obesity in the amenorrhoeic patients was normal or abnormal.

In order to decide this question 150 normal airwomen were weighed and their weight on entry to service was obtained from their original medical documents. Thus the increase or decrease in weight and length of service could be plotted on a chart (appended below). Those patients suffering from delayed menstruation are marked in red ink for comparison.

It will be seen from the graph that the increase in weight in patients with delayed menstruation is greater than the average increase in weight of normal airwomen for comparison.

A number of other interesting features are illustrated in the chart.

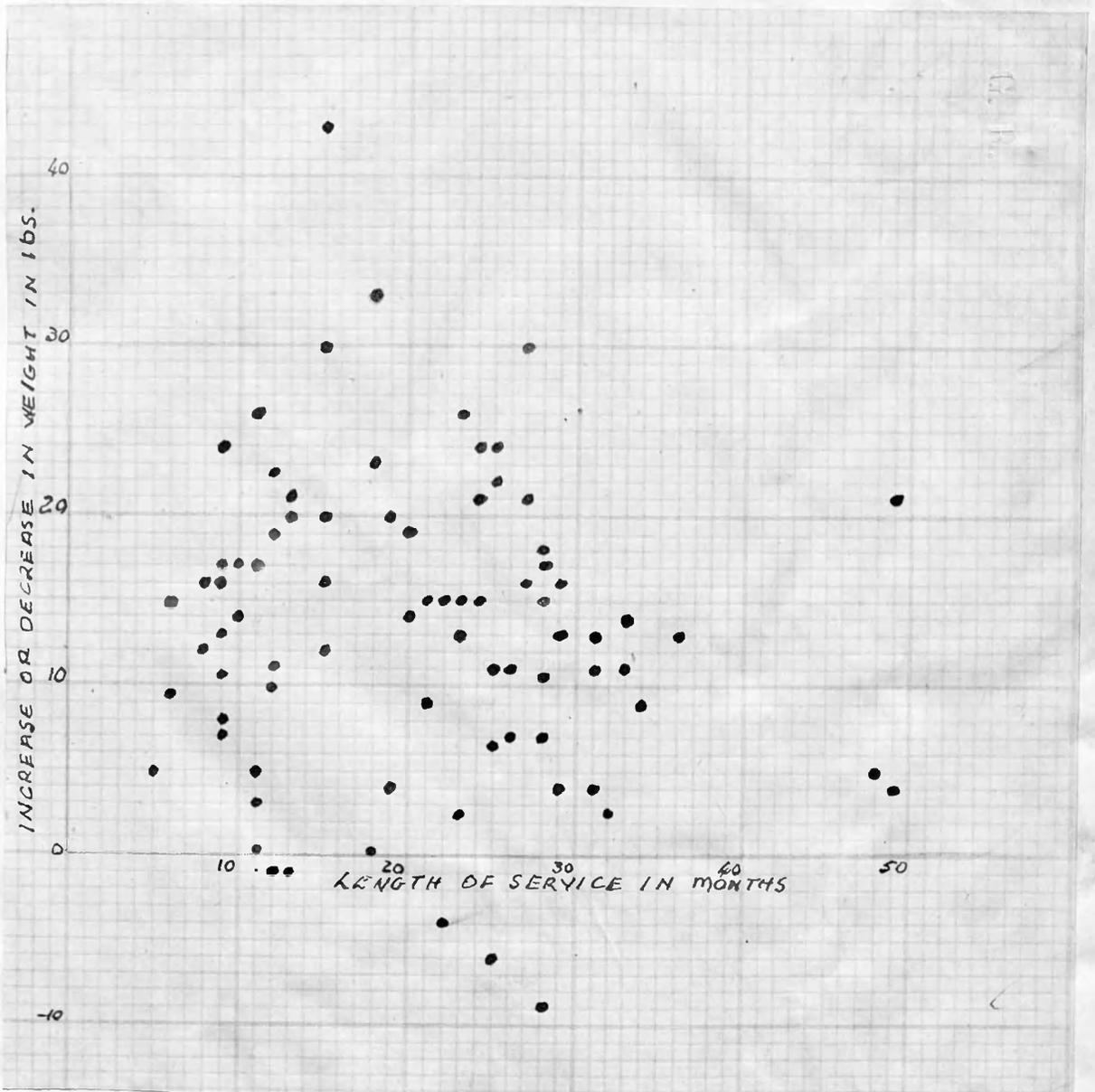


Fig. 1. Graph of length of Service to increase in weight in 75 airwomen.

- Normal.
- Amenorrhoeic.

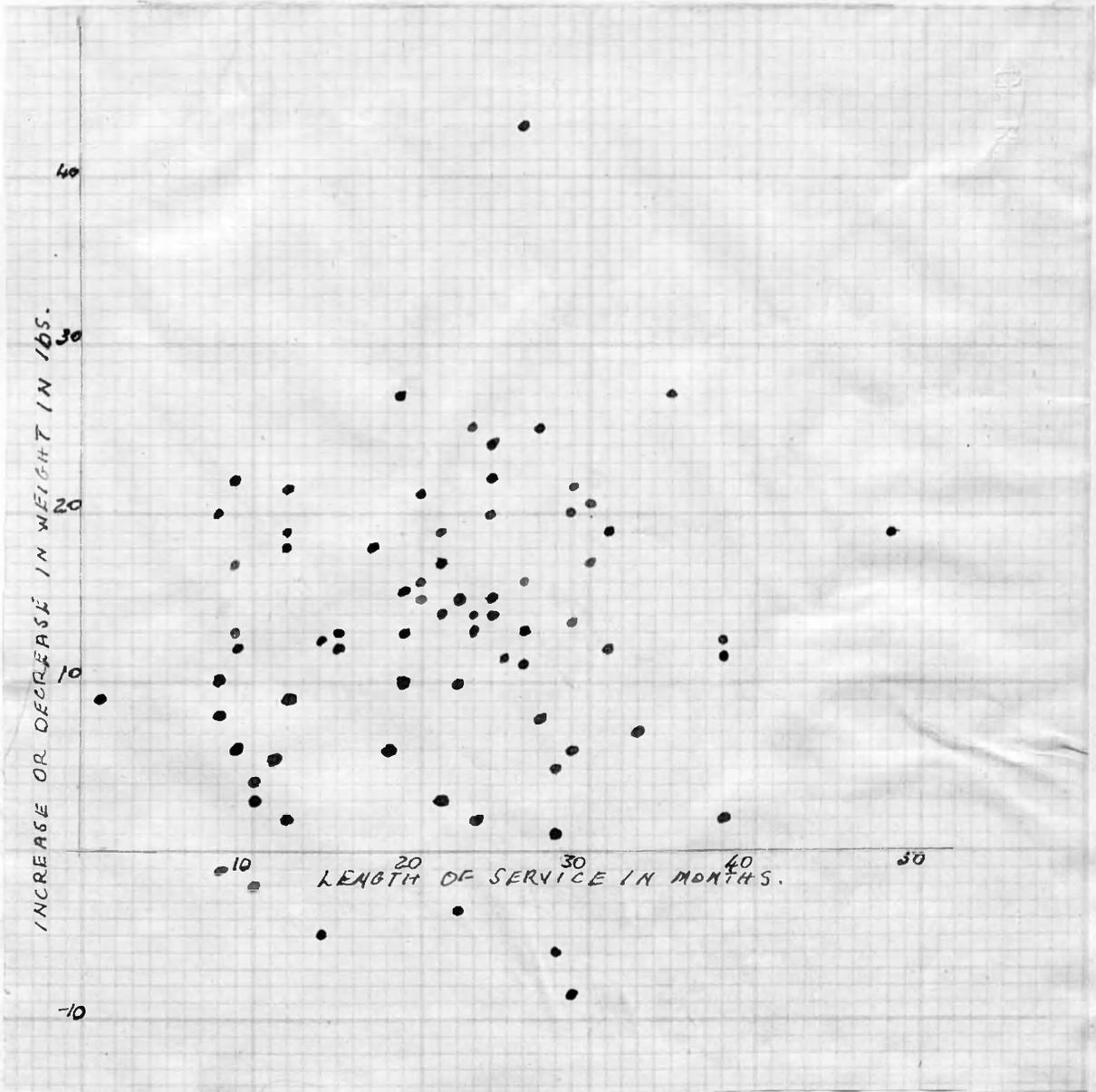


Fig. 2. Graph of length of service to increase in weight in 75 airwomen.

Of the 150 airwomen weighed 137 had increased in weight since entry to service, 11 had lost weight while 2 remained stationary. That is 91.3% of the total weighed increased in weight. The greatest increase appears to occur from 10 to 30 months after joining the service.

The cause of this increase in weight is not difficult to explain.

Firstly, we have the regularity of the meals, each adequate in calorie value and essential foods. Furthermore, the meals are eaten in congenial company and sufficient time is given to enjoy and digest the food.

Secondly, the work in many cases is hard, thus stimulating the appetite.

Thirdly, unrationed articles of food are made easily available by the N.A.A.F.I. canteen services.

The loss in weight in each of the 11 patients mentioned can be explained by some illness prior to weighing.

5. Differential Diagnosis and Choice of Case.

At first sight it might appear comparatively easy to make a diagnosis of delayed menstruation, but a brief reference to the table on pages 3 and 4 will illustrate the many difficulties which arise.

It is essential to make a correct diagnosis in this condition before treatment is begun as obviously in the wrong type of case no results can be expected and a more serious condition which has been overlooked may be progressing

apace. At the outset it may be stated that the diagnosis of delayed menstruation is made by a process of elimination. The amenorrhoea must not be regarded as benign until all local disease in the uterus and adnexa has been eliminated and such general conditions as endocrine dysfunction and organic debilitating diseases, e.g. tuberculosis and anaemia, have been ascertained to be absent.

So that the accurate diagnosis of delayed menstruation rests on :

- (1) A complete gynaecological examination to exclude local disease.
- (2) Estimation of basal metabolic rate to eliminate hypothyroidism.
- (3) Estimation of red and white cells and haemoglobin percentage.
- (4) Clinical examination and X-Ray of the chest, if necessary.
- (5) Biopsy of the endometrium to determine whether an active mucosa is present either in the proliferative or premenstrual stages.
- (6) General physical examination to eliminate the other causes of amenorrhoea.

Thus it will be seen if one wishes conscientiously to make an accurate diagnosis, a number of investigations must be undertaken. Fortunately the complete examination as detailed above need not be done as in most cases the various causes of amenorrhoea may be eliminated by clinical

examination alone. In the small series of cases investigated, the facilities for doing any extensive biological examinations were negligible and thus clinical examination had to be depended upon for diagnosis. Failures were therefore inevitable as a result of this and in unsuccessful cases the negative result was as much due to misdiagnosis as absence of activity of the drug used.

Having excluded the presence of organic disease including pregnancy, lactation and climacteric, one could say with more or less certainty that the condition was a case of delayed menstruation.

One important difficulty however arises in diagnosis and that is, the differentiation of minor degrees of endocrine dysfunction from true delayed menstruation. It must be noted that in all cases of delayed menstruation, an increase in weight is a constant feature. This however is not unusual in any airwoman whether she has amenorrhoea or not. Yet it is possible that in some cases the presence of the adiposogenital syndrome, to a minor degree, may have been the cause of the amenorrhoea. One important indicator of probable endocrine dysfunction is a history of irregular menstruation, oligomenorrhoea or epimenorrhoea before complete cessation of the menstrual period, whereas in true delayed menstruation, the periods are usually perfectly regular until the onset of amenorrhoea.

In choosing a case of delayed menstruation for treatment

therefore, the following facts must be borne in mind :-

- (1) There should be no organic disease in any of the body systems.
- (2) There should be no history of previous irregularities in the menstrual cycle.
- (3) The amenorrhoea should not be more than six months duration.

Qualifying this last statement it is reasonable to assume that the absence of the menstrual flow for a prolonged period of time would lead to degenerative changes in the uterine endometrium, which would make it less responsive to therapy.

6. A Form of Therapy.

The therapeutics of delayed menstruation is befogged with the bewildering number of "cures" advised, sufficient evidence that none of these is very effective.

The adoption of a rational basis for therapeutics depends on the accurate differentiations of the various types of amenorrhoea. It is obvious that the treatment prescribed for primary amenorrhoea will be useless or even harmful in secondary amenorrhoea and that delayed menstruation (which I consider to be in a separate category from the above 2 types) will require a still different form of therapy.

Bearing in mind the classifications of amenorrhoea as outlined in pages 3 and 4, it will be seen that in primary ~~ovarian~~ amenorrhoea, the treatment is mainly by oral or parenteral administration of ovarian hormones or the

anterior^{or} pituitary gon^oadotropic hormones. Primary amenorrhoea due to extirpation of ovarian tissue, or as occurs in the climacteric, will react to a greater or lesser extent to the above treatment, although it must be said that except in the latter condition the doses of hormone required are large and the results are disappointing. In these cases it is merely a replacement therapy. Primary uterine amenorrhoea due to a pubescent or infantile uterus or as a result of hysterectomy or as a result of atresia of the cervix, will not of course react to the above therapy. It must be admitted that the administration of ovarian preparations, in the treatment of primary amenorrhoea has proved disappointing, due to the fact that relatively enormous doses of oestrone and progesterone are necessary, that they must be administered over a long period of time, and that active and pure extracts of these hormones are sometimes difficult to obtain. Further, the expense of the treatment is always a disadvantage in those with low economies.

Secondary amenorrhoea if due to an endocrine cause, such as thyroid, pituitary or suprarenal dysfunction requires the appropriate hormone preparation. Secondary amenorrhoea due to anaemia, tuberculosis, and specific fevers requires the treatment of the exciting cause and the menstrual periods should return as a result of cure of the predisposing illness.

I have purposely omitted the details of the treatment

of the above conditions. I have only indicated a line of approach to rational therapy - a modus operandi, which is perhaps simplified by adopting the clinico-pathological classification in pages 3 and 4. Only too often one finds patients indiscriminately treated for long periods of time with oestrone and progesterone without the physician having a true insight into the underlying factors. Sometimes he is successful, more often he is not. Thus one finds patients treated for many months with iron on the mistaken diagnosis of anaemia when the real exciting factor is a thyroid deficiency and vice versa. It is obvious therefore before any treatment for amenorrhoea is instituted, a complete and meticulous examination of the patient is essential with specific reference to (1) disease in the uterus or adnexa (2) basal metabolic rate (3) haemoglobin values and red cell count (4) hormonal dyscrasias (5) the presence of tuberculosis (6) the presence of general diseases such as nephritis, diabetes and cardiac disease.

Having ascertained that none of the above six factors is operative in the production of the amenorrhoea, the condition (after excluding pregnancy, climacteric and lactation) can be considered to be delayed menstruation.

The treatment of amenorrhoea is described by different authors from about 1917 onwards. Unfortunately most of the workers do not state specifically which type of amenorrhoea is referred to. But in most cases it is either primary,

due to ovarian dysfunction or secondary to endocrine dysfunction. No doubt many of the cases are true cases of delayed menstruation.

As has already been noted, Köhler (1917) appeared to have some success using yohimbin and Hirsch in the same year lays great claim to the efficacy of ovarian extracts.

In 1928 Kaplan¹⁹ had good results using high voltage X-ray. Out of 58 cases of amenorrhoea, 30 menstruated. The data given is 200 k.v. and 4 m.a. at 20-30 cm. distant over right and left, posterior and anterior ovarian areas. Alternate doses are given with about 1 week apart. Total dosage is 10-15% skin erythema dose. The rationale of this form of therapy is not explained and one would imagine that if the treatment were administered without due care, instead of the menstrual flow appearing, sterility would occur.

A more recent paper by Kauffman²⁰ on the treatment of amenorrhoea indicated that the doses of hormone necessary for the production of the menstrual flow in castrated women were far larger than those used therapeutically. For the development of the endometrium on one occasion, not less than 1 million international units of follicular hormone are necessary, in a castrated woman. In secondary amenorrhoea, (by which I presume is amenorrhoea in the absence of any organic lesion) Kauffman states that the outlook is more promising but small doses of hormone are useless.

Administration of Prolan A is not encouraging, in the dosage of 200 units or more twice weekly intramuscularly.

The scheme given by Kauffman for substitution therapy is as follows : On the 1st, 4th, 8th, 11th and 15th days 250,000 units oestrone intramuscularly. On the 19th, 20th, 21st, 22nd and 23rd days, 7 rabbit units of progesterone are administered. On the 25th, 26th and 27th days menstruation occurs.

Bernar Zondek²¹ writing of his experience on this subject in his clinic in Jerusalem, states that many of his patients suffer psychically from an absence of menstruation, that an inferiority complex develops and the associated nervous and vaso-motor disturbances prevent the patient from attending to her household duties. The author states that bleeding can occur either from a proliferative endometrium (pseudo-menstruation) or from a progestational endometrium (real menstruation). The doses required are 30 to 40 mg. oestradiol benzoate and 30-40 mg. progesterone. The oestradiol was given in 8 injections of 5 mgm. each spread over 20 days then followed by daily injections of 5 mgm. progesterone for 5 days. Zondek also observed that if a normally menstruating woman receives in the early part menstrual phase 10 mgm. progesterone for 5 days another bleeding will occur about 3 days after the last injection. Biopsy showed that this bleeding comes from a thin mucous membrane, containing only a few glands which have not had time to undergo proliferation.

Using these results clinically, Zondek found that a 5 day treatment with a total dose of 50 mgm. progesterone alone, was sufficient to produce bleeding in amenorrhoeic women. He never succeeded in producing the period by the use of progesterone alone in women with primary amenorrhoea or after bilateral ovariectomy. He treated 20 women with secondary amenorrhoea by progesterone alone, bleeding was obtained in 18, i.e. 90%. Of the 18 successful cases 9 were followed up and it was found that in 4 no further bleeding occurred; in 5 bleeding occurred on 3 subsequent occasions only. He then tried giving 25 mgm. a day for two days and bleeding occurred in 6 out of 7 patients within 4 days of the last injection. Attempts to use 50 mgm. in one injection failed. Thus he concludes that the bleeding depends on 2 factors (a) the dose of progesterone (50 mgm. minimum) (b) the duration of the treatment (2 days minimum). In cases of primary amenorrhoea, he regards the injection of oestrogens as essential and injects 1 mgm. oestradiol benzoate and 10 mgm. progesterone daily for 5 days. The best results seem to be obtained by giving 50 mgm. progesterone spread over 5 days.

The disadvantage in producing menstruation in the above manner is (1) the large number of injections necessary (2) relatively enormous doses required (3) the great expense incurred. 1 milligramme of progesterone costs roughly 1 shilling, so that this form of treatment is

limited to a certain class of population who can afford the expense. Further, there is no doubt that many women prefer to remain amenorrhoeic rather than undergo the discomfort or the expense of injection treatment.

In June 1942, J. Cash King²² described the effect of Roentgen therapy to the pituitary gland on 230 private patients for functional disorders of endocrine origin manifested by disturbances of the menstrual cycle, headaches, nervousness, fatigue, subnormal sex life, sterility, low metabolic rates and abnormal weights. Those patients with definite organic lesions were unsuitable for this form of therapy, e.g. sterility due to definite pathology in the fallopian tubes. The technique employed was as follows : KVP200, added filter 0.50 mm. cu., 1.0 mm. al. distance 50 cm. generating a ray with half value layer of 1.20 mm. cu., and a dosage of 75 measured in air. The treatment is given first through 6 cm. parts in each temporal region towards the pituitary. The second treatment one or two days later through parts 8-10 cm. diameter. A further 1 or 2 courses were given each after a lapse of 28 days.

The effects on cases with symptoms except amenorrhoea will not be given but seem to be uniformly successful.

In 29 patients with amenorrhoea average age 27, average duration of amenorrhoea 10.5 months, a regular monthly cycle was established in 18 of the 29. One of the patients gave birth to a child after treatment, 7 were classified as

unimproved and 4 were not followed up.

Without attempting to discredit the author's obvious success in all the symptoms mentioned above, it is hard to believe that the underlying cause of these symptoms was materially affected. If however these symptoms were merely a manifestation of disturbance of function (as most of them would appear to be) then it is probable that the element of suggestion would be as potent a therapy as the roentgen therapy itself and improvement would have been obtained whether the pituitary, suprarenal or any other part of the body was irradiated.

Text books²³ in gynaecology besides recommending these forms of treatment, also suggest the following :-

- (a) Thyroid (B.P.) $\frac{1}{2}$ -1 grain daily in cases which show a tendency to overweight and hypothyroidism.
- (b) Ferri et ammon. citrate gr. 30 t.d.s. in cases in which hypochromic anaemia is suspected or proved.
- (c) Graduated exercises, psychotherapy and change of environment.
- (d) Gonadotrophic hormones.

A number of cases of delayed menstruation, unfortunately unrecorded, were treated as far as possible on the lines laid down above. Treatment of patients with oestrone-progesterone therapy, as laid down by Kauffman and Zondek, was extremely difficult for the following 2 reasons (1) difficulty of obtaining and prohibitive cost of the hormones (2) non-

co-operation of the patients who did not wish to have a large number of injections and preferred to remain amenorrhoeic. Stilboestrol was therefore administered orally instead of oestradiol benzoate and progesterone in the form of Progestin (B.D.H.) 1 international unit per c.c. was administered intramuscularly.

The treatment given in 2 patients was as follows :- Stilboestrol 5 mgm. t.d.s. daily for 14 days and on 19th, 20th, 21st, 22nd and 23rd days progesterone, 5 international units daily intramuscularly. No bleeding occurred in either of these cases.

Where pituitary dysfunction was thought to be the underlying cause of the delay in the menstrual flow as evidenced by an undue increase in weight, gonadotropic hormone was administered in the form of antuitrin S (Parke, Davis & Co.) 2 c.c. intramuscularly (100 international units per c.c.) 3 times weekly for one month. One case was treated in this manner and again no bleeding occurred.

Thyroid was not administered as it was not considered a useful form of therapy in the absence of more definite evidence of hypothyroidism.

The 3 cases which did not respond to the therapy outlined above were also given ferri et ammon cit. gr. 30 t.d.s. and a course of graduated exercises by the physical training instructress, without any results.

I was unable to keep trace of these patients owing to

postings and therefore the late results of the treatment are unknown.

The realisation that exercises, iron tonics, change of environment, electrotherapy, endocrine therapy and psychotherapy were either not very effective in the treatment of delayed menstruation or were impracticable prompted me to investigate further avenues of approach to this subject.

An exceedingly interesting and important paper by Samuel Reynolds²⁴ in 1939 threw a new light on the whole subject and led future investigators to evolve a new treatment for delayed menstruation, which, as will be shown later, is considered to be eminently successful. Reynold's work was an investigation into the acetyl-choline content of uteri before and after administration of oestrone to ovariectomised rabbits.

Rabbits of a mixed stock were not used for experiment until 17-32 days after operation. The uteri were removed and placed in 10% trichlor-acetic acid using $1\frac{1}{2}$ -2 c.c. per gramme of fresh tissue. Method of extracting and testing were exactly the same as that indicated by Change Gudden (1933) (Jour. Physiol. 7; 9; 255). The extracts were tested on frog's rectus abdominis muscle. A series of graded responses were obtained by using graded doses of acetyl-choline, after which the activity of the unknown extract was tested and compared.

In a series of 19 rabbits which did not receive previous

oestrone treatment and were ovariectomised, extracts were made from the uteri of 8 animals and tested on uneserinised muscle. These extracts were found to be completely devoid of activity except 2. Extracts of the remaining uteri were tested on eserinated muscle and were completely devoid of activity except 5 which were negligible.

In his second experiment a group of 13 rabbits were used following ovariectomy and extracts were made of uterine muscle 1 hour after oestrone injection. 8 extracts were tested on uneserinised rectus muscle and 7 of these extracts were tested on eserinated muscle. 6 of the 8 extracts showed activity equivalent to .5-.4 gm. of acetyl choline per gramme of uterus. On the eserinated muscle all but 2 of 12 extracts tested were active being equivalent to 0.2-1.0 gm. acetyl choline per gm. fresh tissue.

The identity of the active substance was shown by (1) potentiation with eserine (2) atropine inhibition (3) inactivation with sodium hydroxide (4) inactivation with blood unsuccessful.

That the production of acetyl choline was independent if any nerve connection was shown by doing both an ovariectomy and transplanting the cervical region on to the anterior abdominal wall in a series of 3 operations. Extracts of uterus were sufficient for 2 tests both of which were positive for acetyl-choline.

Using eserinated frog's rectus the activity of uterine

extracts of 7 rabbits (ovariectomised) were tested at the end of 6 hours after injection of oestrone. Extracts of 7 others were tested at the end of 12 hours after injection of oestrone. 4 of the rabbits of the 6 hour period failed to have an acetyl choline content. At 12 hours only 2 animals showed any activity.

Thus Reynolds concludes that when oestrone is injected into ovariectomised animals, the initial hyperaemia of the uterus coincided with an increase in the acetyl choline content. In consequence of the vaso dilation profound changes take place in the distribution of fluid in the uterus. It appears that acetyl choline as a vaso-dilator is released as a result of oestrogenic stimulation of the uterus and the hyperaemia attributed to oestrone may be due in part to the liberation of acetyl choline. This action takes place independently of any nerve connections.

This most interesting sidelight on the part played by acetyl choline in producing hyperaemia of the uterus, previously regarded as the result of oestrone stimulation, was further investigated by Hechter, Lev and Soskin²⁵ in 1940. The problem they set out to solve was whether the oestrone directly stimulated the cells of the uterus and vagina and causes hyperaemia by increasing their metabolism or is vasodilation the primary effect and the cellular changes secondary.

64 adult female mice were castrated and 13 days later

were given a subcutaneous injection of 10 R.U. dihydrooestrone benzoate in oil. They were then divided into 2 groups and one group received subcutaneous injection of atropine. After 48 hrs. both groups of animals were killed and the uteri were examined for changes in hyperaemia, distention, water accumulation and proliferation.

The uteri of mice which had received oestrone alone showed definite gross hyperaemia in 48 hrs. The uteri of mice which received atropine as well as oestrone showed no hyperaemia in 24 hrs. Microscopically there was a definite decreased vascularity in the atropine treated animals, in the muscle and endometrium. The inhibitory effect of atropine on the oestrone stimulation of the muscularis mucosa was proportional to the inhibition of the hyperaemia. It is evident from these results that the effect of oestrone on the uterine lining epithelium is not secondary to hyperaemia since oestrone exerts its usual action in the absence of increased vascularity. It appears, however, that the maximal hypertrophy of the endometrial stroma, of the endometrial glands and of the muscularis mucosa is dependent on hyperaemia.

Attempts were then made to produce hyperaemia in the absence of oestrone. Prostigmin could not be used for this purpose as the mice died with sublethal doses. Yohimbin was used instead: 16 adult female mice were castrated, 8-30 days later each mouse was given yohimbin subcutaneously.

48 hours after the first injection the animals were killed. The following table is quoted from the author's article showing the relationship between hyperaemia and vaginal cornification following (1) oestrone injection (2) oestrone + atropine (3) yohimbin.

<u>No. of animals</u>	<u>Vaginal cornification in 48 hours</u>
Oestrin alone	8
Oestrin + atropine	0
Yohimbin	13

It is clear that atropine prevents the usual action of oestrone on the vaginal mucosa. The results indicate that the action of oestrin on the vaginal mucosa is not specific but is secondary to the vascular effects. "Since Hyperaemia", the authors state, "is under the influence of the parasympathetic system, it is not difficult to understand the well known profound influence of mental and physical strain on the menstrual history of women".

This is the first published attempt at a scientific explanation of the various anomalies of the menstrual cycle as it occurs under different environmental states. Further experimentation (which will be detailed later) by Taubenhaus and Soskin in 1941 has gone a long way to elucidate the factors governing delayed menstruation itself. Here we have an inkling into the part played by the parasympathetic nervous system in production of hyperaemia in the uterine mucosa - an effect previously thought to be due to oestrin itself. From the work of the authors quoted alone it

appears that a substance, which if not acetyl choline itself is closely related to it, is released during the oestrogenic phase of the menstrual cycle. Thus 2 possible causes can be postulated for the production of delayed menstruation (1) inhibition of acetyl choline or acetyl choline like substance (2) overstimulation of the sympathetic nervous system with the production of excessive quantities of adrenalin. No proof however has yet been forthcoming that acetyl choline is directly responsible for the bleeding of the menstrual cycle although its hyperaemic effects on the uterine mucosa have more or less been established.

Continuing their investigations on delayed menstruation Soskin, Wachtel and Hechter²⁶ (1940), utilising the results in the previous experiments made the first clinical approach to the subject and treated a number of women for delayed menstruation. They state that the various components of the oestrone cycle can be classified into 2 categories (1) proliferative effects of oestrogen (2) effects secondary to hyperaemia.

The mechanism of the hyperaemic action of oestrogen suggested the use of acetyl-choline but since it seemed not without danger, the effect of prostigmin methyl sulphate which potentiates the effect of acetyl choline was tried. Although it was possible to rule out pregnancy in cases of delayed menstruation by physical examination it was necessary to see that the treatment would not disturb the

pregnancy should the diagnosis be missed. For this purpose a series of freshly impregnated rats were used. The animals were injected in the first 3 successive days of pregnancy, the dose of protigmin varied between that actually used on the patients to large doses within the lethal range. Prostigmin did not terminate pregnancy in any one animal even after comparatively enormous doses were given. All animals affected died of the lethal dose, the others went on to normal gestation and bore healthy litters.

The authors then proceeded to try the substance on pregnant women. In all, 23 cases received prostigmin between the ages of 18-58 years. Some had one or two previous pregnancies. Others were nulliparous and were between 11-42 days late in their period. The Friedman test was positive in all cases. 2 c.c. of a 1.2,000 solution of prostigmin was given intramuscularly on 3 successive mornings. None of the pregnancies were affected and no untoward or unpleasant subjective or objective effects were observed.

Another series of 25 cases between the ages of 19-58 years ~~old~~, with menstrual delay between 3-35 days and all having a Friedman negative test were then treated 1 c.c. - 2 c.c. prostigmin 1.2,000 solution were administered intramuscularly on 3 successive mornings. All menstruated from 4 hours after the last injection to 78 hrs. after the last injection. The average time taken was 28 hours. In some cases the flow was somewhat heavier than normal. With one exception,

all patients reported a normal menstruation at the next period.

The authors point out that they are aware that the patients may have menstruated anyway if no treatment had been given but the invariable nature of the results and the fact that the flow started after an average of only 28 hours leaves no doubt that prostigmin precipitates menstruation when it would otherwise not occur. "Indeed", they continued, "If the patient does not menstruate then pregnancy can be diagnosed as accurately as with the Friedman test". The authors emphasise that the treatment applies only to those who have a normal menstrual history up to the time of treatment and does not apply either to early or prolonged amenorrhoea due to endocrine dysfunction or to local organic changes. And finally they suggest that the hyperaemia in the oestrone cycle is important and delayed menstruation is probably a lack of vascular response rather than an endocrine dysfunction.

Winkelstein²⁷ in 1942 treated 90 unselected cases of amenorrhoea with prostigmin methyl sulphate. 65 of these cases were not pregnant as evidenced by the negative Zondeck-Aschheim test and physical examination. 57 of these cases bled while 8 gave no result. The successful cases were between the ages of 18-44 and the dose of prostigmin methyl sulphate was 1-3 injections of 1 c.c. - 2 c.c. of 1:2,000 solution intramuscularly. The menstrual delay was

between 3 days - 8 weeks and precipitation of the period occurred in 1-72 hrs. after the last injection. 21 cases, proved to be pregnant, did not menstruate after similar treatment but 4 pregnant cases bled following injection with prostigmin.

Thus 87% of the 90 cases gave correct results in the pregnancy test. The 9 non-pregnant cases which did not bleed following prostigmin therapy had, however, symptoms of organic pelvic pathology, or endocrine dysfunction as evidenced by the presence of a small uterus, cystic ovaries and excessive obesity. This would account for the high percentage of failures.

One important feature arising out of this clinical study is that 4 patients who were gravid bled and thus the possibility of abortion must be kept in mind even in the face of the previous author's experiments on mice.

One or two patients gave a correct diagnosis with the prostigmin test after the Aschheim-Zondek test had been negative. This occasionally happens when the Aschheim-Zondek test is done shortly after the first missed period.

In the 4 pregnant cases who bled, the author does not state whether delivery occurred normally or whether abortion or premature birth took place. Should this occur even in the smallest percentage of cases it would immediately rule out prostigmin as a useful test for pregnancy. In view of the work of Hechter, Wachtel, and Soskin whose results are

contrary to this, a greater series of cases must be treated and those who are pregnant must be followed up until delivery has taken place, before a definite decision can be taken on this point.

Winkelstein does not believe that the prostigmin test can replace the Aschheim-Zondek test in deciding pregnancy. He concludes by saying: "The use of prostigmin methyl sulphate as a therapeutic measure by regulating the menstrual function, after non gravidity has been established, has not been fully studied. Its field would appear to be here, rather than in the diagnosis of pregnancy." I am inclined to agree fully with this last statement.

The view held by Hechter and co-workers that prostigmin will not precipitate bleeding in gravid patients is fully supported by the results of Dominick Parella²⁸. He states: "In terms of frequency, the phenomenon of amenorrhoea is an important problem confronting gynaecologists."

65 cases of amenorrhoea were treated with 3 injections of 2 c.c. of a 1:2,000 solution of prostigmin methyl sulphate. The ages of the patients were between 19 and 41 years. In 37 of the cases delay was 1-56 days. All started to menstruate in an average of 48 hours. In 3 cases, however, the induction of menstruation was delayed for 24 days. Of these, one was found to have a fibromyoma of the uterus, one was a lactating mother and the other case had no pelvic pathology. The other 25 cases did not menstruate

and were later shown to be pregnant by the Aschheim-Zondek test. In 2 cases, however, the prostigmin test was successful where the Aschheim-Zondek test failed.

Edward Settel²⁹ treated another series of 16 cases of amenorrhoea with prostigmin methyl sulphate. 9 of these cases were not pregnant, confirmed by history, physical examination and Zondek-Aschheim test. The patients were between 18-24 years of age. The dose of prostigmin was 1-3 injections of 2 c.c. on successive days and the menstrual flow began in all 9 cases in 12-70 hours after last injection. The rest of the series consisted of 6 pregnant women, confirmed by palpation and Zondek-Aschheim test. They were given 3 injections of prostigmin methyl sulphate. None of them menstruated. The other case was not pregnant and delay was 8 days. She was given 3 injections in the doses stated. She did not menstruate, however, till 22 days following treatment. This of course might be explained as being the time taken for the release of luteinising hormone and the eventual retrogression of the corpus luteum but Settel admits that this case was never regular at any time and thus may have menstruated on that day whether she was given prostigmin or not.

A further critical survey of the value of prostigmin as a test for pregnancy appears in the Illinois Medical Journal by M. J. Sneider³⁰. He like Hechter et alia emphasises that the test is not applicable in cases of

delayed menstruation known to be due to some endocrine disorder nor in cases in which the previous menstrual history has in any way been abnormal. Nor is it applicable in any case where there is any pelvic pathology. A careful history and a complete examination is necessary to exclude these conditions.

27 cases of delayed menstruation between the ages of 19-30 were treated. All had a previous normal menstrual history and the menstrual delay was 3-30 days. The Aschheim-Zondek test was not done in every case. Each patient was given 1-3 injections of prostigmin methyl sulphate 1.4,000 each of 1 c.c. dose and the menstrual flow started from 4-72 hours after the last injection in 17 of the cases. The other 10 cases did not have any menstrual bleeding and were shown to be pregnant both by physical examination and Zondek-Aschheim test.

One case did not menstruate till 7 days after last injection. This was subsequently diagnosed as thyro-ovarian deficiency. In this case the bleeding is said to have occurred as a result of release of luteinising hormone and retrogression of the corpus luteum. It seems extremely unlikely, however, that the same drug will produce the menstrual flow by having a direct effect in a few hours in some cases and in others only act through the medium of the pituitary gland and retrogression of the corpus luteum.

The work of the American authors quoted above was

confirmed in this country by Friedmann³¹ who treated a series of 90 patients suffering from amenorrhoea with prostigmin methyl sulphate. Of the 90 cases, 30 were pregnant. The duration of the amenorrhoea beyond the expected menstruation was from 3-47 days, and the ages of the patients were between 16-47 years. 1 mgm. of prostigmin was injected intramuscularly on three successive days.

None of the 30 pregnant cases bled, while the menstrual flow was precipitated in 82.8% of cases in one group of 24 patients, while in the other group of 36, the menstrual period was precipitated in 94.5% of cases. 10 patients who were injected with sterile water as a control did not menstruate.

Some complications such as sialorrhoea and palpitations occurred in one case.

Friedmann suggests that prostigmin should be tried in all cases of delayed menstruation except those of endocrine origin and those in which pregnancy has been established.

Treatment of Delayed Menstruation with Carbaminocholine Chloride.

As a result of the apparent success of the above workers in the use of prostigmin methyl sulphate both as a therapeutic measure in the treatment of delayed menstruation and as a test for early pregnancy it was determined that an attempt would be made to treat a series of airwomen suffering from delayed menstruation with a parasympatheticomimetic drug.

After due consideration prostigmin was decided against due to (1) discomfort of injections (2) cost of treatment.

An oral preparation seemed to be the best way out of the difficulty. For this purpose carbaminocholine chloride (carbachol B.P.) was chosen in the form of the proprietary preparation known as "MORYL"*. Each tablet has the following constitution: carbaminocholine chloride - 0.002 gm., sacch. lact. - 0.15 gm., amylum - 0.063 gm., and talcum - 0.005 gm. The rate of absorption, destruction and excretion of the drug is unknown and the effective dose was calculated by trial and error.

Carbaminocholine chloride, unlike prostigmin does not potentiate the effect of acetyl choline by preventing its hydrolysis by the choline esterase. It acts by direct stimulation of the para-sympathetic nervous system and so will eventually produce acetyl choline at the terminal nerve endings of the parasympathetic nerves. It was felt that if a deficiency of acetyl choline was in some way responsible for the delay in menstruation then the administration of carbaminocholine should produce similar results to those of the American workers using prostigmin methyl sulphate, provided that the carbaminocholine was not destroyed in the stomach and was absorbed from the gastric mucosa.

Owing to the exigencies of the Service and many other factors outside my personal control, I was unfortunately not

* This drug was kindly supplied by Savory & Moore, Standard Works, Lawrence Road, London, N.15, who also supplied the placebos in generous quantities.

afforded the opportunity of investigating a larger series of cases as was originally intended, and only 4 cases of delayed menstruation were obtained, suitable for treatment.

Four cases, therefore, of delayed menstruation were chosen as described in the section on differential diagnosis. Each case was examined thoroughly to (1) exclude the presence of any gynaecological abnormality (2) exclude any endocrine or general debilitating diseases, such as tuberculosis and anaemia. Cases were only chosen therefore when there was no sign of any general disease, or local disease in the generative system and whose menstrual cycle had been perfectly regular until onset of amenorrhoea and in whom the periods stopped without any obvious cause. Pregnancy was excluded either by physical examination or by the Zondek-Aschheim test. Fortunately no extensive investigations were necessary to exclude the conditions mentioned above beyond physical examination and X ray of the chest when necessary.

Realising that patients might menstruate as a result of the psychological effect of administering any drug, they were divided into two groups. Two of the cases were given carbaminocholine chloride, while the other two were given a placebo, consisting of starch, lactose and saccharine. The placebo looked and tasted exactly like the tablet containing active drug. Neither group knew whether they were receiving the placebo or the carbamino-

choline.

Owing to the possibility of unpleasant side effects, all patients, regardless as to whether they were getting the placebo or the active drug, were instructed to report daily and the presence of such symptoms as excessive salivation, rhinitis, and gastro-intestinal disturbance was recorded. A daily record of the blood pressure and pulse rate was also kept to determine whether there was any significant fall resulting from an increase in vagal tone.

The first two cases were treated with $\frac{1}{2}$ -1 tablet (0.001 - 0.002 gm. carbaminocholine chloride) "Moryl" three times daily, while the other two cases were treated with one tablet of the placebo three times daily. When the latter cases did not menstruate after 3-4 days treatment, the placebo was replaced by the active drug. The ages of the patients were between 21-30 years, the menstrual delay was from 6-19 months and in 3 of the 4 cases the menstrual period was precipitated from 17-72 hours after onset of treatment, while the fourth case menstruated in 35 days after treatment. The dosage of Moryl required was 3-15 tablets or 0.006 gm. - 0.035 gm. carbaminocholine.

Tables 9 and 10 on pages 67 and 68 summarise the results.

In order to analyse the results obtained a resumé of the history of each case will be given.

Case No.	Name	Age	Menstrual Delay	Gynaecological findings	Treatment	Total Dose of Carbaminocholine	Results	Time from onset of treatment to precipitation of period	Abnormal symptoms	Successing Period
1	P.R.	21	5 months	Nil	$\frac{1}{2}$ tablet Moryl T.D.S.	0.012 gm. (6 Tablets)	Menstruated, normal blood loss 5 days	96 hours	Epistaxis	Normal
2	W.F.	31	6 days	Bilateral Salpingectomy and Pelvic Cellulitis	1 tablet Moryl T.D.S.	0.006 gm. (3 Tablets)	Menstruated, normal blood loss 4 days	17 hours	Nil	Normal
3	A.R.	21	19 months	Nil	1 tablet Placebo T.D.S. 1 tablet Moryl T.D.S.	12 Tablets 0.030 gm. (15 Tablets)	Nil Menstruated blood loss 10 days	- 35 days	Nil Nil	- Absent
4	A.K.	30	31 days	Nil	1 tablet Placebo T.D.S.	3 Tablets	Menstruated blood loss 5 days	24 hours	Nil	Normal

TABLE 9. Effects of carbaminocholine chloride and placebos in 4 cases of Delayed Menstruation.

Case No.	Days of Treatment	Blood Pressure	Pulse Rate	
1	1st	115/65	78/min.	
	2nd	120/65	88/min.	
	3rd	116/68	80/min.	
2	1st	125/75	80/min.	
3	1st	122/70	78/min.) Placebo
	2nd	125/75	72/min.	
	3rd	120/75	78/min.	
	4th	118/73	80/min.) Moryl
	5th	122/70	80/min.	
	6th	116/75	76/min.	
	7th	125/75	84/min.	
	8th	120/75	78/min.	
	9th	118/73	76/min.	
4	1st	128/80	78/min.	

TABLE 10. Blood Pressures and Pulse Rates During Treatment with Carbaminocholine.

Case 1.

Aircraftswoman P.R., age 21, menarche 13 years, entered Service 26/1/43, last menstrual period 12/1/43, M.T. driver, menstrual delay approximately 5 months. Increase in weight since entry to Service was 15 lbs. Past gynaecological history was normal. Treatment began on 8/7/43 with $\frac{1}{2}$ -1 tablet Moryl 3 times daily. Period returned after 6 tablets (0.012 gm. carbchol) had been taken, 96 hours after onset of treatment. One peculiar feature of this case was the occurrence of epistaxis during menstruation. This may have been produced by bleeding from the genital spots of Fleiss (1897). This is also in accord with the results obtained by Rosen (Jour. Mount. Sinai. Hosp., Vol. 9, No. 4, 755, 1942) who found swelling of erectile tissue over the turbinates and septum, during, just after, or just before the menstrual period. Rosen also quotes McKenzie who called attention to these areas and stated that it was analogous to the erectile tissue over the penis, being made up of myriads of blood vessels and connective tissue. If the epistaxis was produced as a result of stimulation by carbaminocholine then it could have been brought about in the following manner: (1) general vaso-dilator effect of carbaminocholine causing congestion in the uterus and nasal mucosa and in the mucosa of other organs, (2) effect through the pituitary causing menstruation, and due to the nasogenital relationship as described by Rosen, bleeding occurred

from the two organs simultaneously. The patient's next period was on 3/8/43 and appeared to be rather heavier than normal lasting 4 days, but again she had epistaxis on 2/8/43. Next 3 periods occurred at approximately 28 day intervals and were normal in every respect.

Case 2.

F/Sgt. W.F., age 31, administrative staff, married, nulliparous, l.m.p. 27/9/43, delay 6 days. This N.C.O. has a long gynaecological history which culminated in a bilateral salpingectomy in 1939 as a result of pelvic cellulitis. Following a gynaecological examination by the specialist on 26/9/43 her period began on 27/9/43. She bled excessively and prematurely, as the period before that was on 6/9/43. She reported on 30/10/43 with a menstrual delay of 6 days. Treatment was begun with one tablet Moryl t.d.s. and patient began to bleed after 3 tablets had been taken 17 hours after beginning of treatment. That is 0.006 gm. carbaminocholine precipitated the period. At first sight it might be thought that this would be a poor case for parasympathetic therapy as in a previous page it has been stressed that all gynaecological abnormalities must be excluded before one can confidently diagnose delayed menstruation. But this patient's periods had always been regular in spite of the fact that she had a salpingectomy and pelvic cellulitis, it was I think reasonable to assume that her ovaries and uterus would function normally in response to therapy.

It would be true to say, therefore, that provided the uterus and ovaries are considered to be healthy the presence of pathological conditions in other parts of the female pelvic organs is of no great importance from the point of view of treatment of delayed menstruation.

Case 3.

L.A.C.W. A.R., age 21, entry to Service 8/1/42, l.m.p. 8/1/42, menarche 14 years. This patient had a 56 day menstrual cycle, the flow lasting 7-9 days. Her last period began on the day she entered the Service and lasted 7 days. Since then up till the time of examination on 27/9/43 no bleeding had occurred. She is employed as a cook and has increased by 19 lbs. in weight since entry to Service. She complains of frequent headaches, dizziness, and lassitude. No abnormalities detected in any of the body systems. Treatment begun with 1 tablet placebo t.d.s. and 12 tablets were administered with no result. 1 tablet Moryl (0.002 gm. carbachol) t.d.s. was then given. A total of 15 tablets was administered with no result. However she menstruated on 5/11/43, 35 days after treatment with the potent preparation. But following period was absent and after a menstrual delay of approximately 2 months she was again treated with a total of 12 tablets Moryl (0.024 gm. carbachol) but no result was produced.

It is not suggested that the carbaminocholine administered was effective in producing the menstrual

period on 5/11/43. In fact she confessed that on 4/11/43 she was involved in an air raid near her home and I am willing to believe that this had a lot to do with the precipitation of her period. Neither is it suggested that the time taken for the precipitation of the menstrual period is due to the production of luteal hormone and corpora lutea, and as a result of the subsequent degeneration of the latter, bleeding occurred.

This type of case well illustrates the difficulty in deciding where some organic endocrine dysfunction is the causative factor. It is felt that the above is a case of mild hypothyroidism or exhibits a minor degree of the adiposo-genital syndrome.

Case 4.

Aircraftswoman A.K., age 30, l.m.p. 10/12/43, delay 31 days, menarche 13 years. Periods always perfectly regular until entry to Service on 3/3/43. No gynaecological abnormality detected and no disease in any of the other body systems discovered. Increase in weight 16 lbs., during examination she confessed that she was depressed and unhappy in her work. She is employed as a clerk. Treatment was begun on 7/2/44 with one tablet placebo t.d.s., she menstruated after 3 tablets had been taken, 24 hours after interview.

It is rather remarkable that this patient should have menstruated so soon after treatment with the placebo. As

these tablets contain no more than starch, lactose, and saccharine, they could not have affected the menstrual period to the slightest degree. There are however two possible explanations :

- (1) The onset of the menstrual period was merely a coincidence with the treatment and that she would have menstruated anyway even if she had no treatment.
- (2) The interview was partly in the nature of a psychiatric examination and this may have, by making her feel slightly happier, helped to precipitate the period. Similar "cures" have been reported from American sources by the same form of "therapy".

It is impossible to draw any adequate conclusions from the results of the 4 cases treated. Whereas carbaminocholine chloride has been successful in precipitating the menstrual flow in 2 cases, of the 2 controls one menstruated on administration of the placebo, while the other did not menstruate either with the placebo or the active drug. On the face of it, it would appear that carbaminocholine is successful in 50% of cases. It is evident, however, that a larger series of cases would have to be treated with both the active preparation and the placebo to draw any definite conclusions. It is felt that carbachol can, in a fair percentage of cases precipitate the delayed period in 2-3 days, and therefore it is certainly worthy of extensive clinical trial in all cases where amenorrhoea occurs in the

absence of organic disease in the generative, or any of the other body systems. It has often been asked, why precipitate the delayed period at all? - the patient is relatively well, there is no organic cause and the period inevitably returns. To all this, I agree. But surely the absence of the menstrual period can not by any means be regarded as unimportant. The menstrual period should be precipitated in all cases of delayed menstruation for the following reasons :

(1) The absence of the menstrual flow sometimes sets up an anxiety state in the patient which, in turn, prolongs the amenorrhoea, thus we have a vicious circle set up.

(2) If the menstrual period is absent for a period of six months or more, degenerative changes are likely to occur in the endometrium, which will firstly make the period more difficult to precipitate no matter what treatment is used, and secondly may lead to sterility as a result of the fertilised ovum being unable to embed itself in the unhealthy endometrium.

The above statements have not been proved or disproved, as this would require endometrial biopsies. Such an investigation was rendered impossible due to factors beyond my control.

NORMAL CONTROLS.

A further control was devised in order to determine whether carbaminocholine only produced bleeding amenorrhoeic patients or whether it produced bleeding in normal women. For this purpose two female nursing orderlies volunteered to undergo a course of treatment. Each was given 1 tablet Moryl t.d.s. and a total of 9 tablets (sufficient to cause bleeding in delayed menstruation) were given in each case. Blood pressures and pulse rates were recorded daily in order to determine whether the parasympathetic nervous system was sufficiently stimulated to cause a depressor effect on the heart and pulse rate. Neither of the subjects menstruated, following treatment, nor was there any great change in the blood pressure or pulse rate, and considering the various factors which influence these functions I do not think the variations were significant. The next menstrual period appeared normally in one subject but paradoxically was delayed in the other subject for two days. The following is a summary of the results :-

Name	Age	Days of Treatment	Dosage of Carbamino-Choline	Blood Pressure	Pulse Rate	Abnormal Symptoms
O.D.	26	1st	0.004 gm. (2 tabs.)	118/75	72/min.	Menstrual period delayed 2 days
		2nd	0.006 gm. (3 tabs.)	116/70	72/min.	
		3rd	0.006 gm. (3 tabs.)	110/70	70/min.	
		4th	0.002 gm. (1 tab.)	108/70	72/min.	

Name	Age	Days of Treatment	Dosage of Carbamino-Choline	Blood Pressure	Pulse Rate	Abnormal Symptoms
C.H.	27	1st	0.006 gm. (3 tabs.)	100/55	68/min.	Nil
		2nd	0.006 gm. (3 tabs.)			
		3rd	0.006 gm. (3 tabs.)	98/55	64/min.	Nil

TABLE 11. Blood Pressures and Pulse Rates in Two Normal Airwomen, following treatment with Carbaminocholine Chloride.

No explanation of the delay in the appearance of the menstrual period in the first subject can be offered. It is suggested that the apprehension induced as a result of the experiment caused a mild anxiety state thus delaying the appearance of the period.

As can be seen therefore, from the table, a dose of 9 tablets Moryl (0.018 gm. carbaminocholine) does not cause premature bleeding in a normal individual, and the blood pressure and pulse rate vary very little from day to day, certainly no more than would be expected if the carbaminocholine had not been taken. No other complications whatsoever were noted following the treatment.

CARBAMINOCHOLINE CHLORIDE AS A TEST FOR PREGNANCY.

It was previously shown that Soskin et alia, Winkelstein, Settel and Sneider used Prostigmin as a test for pregnancy with results comparable to those obtained by the Zondek-

Aschheim test. It therefore appeared to me that a parasympathetic stimulant such as carbaminocholine chloride could be used similarly.

In order that carbaminocholine may be used in the diagnosis of pregnancy with any degree of accuracy and safety, two main requirements are essential: (1) that it precipitates the menstrual period in every case of delayed menstruation and (2) that it has no effect whatsoever in cases of pregnancy. Only if these two facts are true can carbaminocholine be used as a diagnostic test. As to the first statement, in the small series of cases treated, precipitation of the period can be depended on at least in 50% of patients. As to the second statement the effects of carbaminocholine in early pregnancy is shown below.

The importance of deciding whether carbaminocholine can disturb pregnancy can not be over emphasised. In most cases early pregnancy can not be diagnosed with absolute accuracy, before three months, without resort to biological test of the urine. Should carbaminocholine produce bleeding in the early stages of pregnancy, misdiagnosed as delayed menstruation, disastrous consequences would result.

Two cases of amenorrhoea, who adamantly denied any suspicion of pregnancy, probably with the motive of obtaining some drug to act as an abortifacient, were treated. Each case was examined and no gynaecological or other abnormality was found. It was felt therefore that they were true cases

of delayed menstruation and thus justified treatment with carbaminocholine. The first was treated in the usual manner with a total of 11 tablets of the placebo, followed by a total of 9 tablets of Moryl. The second case was treated with a total 12 tablets placebo and 12 tablets Moryl. In neither case did uterine bleeding occur or were there any other abnormal symptoms. Examination in 4-6 weeks following treatment revealed the presence of pregnancy.

The absence of bleeding in the above two cases encouraged me to administer the drug to one further case of pregnancy (7 weeks gravid) diagnosed by the Aschheim-Zondek test. She was given 12 tablets carbaminocholine in all and no bleeding or other abnormal symptoms occurred. The following is a resumé of the results :-

Name	Age	Menstrual Delay	Gynaecological Findings	Treatment	Result	Abnormal Symptoms
L.M.	19	21 days	Nil	11 tabs. placebo 9 tabs. Moryl	Nil Nil	Nil Nil
P.M.	26	30 days	Nil	12 tabs. placebo 12 tabs. Moryl	Nil Nil	Nil Nil
T.G.	22	24 days	7 weeks gravid	12 tabs. Moryl	Nil	Nil

TABLE 12. Effect of Carbaminocholine in 3 Gravid Patients.

The tablets were given three times daily. Thus after a total dosage of 0.022 gm. in case 1, and 0.024 gm. in case 2, and 0.024 gm. in case 3 of carbaminocholine, no bleeding was

produced. In these doses the period would normally be expected to be precipitated in true cases of delayed menstruation. Up till the time of writing in March 1944, the pregnancies have continued normally (personal communication).

It is realised that the number of cases are too few (and perhaps the dose carbaminocholine too small) to draw any definite conclusions as to the effects of carbaminocholine in early pregnancy. But similar results would be obtained in a larger series of cases. True, it is not known, as yet, whether the birth will be normal or the child normal at birth. But I believe that any eventuality which does arise can not be attributed to the administration of carbaminocholine.

One great difficulty which arises in interpreting the results, is the number of cases amenorrhoea, who are not pregnant and in whom the menstrual period is not precipitated despite parasympathetic stimulant therapy, thus leading to a false diagnosis of pregnancy. These cases are probably due to minor endocrine disturbances.

Further, Winkelstein reported 4 cases of bleeding in early pregnancy as a result of prostigmin therapy. If this does occur then it immediately rules out the possibility of prostigmin ever being used in the diagnosis of pregnancy.

From the above results I feel that carbaminocholine might be used as a test for pregnancy. The relative

rapidity with which results are produced (24-96 hours), the cheapness of the preparation and the ease of administration makes certain advantages clear. It is not by any means suggested that it can replace the Zondek-Aschheim or Friedman tests, but it is definitely worth while to try the effects of carbaminocholine. If the period is precipitated then the diagnosis is clear. If the patient still remains amenorrhoeic, however, following treatment, then it would be necessary to perform a biological test to confirm pregnancy.

Summing up the advantages and disadvantages of carbaminocholine as a test for pregnancy :-

Advantages.

- (1) Rapidity of result.
- (2) Ease of performing the test.
- (3) Cheapness of the preparation.
- (4) Absence of complicated apparatus, and experienced technicians, as required by the Zondek-Aschheim and Friedman tests.

Disadvantages.

- (1) A number of cases of delayed menstruation do not menstruate following carbaminocholine therapy.

The efficiency or otherwise of this test will only be proved in time, when a greater series of cases can be investigated.

The Relationship Between Ovulation and Menstruation.

That ovulation can occur apart from menstruation has

been proved time and again by the number of women who have become pregnant during a period of amenorrhoea. Such cases have been reported by Schweitzer, Hannes, Siegel and Teebken besides others. As we believe that menstruation occurs as a result of degeneration of the corpus luteum we are led to two conclusions: (1) that the corpus luteum does not degenerate and (2) that corpora lutea are not necessarily formed following ovulation.

In order to definitely establish that ovulation occurs during delayed menstruation frequent biopsies of the endometrium would be required. This type of investigation would be extremely useful in determining (1) whether proliferative and premenstrual changes occur in the absence of menstruation (2) whether atrophic changes occur in the endometrium in prolonged amenorrhoea.

It was hoped to incorporate this type of investigation into the thesis but it was found impracticable due to circumstances beyond my control.

7. Probable Mechanism of Production of Delayed Menstruation.

The processes involved in the production of delayed menstruation would seem to be rather within the realm of the experimental biologist or endocrinologist than the clinical investigator. However by culling the works of others I have reached a working hypothesis, which if not already proven is at least logical and fits in with the clinical and experimental findings at our present disposal.

It might be well worth while to begin by recapitulating a few of the well known facts relating to the control of the ovulation and menstruation by the anterior pituitary gland. The pars anterior of the hypophysis an extremely complex structure producing an almost bewildering variety of hormones. These are (1) growth factor (2) thyrotropic factor (3) adrenotropic hormone (4) lactogenic hormone (5) parathyrotropic hormone (6) diabetogenic and ketogenic hormones and finally (7) gonadotropic hormone. The latter only will be considered in more detail. This hormone has been shown to consist of two factors, a follicle stimulating hormone (F.S.H.) or prolan A and luteinising hormone (L.H.) or prolan B. The former is responsible for the maturation of the Graafian follicle to the mature ovum, while the latter is responsible for the production and maintenance of the corpus luteum. In this way the anterior pituitary influences indirectly the functions of the rest of the genital apparatus and possibly the secondary sex characters. The presence of the prolans has been proven by the injection of extracts of anterior pituitary into animals. If an acid extract is injected, the Graafian follicles grow rapidly and many dozens of ova may be discharged at the same time. This is due to the F.S.H. or prolan A. On the other hand if alkaline extracts of the gland are injected into adult females, totally distinct changes occur. The development of the Graafian follicle is arrested at an early stage and

ovulation does not occur. The immature follicles become transformed into corpora lutea which grow to a considerable size, many of these corpora lutea still containing an immature ovum in their centre. This is effected by prolans B (L.H.). Further if a transplant of the anterior pituitary gland is made into the immature mice precocious ovarian activity occurs. Graafian follicles develop prematurely and rapid formation of corpora lutea takes place. Thus premature sexual maturity is established, no doubt due to the liberation of both prolans. If further proof is wanting in relation to control of the anterior pituitary gland over the gonads the following facts are given:

(1) the onset of the ovarian activity in normal animals may be delayed by hypophysectomy: (2) in the rabbit where ovulation occurs only in response to copulation, the absence of the anterior pituitary prevents ovulation following coitus: (3) clinically defective pituitary secretion is associated with infantilism, defective sexual development and amenorrhoea.

Owing to the fact that the urine of pregnant women also contains gonadotropic hormones Aschheim and Zondek evolved their test for pregnancy which consists of the appearance of ripe follicles, haemorrhagic follicles (Blutpunkte) and corpora lutea in the ovaries of immature female mice following injection of pregnancy urine. The Friedman test is somewhat similar, only rabbits are used instead of mice and

results are quicker and easier to obtain.

Our conception of the production of menstruation is at present as follows :- The prolan A from the anterior pituitary stimulates the production of Graafian follicles and is responsible for the liberation of the ovarian hormone dihydro-oestrone from the ovary. This substance acts on the uterine mucosa to produce the changes characteristic of the proliferative phase of the menstrual cycle, i.e. thickening of the mucosa and lengthening of the glands. Between about 12th - 14th day counting from the first day of the last menstrual period the ovum is liberated into the abdominal cavity and fallopian tubes and we get a formation of a corpus luteum which is maintained by the activity of the prolan B from the anterior pituitary gland. The hormone liberated by the corpus luteum is progesterone and is responsible for the endometrial changes known as premenstrual or progestational, which consists in further thickening of the mucosa enlargement and increase of mucous secretion of the glands and marked capillary congestion. On or about the 28th day of the menstrual cycle the corpus luteum degenerates and blood diffuses from the capillaries by diapedesis, raising the mucosa and finally reaches the exterior by stripping off parts of the uterine lining together with leucocytes, mucus and debris. The degeneration of the corpus luteum is presumably brought about by the cessation of the activity of prolan B. During the

progestational period dihydro-oestrone or oestradiol as shown by Doisy et alia continues to be secreted.

Thus nature has provided us with a beautifully regulated mechanism, whereby cyclical liberation of hormones from the anterior pituitary gland provides a train of events which is eventually responsible for ovulation and menstruation. What factor or factors then are responsible for the sudden cessation of menstruation in what appears to be a normal healthy subject? What link in the chain of events already described breaks down? In the following pages I will make an attempt to answer these questions.

As far back as 1936 Marshall and Verney³² showed that by stimulation of the brain of a rabbit ovulation and pseudo-pregnancy can occur. A similar effect took place on stimulation of the spinal cord. This indicates that an electrical stimulus can act on the pituitary with the production of the prolans and ovulation or that the stimulus acts directly on the ovaries with the production of ova. The paths for the electrical stimuli are probably nervous but the pathways have not yet been determined. Thus we see that the production of the prolans and ova are not autonomous but may be under the control of the nervous system or at any rate can be affected by changes in the action potentials in certain nerves at present unknown. The fact that the nervous system does play some definite, although undefined, part in the production of ovulation and

possibly menstruation is borne out by the fact that rabbits ovulate only 12 - 18 hours after coitus. This stimulus is probably neurogenic from the vagina to the hypophysis through an undetermined pathway. However the possibility of a humoral stimulus, by absorption of a fraction of the semen from the vaginal mucosa and carried round to the pituitary in the blood stream, cannot be denied.

Further evidence of the neural control of ovulation was produced in 1937 by Chandler C. McBrooks³³ who found that complete removal of the sympathetic chain in the rabbit did not prevent ovulation on coitus. If a reflex stimulation of the anterior lobe is essential to ovulation then it is obvious that some other pathway than the sympathetic must carry the responses.

14 rabbits had their pituitary stalk sectioned and all failed to ovulate though they mated frequently. 10 of these had intact sympathetic nervous systems. There was no evidence of any other pituitary abnormality that is, body weight, growth, genital tract, ovaries, thyroid were normal. Yet follicles ripened and ovulation occurred on injection of pregnancy urine. Histological studies showed degeneration in the posterior lobe and changes in the basophils and eosinophils of the anterior lobe. With the silver impregnation technique, fibres resembling nerve fibres were found in the anterior pituitary. McBrooks' work indicates (1) a connection between the pituitary

stalk and the brain is essential for ovulation in the rabbit: (2) that if performed prolans such as are found in pregnancy urine are injected into a pituitary stalk sectioned rabbit ovulation occurs. The author himself believes that normally a nervous stimulation occurs on mating and the nerves involved pass down the pituitary stalk to the anterior lobe. Although it is always dangerous to apply the biological results obtained in one animal as an axiom in another species, it is reasonable to assume that in man a nervous stimulus to the pituitary gland is necessary to produce the prolans and thus ovulation. Should this stimulus be absent as in pituitary stalk section, ovulation will still occur by giving gonadotropic hormone in the form of pregnancy urine.

More definite anatomical evidence of what was suggested by the above experiments was obtained more recently by McBrooks and Gersh in 1941³⁴, working in John Hopkins University. They investigated the innervation of the hypophysis in the rabbit and the rat and were able to show terminal nerve endings in the anterior pituitary. As I consider this paper of some importance it shall be quoted in detail.

The hypophysis and the hypothalamus attached were prepared by the pyridine silver method and sectioned serially at 10 U. Young animals were used throughout. Normal rabbits. Numerous fibres pass down the hypophyseal

stalk to the infundibular process. A very small number of fibres from the infundibular stem enter the pars intermedia directly. Fibres could also be traced along the capsular artery directly into the pars intermedia. It is apparent that fibres entered the anterior lobe from three directions: (1) the infundibular stem (2) the infundibular process by way of the pars intermedia (3) the capsular arteries.

Stalk sectioned rabbits. Animals were operated on four days old and killed seven days later. Only a few fibres in the anterior portion of the stalk continued down to the infundibular process. The majority of the sections through the pars intermedia showed no nerve fibres. Sections through the anterior lobe showed 5 - 10 nerve fibres.

Normal rats. In this species the majority of nerve fibres appear to enter the gland as a small bundle from the anterior part of the median eminence and a small number of fibres was visible as a group in the posterior portion of the median eminence. After passing into the stalk these two bundles immediately broke up into smaller bundles which twisted tortuously in the infundibular process. Nerve fibres were rare in the pars intermedia and scarce in the anterior lobe.

Rats with superior cervical ganglionectomy. Terminal pericellular networks are seen at the termination of nerve fibres. Fibres entering along the capsular arteries also

receive some sympathetic nerve fibres and constituted the sympathetic supply to the anterior lobe. Some fibres in the anterior lobe appear to terminate in a network round the gland cells.

The authors then conclude that they feel that these observations furnish anatomical evidence of the physiological experiments indicative of a neural control over water exchange normally influenced by the neurohypophysis and certain endocrine functions of the anterior lobe. However Dempsey and Uotila³⁵ commenting on the fact that the activity of the anterior pituitary may be modified by nervous stimuli reaching the gland through the fibres of the pituitary stalk, state that this mechanism is not necessary for the production of thyrotropic and luteinising hormones of the spontaneously ovulating rat and guinea pig and these hormones may be produced normally after pituitary stalk section.

27 female rats had the pituitary stalk sectioned, 9 had normal oestrous cycles, 8 were irregular and absent in 10. 7 of the animals whose cycles were normal, after section of pituitary stalk, were then exposed to a temperature of 2-5% C. in company with normal unoperated animals. The oestrous continued normally and corpora lutea were found at death. The unoperated animals showed a progressively longer cycle and atretic follicles at post mortem. Some of the animals who were operated on and showed irregularities in the cycle produced normal litters. The dioestrous

animals were injected with pregnancy urine and examination of the ovaries showed numbers of corpora lutea. From these experiments the authors conclude that inhibitory influences produced through the pituitary stalk are abolished on section. It seems that the integrity of the pituitary stalk is necessary for the increase or decrease of the rate of hormone production which follows certain environmental stimuli, e.g. normal gonadotropic hormone normally inhibited by cold is not affected by cold after stalk section.

Dempsey and Uotila however do not explain the striking paradox in their results. For example 10 animals were dioestrous while 9 were unaffected following pituitary stalk section. This shows that the results are at the most equivocal, and if any conclusion is to be drawn at all from the experiments, it is that pituitary stalk section is more likely to produce dioestrous. It is possible however that in sectioning the pituitary stalk, other parts of the brain are injured by (1) damage to the blood supply, or (2) by direct destruction of nerve cells, thus leading to some irregularities in the results obtained.

The following few pages of this investigation were intended to demonstrate the existence of nerve connections between the pituitary gland and the hypothalamus and the part played by the hypothalamus in the control of menstruation through the pituitary gland. It may well be asked, on what facts is the assumption based that the

hypothalamus plays a role in the already complicated factors governing the menstrual cycles. That the hypothalamus plays some very definite, but as yet unexplained, part in the control of menstruation will be borne out by perusal of the literature quoted below. Attempts to elaborate on the above line of thought, led me through literature dealing with neurological anatomy, physiology, psychiatry and endocrinology. Unfortunately, some rather important papers, in French and German, are not available in this country at the present time. One fact, however, remains eminently clear out of the divergent view points expressed by the various authors and that is, that the hypothalamus plays some part in the precipitation of the bleeding phase of the menstrual cycle. The exact mechanism of this function is still unknown, but a point of view will be expressed which although lacking accurate experimental proof, is at least in accord with our present knowledge and offers us a logical working hypothesis.

The hypothalamus or diencephalon has come into great prominence in the past few years. In its substance has been localised many physiological functions, previously ascribed to the other parts of the brain, or whose centres were unknown. With the growth of knowledge concerning the hypothalamus, concurrently arose the danger of ascribing to that small structure the control of various physiological functions, which had hitherto been only imperfectly known.

This danger is not yet past. But even approaching the subject of hypothalamic control as a sceptic, the wealth of evidence offered by various authors is extremely convincing and one is again amazed at the complexity of the human organism.

It would be best to commence this part of the investigation with an anatomical and physiological review of the literature on the hypothalamus. Only a brief resumé of the salient points will be given.

The hypothalamic nuclei³⁶ may be divided into 3 groups - anterior, posterior and middle.

Anterior Group. There are two principal cellular masses; (1) paraventricular nucleus (filiform) close to the ependymal lining of the third ventricle and (2) supraoptic nucleus lies immediately above the optic chiasma. This nucleus gives rise to the supraoptico-hypophyseal tract which passes via the pituitary stalk to the pars posterior and the pars intermedia.

Middle Group. Sometimes called the pars infundibularis, occupies the middle part of the tuber cinereum. It is made up of the ventro-medial hypothalamic nucleus, the dorso medial hypothalamic nucleus and the nucleus tuberalis.

Posterior Group consists of two nuclei :

(1) Nucleus hypothalamicus posterior lies above and just rostral to the mammillary bodies. This nucleus is important as it gives rise to one of the principal efferent

projection systems from the hypothalamus to the medulla and spinal cord. The fibres to the cord terminate in the lateral horns.

(2) Nucleus corpore mammillare are conspicuous structures at the base of the brain in the interpeduncular fossa. In addition there is the stratum grisea centralis.

The connections are imperfectly known. The paraventricular nuclei project to the supraoptic and probably to the posterior hypothalamic nuclei and medulla. The supraoptic nucleus gives rise to the supraoptico-hypophyseal tract which terminates in the pars posterior of the pituitary. The tuber nuclei receive fibres from the frontal region of cerebral cortex and send fibres to the mid brain but the details have yet to be worked out. The mammillary bodies give rise to the tract of Vicq D'Azyr which links with the anterior nucleus of the thalamus and through this with the cingular gyrus of the cerebral cortex.

Functions of the Hypothalamus.

In 1928 Philip Bard established that the posterior hypothalamic area is largely responsible for the autonomic discharges. When both cerebral hemispheres are removed, periodic discharges occur affecting all divisions of the sympathetic system. These discharges are accompanied by signs of anger designated as "sham rage". During outbursts, the pupils dilate, the hair stands on end, the heart rate increases, blood pressure rises and there are

other signs of sympathetic hyperactivity. These reactions occurred until the posterior hypothalamic nuclei were excluded in section. Further, large bilateral lesions of the posterior hypothalamic area are accompanied by ptosis, enophthalmus and myosis (Horner's syndrome).

It has been postulated that in encephalitis lethargica, some region close to the third nucleus was involved. Stimulation of the hypothalamus especially of the mammillary bodies can produce sleep.

Stimulation of the tuber nuclei appears to give parasympathetic response, thus the heart rate is slow and auriculo-ventricular conduction time increased, increase in the intragastric pressure of the fasting cat occurs and increase in bladder tone, abolished by atropin. Lesions in the tuber cinereum nuclei are said to cause Frölich's syndrome.

The anterior nuclei have come into prominence because of their association with diabetes insipidus. Lesions in this area cause polyuria. The supraoptic nuclei which give rise to the supraoptico-hypophyseal tract are specifically responsible for the production of diabetes insipidus (when injured or destroyed) in both cat and monkey. It has further been postulated that polyuria is due to interruption of the supraoptico-hypophyseal tract and as a result, degeneration of the posterior lobe of the pituitary occurs, and thus the antidiuretic principle is

withdrawn.

Heat regulation is maintained by the integrity of the hypothalamus, destruction of the latter may lead to hyperthermia.

Disturbances of carbohydrate metabolism, as a result of lesions in the hypothalamus were described ^{by} Aschner in 1912. Hyperglycaemia is induced by hypothalamic stimulation. On stimulation of the posterior hypothalamic nuclei, a mobilisation of the carbohydrate reserve occurs through the sympathetic-adrenal mechanism. Lesions in the tuber cinereum prevent the onset of experimental diabetes.

Fat metabolism, being closely associated with carbohydrate metabolism, is also affected by injury to the tuber cinereum, producing the adiposo-genital syndrome.

Isolated injury to the tuber cinereum, as already pointed out, causes sexual dystrophy despite the integrity of the anterior lobe of the pituitary. The cause is not clearly understood. Brooks believes it may be due to withdrawal of innervation of the pituitary gland, since the anterior lobe appears to receive fibres from the hypothalamic region by way of the pituitary stalk.

With the syndromes quoted above, there appear§ to be likely changes in personality, varying from depression to outspoken manic states. Corresponding behaviour in animals with hypothalamic lesions have been noted. Lesions in the anterior hypothalamus tend to produce

excited states, while posterior lesions are more likely to be accompanied by lethargy and a tendency to catatonia.

At this stage it may appear that I have digressed somewhat from my original thesis on delayed menstruation. The intention is however to prove the following :-

- (1) That stimulation of the hypothalamus leads to a sympathetic and parasympathetic discharge.
- (2) That the hypothalamus governs our emotional responses, or in other words our reactions to our external environment and that this in turn is dependent on autonomic discharge.
- (3) That autonomic discharge can affect the anterior pituitary gland or the uterus directly in such a way as to inhibit the menstrual flow.

The work of a number of authors in support of the above hypotheses will be quoted.

In support of the first contention, Ernst Gellhorn³⁷ showed that hypothalamic stimulation can lead to parasympathetic as well as sympathetic discharges but due to the preponderance of the sympathetic innervation, the final effect is that of sympathetic response. In order to decide this question the hypothalamus was stimulated by oxygen lack and administration Metrazol, while suppressing the sympatheticoadrenal system. The experiments were carried out on rats and showed that, whereas anoxia regularly produces a rise in blood sugar in normal rats, it leads to a distinct hypoglycaemia when carried out on adrenalectomised

animals. This seems to indicate that anoxia stimulated not only the sympatheticoadrenal system but also, at the same time, the vagus leading to an increase of insulin secretion. If this interpretation is correct then division of the vagus should abolish this effect. The experiments showed, indeed, that division of the vagi and adrenalectomy prevented hypoglycaemia in animals when exposed to anoxia. Similar experiments with Metrazol gave similar results.

Further experiments were also performed on cats, which on account of sectioning of the spinal cord at the lower cervical level, the sympathetic nervous system was cut off from the diencephalon, and the medullary centres. These animals were excited by a barking dog and the blood sugar determined before and after the period of experiment. It was found that blood sugar fell. Sections of the vagi abolished this effect.

These experiments show conclusively that anoxia, Metrazol and excitement lead to simultaneous excitation of the parasympathetic and sympathetic nervous systems. The effects on the parasympathetic system are however masked by the predominance of sympathetic innervation.

Further evidence that hypothalamic excitation leads to sympathetic responses comes from the work Pitts and Bronk³⁸, who state that it is generally conceded that the lateral and posterior hypothalamic areas form a homogeneous system, excitation of which leads to widespread sympathetic

discharge. Single neurones of the cervical sympathetic may be excited by stimulation of a fairly extensive area, not only on the same side of the hypothalamus but on the opposite side as well.

The pathways, the authors continue, connecting the hypothalamus with the preganglionic sympathetic neurones, as far as is known, descend from the lateral hypothalamic areas through the central grey, and tegmentum of the mesencephalon into the pons where they are concentrated chiefly in the tegmental region. In the medulla, they pass more caudally in the lateral portions of the reticular formation through the region of the myelencephalic centre. In the cord they are situated in the antero-lateral funiculus. The pathways are made up of crossed and uncrossed connections. It is apparent that each preganglionic neurone of the sympathetic nervous system is in functional connection with many different regions within the hypothalamus. The corollary that each neurone within the hypothalamus is in functional connection with many preganglionic neurones on both sides of the cord is obviously equally true. Stimulation of the hypothalamus with low intensity, high frequency shocks, causes preganglionic neurones of the cervical sympathetic to fire rhythmically and repetitively, at frequencies proportional to the intensity and frequency of stimulation. If both sides of the hypothalamus are stimulated simultaneously, the neurones fire at higher

frequencies which may be greater than, equal to or less than the sum of the frequencies obtained on stimulation of the two sides separately.

Thus we have anatomical evidence of the connections between the hypothalamus and the preganglionic neurone of the cord and that stimulation of isolated areas of the hypothalamus excites the particular preganglionic neurone to which it is connected.

If further proof is required that sympathetic responses are produced as the result of hypothalamic excitation, reference may be made to the work of Bender and Weinstein³⁹ who showed that adrenalin is liberated on stimulation of the hypothalamus using the denervated iris as an indicator of the circulating adrenalin. The pupil of such a preparation in the cat is very sensitive and dilates with intravenous adrenalin in concentrations of 1×10^{-8} per kilo body weight.

The hypothalamus was stimulated by a bipolar electrode, carried out under light nembutal anaesthesia. In the cat the blood pressure rose as much as 100 mm. mercury, and dilatation of the pupil and retraction of the nictitating membrane occurred. The mydriasis persisted for over 60 seconds and then the blood pressure fell as much as 40 mm. mercury. The depressor effect was not accompanied by bradycardia, was not blocked by atropine and was not potentiated by eserine. The reactive foci were in the

region of the third ventricle.

Unilateral adrenalectomy did not alter the results. Low concentrations of excised adrenal gland was injected into adrenalectomised animals. This produces the humoral response obtained on hypothalamic stimulation, viz. : a fall in blood pressure and dilatation of the denervated iris. Elliot and Durham (1906) have shown that, in small quantities adrenalin can produce a drop in blood pressure, when given ~~in~~ intravenously. The amount of adrenalin discharged on hypothalamic excitation is probably in the order of 0.01 gamma per kilo per second.

It may be that in different emotional states, the authors conclude, varying quantities of adrenalin are liberated, the larger yielding pressor and the smaller depressor effects.

From what has already been said, therefore, there is little doubt that hypothalamic excitation is responsible for the liberation into the blood stream of both adrenalin and acetyl choline, provided that the sympathetico-adrenal system and the vagi are intact. Thus the first contention may be taken as proved.

The next question to be decided now is, does the hypothalamus govern our emotional responses to our external environment? and if that is the case, does it do so through the production of adrenalin and ac^etyl choline, the varying responses thus produced dependent on the relative quantities

of acetyl choline and adrenalin liberated into the blood stream?

The first premise to be established is that the hypothalamus is the centre for emotion. Concerning this vexed question exists a great deal of controversy in which the psychiatrists mainly participate. Thus the whole subject is still in the melting pot and no decision has yet been reached. However, this much does remain clear and that is, the hypothalamus is associated in some way, small or large, with our emotional reaction to our external environment. In what manner this comes about has not yet been clarified. The work of various authors on this subject will merely be quoted and I shall draw my own conclusions.

Jules H. Masserman⁴⁰ in 1941, found that when a 60 cycle current from 2-4 volts is applied through an implanted bipolar electrode directly to the hypothalamus on an unanaesthetised freely moving cat, the animal begins to growl, raise its back, lash its tail and the following typical sympathetic reactions occurred - hyperpnoea, salivation, mydriasis, piloerection, striking movements with the claws and precipitate running as though in an attempt to escape. Similar reactions may be produced by the intra-hypothalamic injection of a 0.05 cc. of 10% metrazol or 0.01 cc. picrotoxin. It will probably be realised that the salivation and hyperpnoea are the vagal components of the whole response. The author however states that this is

merely an objective reaction and the animal does not experience any subjective sensation of rage. As evidence of this Masserman finds that an animal will continue feeding and cleaning its fur while stimulation by electrodes produces the typical rage reaction. Ransom and his associates have found that bilateral lesions of the hypothalamus render the animal somnolent and cataleptic.

There would be little value in mentioning all the other experiments done by Masserman. These consist of electroencephalographic studies, action currents of the hypothalamus, etc. He eventually concludes that the hypothalamus may integrate the affective neural impulses controlling some of the sympathetic and motor manifestations of fear and rage but there is no basis for the view that the hypothalamus governs emotional experiences themselves.

One cannot help feeling that Masserman approaches the subject with already prefixed views. For example he states, "Were we to accept the thesis that man's emotional life originates in or is even controlled by this tiny substructure of the diencephalon psychiatry would then become, in large part, the study and treatment of various disorders of the hypothalamus and many psychosomatic problems would resolve themselves into sophistries". One is tempted to say "So what!"

With further reference to the question of the relation of the hypothalamus to psychiatry, Beverly R. Tucker⁴¹ in

1941 states that the cells of the hypothalamus contain several nuclei and vary so much in size and shape and various characteristics that they have been termed by some neuropathologists, pseudo-pathologic cells. There seems to be abundant evidence that there exists connections through the sympathetic and parasympathetic systems, which may justify our classification of some of the hypothalamic grey matter as vegetative centres. As far as organic disturbance is concerned, the hypothalamus is affected in practically all cases of encephalitis, and somnolence or wakefulness may ensue. Tumours of the brain, cerebral haemorrhage and brain trauma to the hypothalamus give many emotional symptoms.

Tucker also attempted to explain certain lesions in other body systems as being due to functional disturbance of the hypothalamus, e.g. a patient may have a gastric ulcer caused by functional hyperexcitability of the hypothalamus through its vegetative gastro-intestinal connections. A surgeon may operate on an acutely inflamed appendix or gall bladder, or ovary and do a successful piece of work confirmed pathologically but the patient may continue to have symptoms due to the non recognition of a functional hypothalamic lesion.

There are certain states which have been classified as neurasthenia, psychasthenia, psychoneurosis and anxiety states, which Tucker believes are due to hypothalamic

emotional disturbance, expressed through the feeling tone and carried to the various parts of the body by the hypothalamic sympathetic and parasympathetic nervous system connections. These disturbances, he continues, will soon be gathered into a syndrome. The symptoms most common to hypothalamic disturbance are fear states, emotional instability, insomnia or drowsiness. These are combined with vegetative symptoms of visual change, vertigo, nausea and vomiting, constipation, hypo or hyperacidity, shivering sensations, polyuria, flushings, sensations of heat and cold, changes in blood pressure and temperature.

If the above statements are true, and indeed there is enough experimental evidence to justify most of them, we are amazed at the versatility of such a tiny area of the brain.

Masserman in a further article⁴² in 1942 merely reiterates his previous results on the effects of stimulation of the hypothalamus by bipolar electrodes or by amytal or metrazol, which produces in the unanaesthetised animal piloerection, mydriasis, hissing, growling, lashing of the tail, clawing and biting. Hypothalamic destruction on the other hand makes the animal stuporose, somnolent and apathetic. However contrary to this he found that further stimulation of the area produces a "pseudo-affective response". Further as the surviving animals recover they regain their capacity for spontaneous emotional responses.

Thus in reviewing the literature dealing with the

relationship of the hypothalamus to emotional response one is left somewhat bewildered. On the one hand Tucker is willing to ascribe to this small portion of the nervous system almost all the ills both physical and mental to which the human being is heir to, and the other, Masserman condemns wholeheartedly any attempt to limit the problems of emotional response to this small organ. Whom are we to believe? Perhaps it were best for the impartial observer to maintain a via media and to temporise between the two view points. It appears, therefore, that the hypothalamus plays some very definite part in the control of our responses to our external environment - mediated probably through autonomic discharge. The type of response obtained would probably therefore be dependent upon the relative preponderance of the sympathetic and parasympathetic nervous systems in any particular individual or the degree of their representation in the hypothalamus. Thus we can explain why two apparently normal people react quite differently to a similar environment. Taking, for example, the fear state which produces mydriasis, piloerection, increase in blood pressure and heart rate in one individual would only affect another individual to a lesser degree dependent on the predominance of the sympathetic nervous system as mentioned above. Whether the particular individual experiences the sensation of fear which he does, or does not, express in the reactions cited above, is a difficult

psychological question to answer.

I feel now that the second hypothesis, if not proved at least carries a large element of truth, and I now come to the proof of the third hypothesis, i.e. that autonomic discharge can affect the anterior pituitary gland or the uterus directly in such a way as to alter or inhibit the menstrual flow. I can do this, I hope, by quoting the work of Taubenhaus and Soskin⁴³ who showed that luteinising hormone is released from the anterior pituitary by an acetyl choline like substance, liberated from the hypothalamic region. This article is perhaps one of the most important in the many quoted, as it integrates the thesis and is the keystone round which my arguments on the relationship between the hypothalamic function and amenorrhoea, are built - I offer no excuse therefore for quoting it more or less in full.

The authors state that it is a well established fact that stimulation of the hypothalamus in some way activates the anterior pituitary causing ovulation in the rabbit, an animal which only ovulates in the response to sexual excitement. It is assumed that corpus luteum formation and pseudo-pregnancy which is induced in rabbits, rats and other animals by mechanical or electrical stimulation of the genitalia results from afferent nervous impulses to the hypothalamus.

The existence of a direct nervous pathway, they

continue, from the hypothalamus to the anterior pituitary gland is not certain. Although a number of investigators have described fibres leaving the hypothalamic nuclei to pass through the hypophyseal stalk to various parts of the pituitary, it is difficult to verify their terminations in the pars anterior. Hinsey concludes that: "Until more conclusive evidence from degenerative procedures is introduced, the matter of direct innervation of the anterior pituitary lobe from the hypothalamus must be left a matter of question". Functional evidence obtained from section of the pituitary stalk is also equivocal. Both positive and negative results have been reported with regard to interference with the sex functions and ovulation. In those cases in which a disturbance was reported, it was impossible to say how much this was due to the injury of the blood supply of the hypophysis. Dempsey and Uotila³⁵ have published convincing evidence that the reproductive cycle ovulation, mating, pregnancy and lactation can occur after complete section of the pituitary stalk in the rat. However, a certain proportion of the animals did show some suppression of ovarian activity. A possible explanation, according to Taubenhaus and Soskin, might be that there is no direct nervous connection between the hypothalamus and the pituitary, because of the production of a neuro-humoral substance there or in the pituitary stalk and this substance is conveyed to the anterior pituitary by the

portal sinusoids. If that were the case then the paradoxical results obtained by Dempsey and Uotila may be due to the extent of the damage between the vascular connections of the pituitary and hypothalamus in carrying out complete section of the stalk. It might also explain the fact that the hypophysis must be left in situ for a period of $1-1\frac{1}{4}$ hours after coitus or genital stimulation in a rabbit in order that ovulation may occur. This time interval may not be so necessary for the release of luteinising hormone as for a cumulative stimulation in the anterior lobe by the production of a pharmacodynamic substance arriving via the portal vessels.

Taubenhaus and Soskin continue with the details of their experiments. The existence of a normal oestrus cycle in female white rats of the Evans-Long strain weighing from 150-180 gm. was ascertained by the vaginal smear test. On the first or second day of oestrus the pituitary gland was exposed under avertin anaesthesia. The drugs used were dissolved in physiological saline pH6.3 and dropped directly onto the gland with a capillary pipette. Physiological saline at the same pH was used as a control. The pituitary was protected by the clot of retracting blood. Daily vaginal smears were continued following pituitary stimulation. When dioestrous persisted for more than 4-6 days, a laparotomy was performed and the uterus was pierced with a silk thread. The criteria for a

pseudo-pregnancy consequent to the release of luteal hormone was the continued presence of dioestrous and formation of histologically confirmed decidua at the site of traumatisation.

The following table summarises the results :-

TABLE 13.

Solution applied to exposed pituitary	Approximate amount of drug	No. of Rats	Results	
			Pseudo-pregnancy	Normal Cycles
Physiological Saline	0.1 c.c.	20	1 (injury)	19
Acetyl choline (10 Y c.c.) + Prostigmin	1.0 Y 0.5 Y	20	13	7
Atropine 20 Y per c.c. followed by acetyl choline + prostigmin as above	2.0 Y as above	20	4	16
Epinephrine (1 Y c.c.) + Ephedrine (5 Y c.c.)	0.1 Y 0.5 Y	5	0	5
Subcutaneous injection of acetyl choline + prostigmin	50Y/100 gm.wt. 40Y/100 gm.wt.	10	2	0

Two possible objections to a direct parasympathomimetic stimulation of the anterior pituitary are answered.

(a) Did the acetyl choline produce its effects by a non-specific irritant action on the gland? The fact that atropine abolished the effect and that controls and epinephrine had no effect militates against this.

(b) Did the acetyl choline mixture spread to the adjacent

hypothalamus or was it absorbed in the general circulation thus affecting the uterus directly. Against this we have that subcutaneous injection of very large amounts of the drug have a much smaller effect. The authors therefore conclude that the anterior pituitary reacts to the presence of parasympatheticomimetic substance by the production of luteal hormone.

Taubenhaus and Soskin, continuing their experiments then show that inhibition of the genito-hypothalamic-anterior pituitary reflex for the release of luteinising hormone can occur by direct application of atropine to the exposed gland. The experiments were designed to see whether an autogenous, neuro-humoral substance similar to acetylcholine and prostigmin is involved in the reflex release of luteinising hormone initiated by stimulation of the cervix. However, anaesthesia can itself interfere with the occurrence of pseudo-pregnancy, following genital stimulation. The results in the table below show that each of the three anaesthetics tested exerts a definite inhibitory effect on the reflex release of luteinising hormone. It was clear that the experiments could not be done on the anaesthetised animals and the atropin would have to be applied to the exposed pituitary at some suitable time interval before or after genital stimulation, and the animal allowed to recover from the anaesthetic.

Fee and Parkes had previously shown that luteinising

hormone was not released if the pituitary gland was damaged or removed or if the pituitary stalk was sectioned within one hour after genital stimulation. It seemed likely that avertin would have an effect similar to mechanical interruption of the pathway. The most favourable method was therefore to cause genital stimulation after the effects of the anaesthetic wore off. The author's results of the relation between the time of anaesthesia and the time of genital stimulation on the incidence of pseudo-pregnancy is expressed in the following table :-

TABLE 14.

Time of Anaesthesia	No. of Rats	Pseudo-Pregnancy	Normal Cycles
5 mins. after stimulus	6	-	6
20 mins. do. do.	6	3	3
60 mins. do. do.	6	6	-

Following on these experiments the authors show that pseudo-pregnancy which takes place following genital stimulation can be negated by the direct application of atropine to the pituitary gland. The results were as follows :-

TABLE 15.

Atropine application, after and before stimulation	No. of Rats	Pseudo-Pregnancy	Normal Cycles
Anaesthesia alone 60 mins. after stimulation	6	6	-
Atropine application during anaesthesia 60 mins. after genital stimulation	8	6	2
Anaesthesia 60 mins. before stimulation	15	8	7
Atropine during anaesthesia 60 mins. before stimulation	15	2	13

The results in the above table indicate that the induction of anaesthesia less than one hour after cervical stimulation interfered with the reflex. They also show that some interference of hypothalamic function persists for one hour after recovering from anaesthesia, but at this time half the animals became pseudo-pregnant. Accordingly, the atropine application to the exposed pituitary gland was performed 60 mins. after cervical stimulation in one group of animals and 60 mins. before, in another group. Table 15 shows that atropinisation 60 mins. after stimulation was too late to interfere significantly with the reflex and that atropine does not interfere significantly with any of the events following the release of luteinising hormone. The application of atropine under anaesthesia 60 mins. before stimulation resulted in a significantly lower incidence of pseudo-pregnancy, than follows stimulation under anaesthesia alone.

The above results, the authors conclude, lead to the conclusion that the reflex release of this luteinising hormone, initiated by genital stimulation, involves the action in the anterior pituitary of a neurohumoral substance from the hypothalamus, which can be inhibited by atropine. The demonstration of the probability of an acetyl choline like humoral substance transmitted between the hypothalamus and the anterior pituitary can therefore explain the effect of prostigmin and carbaminocholine in precipitating the menstrual flow in "Nervous Amenorrhoea". These substances have a hyperaemic effect directly on the uterus which may account for the flow a few hours after injection. However, this does not explain the precipitation of the flow three days after administration of the drug in other subjects. This would suggest that an injection of prostigmin stimulates luteinising hormone with the production of a corpus luteum, which on retrogression gives rise to bleeding.

The work quoted above is, I feel, a brilliant piece of biological research, which has gone a long way to solve many of the problems which beset us, in attempting to establish the cause, or causes, of delayed menstruation, and its precipitation by parasympathomimetic drugs. Although their work has not been confirmed in this country, we can probably accept the following facts with little criticism.

(1) Direct application of acetyl choline to the exposed

pituitary gland in the rat causes pseudo-pregnancy, as a result of the release of luteinising hormone, as shown microscopically by the presence of decidua.

(2) Pseudo-pregnancy, produced by cervical stimulation, is inhibited by the direct application of atropine to the exposed pituitary gland - thus strengthening the view that acetyl choline or a similar substance is released (probably from the diencephalon) and acts on the pituitary gland, causing the release of luteinising hormone.

A number of difficulties in assessing the effects of atropine were experienced by the authors, owing to the fact that anaesthesia itself interferes with pseudo-pregnancy, but these were overcome as described above, by determining the effects of anaesthesia on pseudo-pregnancy at various times up to one hour following genital stimulation.

Thus they explain the precipitation of the menstrual period by administration of a parasympathetic stimulant can be effected in two ways :-

(a) An immediate response as a result of hyperaemia of the uterus.

(b) A delayed response as a result of the production of the luteal hormone, and consequently the corpus luteum and the eventual degeneration of the latter leading to menstrual bleeding.

It is difficult to understand, however, and indeed hard to believe, that in different patients the same

substance will produce its therapeutic effects in the one case, by a direct action on the uterus, and in the other, through the medium of corpus luteum production. The acceptance, however, of hypothesis (b) would explain the long delay before onset of the period after treatment with a parasympathetic stimulant.

The danger of applying results obtained by experiment on the lower animals, such as the rat and the rabbit, to the human species has already been emphasised. It should be particularly noted that menstruation is not the same phenomenon as oestrus in rodents. A number of important differences exist. For instance, whereas in the rabbit ovulation and pseudo-pregnancy occur as a result of cervical stimulation or copulation, in the human ovulation occurs in a definite cycle regardless of stimuli from the cervix, but in view of the therapeutic results obtained with parasympathetic stimulants in delayed menstruation, one cannot help feeling that there is a great deal of truth in support of the theory that an acetyl choline like substance can affect the pituitary gland of the human female with the resultant precipitation of the menstrual flow.

In order to integrate the work of the various authors already quoted, in an attempt to explain the probable mechanism of the production of delayed menstruation, the work expressed in the last few pages will be summarised and embodied in my own conception of the onset of amenorrhoea

as it occurs on entry to service and following emotional disturbance.

Our present conception of the control of ovulation and menstruation by the pituitary gland has already been stated. It was seen that the pituitary gland produced two gonadotropic hormones. Prolan A stimulating the formation of Graafian follicles, the latter finally liberating the mature ovum, whilst the resultant structure left in the ovary was maintained as the corpus luteum by prolan B. The corpus luteum degenerates on about the 28th day of the menstrual cycle and thus menstruation occurs. During the progestational phase of the menstrual cycle the uterine glands become tortuous, the vessels dilate, and there is an increased mucous secretion. In fact it is a preparation to receive the fertilized ovum, and should conception not occur, menstruation takes place. The latter has therefore sometimes been called, the "Weeping of the disappointed uterus". In the majority of women, therefore, there is a more or less regular cycle occupying a period of 28 days. The control of this cycle is attributed to the pituitary gland through the medium of its hormone production.

The menstrual cycle is an amazing phenomenon of nature, the regulation of which is far from understood. Many questions immediately crop up, e.g. Why should the cycle be 28 days, and not say 30, 40 or 15 days? Why

do some women have a cycle of 21 days, and others a longer one of 56 days? The questions could be begged by saying "Why is the cardiac cycle $1/72^{\text{nd}}$ of a minute approximately or the respiratory cycle $1/12^{\text{th}}$ to $1/14^{\text{th}}$ of a minute".

The answer to all these questions would probably be the same.

The pituitary gland, of course, plays a very great part in the regulation of the cycle through the medium of the hormones it produces. But is the pituitary gland the sole regulator of that function - autonomic in its control? As Samson Wright states (Applied Physiology 1940, 243 to 244) "It is almost certain that the activity of the anterior pituitary itself is regulated appropriately, but by means which are at present little known. If we regard the pituitary as the centre of the hormonal reflex arc, then we can say we know a great deal about the efferent side of the arc, i.e. what the pituitary does to other organs, but comparatively little about the afferent side of the arc, i.e. the control of the pituitary itself."

Marshall and Verney showed that ovulation and pseudo-pregnancy in a rabbit occurred following electrical stimulation of the brain and spinal cord. Now as ovulation and corpus luteum formation occurs following the liberation of prolans A and B respectively, we are led to the conclusion that electrical stimulation in some way affects the pituitary to produce these prolans. We can conclude therefore that the pituitary gland can be stimulated to produce its hormones

by certain nerve pathways as yet undetermined. This is extremely likely, as electrical stimulation of the cervix in the rabbit can also produce ovulation, corpus luteum formation and pseudo-pregnancy.

McBrooks offered further evidence on the neutral control of ovulation. He found that rabbits with a pituitary stalk section did not ovulate in response to copulation, but if preformed prolans were injected into pituitary stalk sectioned animals, ovulation and pseudo-pregnancy occurred. The connection between the pituitary gland and the brain, therefore, must be intact for ovulation to occur, and as a corollary the production of prolans is dependent on direct connection between the pituitary and the brain. McBrooks himself believes that a nerve stimulus occurs on mating through fibres passing down the pituitary stalk. However, the possibility of damage to the blood supply of the pituitary gland during section must not be lost sight of, thus affecting the production of hormones. But if damage to the blood supply caused the cessation of prolan production it would also have caused the cessation of the growth hormone and the thyrotropic hormone. But as the animals did not suffer from any deficiency of growth or thyroid dysfunction, we can rule out the possibility of damage to the blood supply, and assume that production of prolan A, at least, is dependent on an intact nerve supply to the pituitary gland.

Definite anatomical evidence of the innervation of the hypophysis as suggested in the work above was presented in the histological studies of McBrooks and Gersh. They found that in the rabbit nerve fibres entered the anterior lobe from three directions: (1) infundibular stem (2) the infundibular process (3) by the capsular arteries. They also were able to determine the sympathetic supply in the rat, and found that the fibres enter the pars anterior along with the nerves entering along the capsular arteries. However, the authors were unfortunately unable to determine the origin of these nerve fibres. This is at the moment a matter of speculation. But as we know that the diencephalon is the centre of autonomic discharge, it is not illogical to suggest that these nerve fibres may arise in the hypothalamus.

Thus we have now formed an important link in the chain of the argument - namely that the anterior hypophysis is probably under the control of the autonomic nervous system. There are still a number of objections, however, to this contention. These are: (1) that although terminal nerve fibres are found in the pars anterior, it does not follow that the functions of the gland are regulated by these fibres (2) the origin of the fibres has not definitely been determined (3) Pituitary transplants in immature female mice will produce precocious ovarian activity and corpora lutea formation, although in the transplant all

nerve connections have obviously been destroyed. If the third objection is the case, then it would appear that the anterior pituitary gland has a certain degree of autonomy and an inherent capacity to produce its hormones independent of nervous control.

Dempsey and Uotila proved that thyrotropic and luteinising hormones were produced in spite of pituitary stalk section, but also showed that following exposure to cold, which in the normal guinea pig causes an inhibition of the gonadotropic hormone, in the operated animal, the oestrous cycle continued normally and corpora lutea were found at death.

The significance of the above observations ^{is} ~~are~~ probably as follows: The pituitary gland will produce its hormones whether its connection with the brain is intact or not, but the regulation of the relative quantities of hormone thrown into the circulation in response to certain environmental states is under the direct control of the nervous system.

Similarly, it is probable that an animal with a pituitary transplant will be able to produce the adrenotropic hormone, the exposure of such an animal to a sudden emergency state will not produce the excess of adrenotropic hormone necessary to affect the adrenal gland to release adrenalin and thus cause the animal to "fly or fight".

Although the results, at present, with regard to the

effect of pituitary stalk section appear to be equivocal - Verney and McBrooks stating that the nervous mechanism is responsible for ovulation in the rabbit, while Dempsey and Uotila find that luteinising hormone is produced following pituitary stalk section. It is probable that the gland has the inherent capacity to produce some of its hormones, certainly the luteal and thyrotropic hormones, whether its nerve connections with the brain are intact or destroyed. But the relative quantities of hormone produced in response to various environmental states is probably under autonomic control. In this respect a striking parallel can be drawn between the properties of heart muscle and the hypophysis cerebri. "A perfect rhythmic activity of the mammalian heart may be maintained for hours after its removal from the body by perfusing the coronary arteries with blood, or with a suitable warm oxygenated perfusion fluid. It is possible to sever all the nervous and muscular connections between the auricles and ventricles without stopping the contractions of the ventricles. A piece of auricular appendix, suspended in warm oxygenated Ringer's solution will continue to beat for hours and a fragment of ventricular wall free from ganglion cells will similarly contract. We may therefore conclude that in the mammalian as well as the amphibian heart every part of the heart muscle possesses the power of rhythmic activity."

(Starling's Principles of Human Physiology, 1941, 8th

Edition, p. 571). In other words heart muscle has the inherent power of contractility independent of nerve connections. But it will not be disputed that the rate of the heart, or the rhythm of the heart is under control of the autonomic nervous system. So that an animal exposed to an emotional environmental state will increase its rate and force of contraction of the heart, but the denervated heart although unable to vary its rate of force of contraction in response to external environment, will still beat rhythmically and regularly, despite severance of all its nerve connections.

Continuing the summary on the mechanism of production of amenorrhoea it was found that, in order to explain the effect of environment on the pituitary gland, literature dealing with the anatomy and physiology of the hypothalamus had to be investigated.

As has already been said, the hypothalamus is a complicated system of nuclear masses divided anatomically into various groups. These are anterior, middle and posterior.

This organ is also credited with an amazing number of functions, many of which have been fully proved and others are at present under investigation. These are briefly:

- (1) Control of autonomic discharge from the posterior hypothalamic areas.
- (2) Encephalitis lethargica, possibly due to lesions of the mammillary bodies.
- (3) Parasympathetic

responses and Frölich's syndrome, centred in the tuber nuclei. (4) Diabetes insipidus, due to lesions ^{of} the anterior nuclei. (5) Heat regulation. (6) Hyperglycaemia and fat metabolism. (7) Sexual dystrophy in tuber lesions. Apart from the above, various psychological changes such as manic and depressive states are localised in the hypothalamus.

From the point of view of this paper, probably the most important facts are that the hypothalamus is responsible for autonomic discharge and that sexual dystrophy can occur due to damage or destruction of nerve fibres in the tuber cinerum.

That hypothalamic stimulation liberates both adrenalin and acetyl choline is more or less established. Gellhorn showed that although both these substances are released from the hypothalamus, the total effect is that of a sympathetic stimulus due to the preponderance of sympathetic fibres, while Pitts and Bronk gave more definite anatomical evidence of the connections of the hypothalamus with the sympathetic nervous system. Bender and Weinstein also showed that hypothalamic stimulation liberates adrenalin. A depressor as well as a pressor effect was obtained, the former paradoxically was not blocked by atropin or potentiated by eserine.

An attempt was then made to show how the hypothalamus controlled our emotional responses to environment, and that the rhythm of the menstrual cycle could be upset by

emotional disturbance, probably through the production of excessive amounts of adrenalin and acetyl choline, as a result of hypothalamic excitation. No definite evidence has been produced to prove that the control of our emotional responses does lie within the hypothalamus, but the possibility is too strong to be denied.

Finally, Taubenhaus and Soskin were able to produce corpora lutea and pseudo-pregnancy in the rat by direct application of acetyl choline to the exposed pituitary gland. Although this may explain the precipitation of the menstrual period following the administration of a parasympatheticomimetic drug, it does not give much indication as to the reasons for the actual cessation of menstruation as a result of environmental or emotional disturbances.

From the work quoted above I shall outline my own conception of the control of the menstrual cycle by the pituitary gland and give possible reasons for the sudden cessation of the bleeding phase under different environmental states. It should be borne in mind that little of this has been definitely proved, and much of it is still theoretical.

The various components which constitute the menstrual cycle assume a definite rhythm. This differs to a slight extent in different individuals, but is more or less constant in the same individual. The cycle consists of three phases: (1) The proliferative phase, corresponding with the ripening of the Graafian follicle. (2) The

premenstrual phase, corresponding with corpus luteum formation. (3) The bleeding phase. Each phase bears a definite time relationship to the complete cycle. The number of days between each cycle is calculated as the time between two successive bleedings. This is on an average 28 days, it being understood that this is an arbitrary average figure in the same way as we assume that 72 beats per minute is the average pulse rate.

The first phase, i.e. the phase of ripening of the Graafian follicle, occupies about the 6th to the 14th day of the cycle (counting from the 1st day of the last menstrual period), at the end of which time ovulation occurs. The rhythmicity of this phase of the cycle is dependent on either the inherent rhythmic character in which the anterior hypophysis produces its follicle stimulating hormone (F.S.H.), or, as we know that ovulation can occur as a result of stimulation of the hypophysis and the hypothalamus, it may occur as a result of rhythmic impulses - neural or neuro-humoral to the pituitary gland. The nerves responsible for this probably arise in the hypothalamus and pass into the hypophysis via the infundibular stem, the infundibular process and the capsular arteries. If this is the case, as it may well be, is it then without the bounds of possibility to postulate what might be termed as an "Ovulatory Centre" analogous to the respiratory centre? This centre, if there is one, would

in all probability be located within the hypothalamus and possess an inherent rhythmicity which would be capable of rhythmic nervous or humoral discharge affecting the pituitary gland. This in turn would lead to the rhythmic production of follicle stimulating hormone. The frequency of the discharge from the hypothetical ovulatory centre is extremely slow in comparison with the respiratory centre, the former occupying a period of about eight days in every cycle of 28 days.

The second phase, i.e. the phase of corpus luteum formation, occupies the time from the occurrence of ovulation to the 28th day of the cycle, that is usually about 13 to 14 days. Now Reynolds showed that oestrone increased the acetyl choline content of the uterus, the oestrone being produced during the state of maturation of the ovum. This could only have arisen as a result of stimulation of the parasympathetic nervous system. If the acetyl choline content of the body is not only increased locally in the uterus but in the body systems as a whole, then the pituitary gland, along with the other organs of the body, would be affected, the acetyl choline being transported to the gland in the portal sinusoids. Taubenhaus and Soskin proved that acetyl choline applied to the pituitary gland would release luteinising hormone and cause pseudo-pregnancy. So that logically it follows that ovulation resulting from neural or humoral impulses to the hypophysis,

and consequent oestrone production would stimulate the parasympathetic nervous system to liberate acetyl choline. The latter is transported in the blood stream to the pituitary gland, and stimulates the release of luteinising hormone with the production of corpora lutea.

The third phase of the menstrual cycle is the bleeding phase, which occupies 4 to 6 days. Our conception at present is that bleeding occurs as a result of the degeneration of the corpus luteum. However, the menstrual flow may only be coincidental with, rather than, the result of corpus luteum degeneration. It is probable that the bleeding component is dependent on hyperaemia of the uterus as a result of the local presence of acetyl choline. The length of the bleeding phase and the quantity of blood lost may be directly proportional to the quantity of acetyl choline in the blood stream or locally in the uterus. This in turn is, as has been shown, dependent on the activation of the parasympathetic system by the presence of oestrone. So that it is evident that any disturbance affecting the production of acetyl choline may interfere with the bleeding phase without necessarily affecting ovulation.

In an attempt to explain the cessation of the bleeding phase during periods of environmental stress, we may begin by saying that the hypothalamus is believed to be the collecting centre for our sensory impressions. Further

our emotional response to such sensory impressions of reactions to different environmental states may be governed by the relative quantities of adrenalin and acetyl choline thrown into the blood stream as a result of hypothalamic excitation. No doubt there is an increase in sympathetic tone during mental and emotional strain which would more than counter-balance the effect of parasympathetic response, leading to a relative deficiency of acetyl choline in the blood stream, insufficient to produce hyperaemia in the uterus or luteinising hormone from the pituitary. As a result of a deficiency of acetyl choline no corpus luteum would be formed and menstruation could not occur. It would be expected therefore that the potentiation of or the artificial replacement of acetyl choline in the blood stream by the administration of a parasympatheticomimetic drug would overcome this. And this is probably the manner in which prostigmin and carbaminocholine precipitate bleeding in delayed menstruation.

One question difficult to explain is why some women develop amenorrhoea and others do not, in response to the same environmental state. It is a truism to say that people differ in their responses to the same environment. Some are elated, others are depressed, some experience fear, others do not, in response to the same emotional stimuli. The particular response which the individual makes is an expression of character. An individual's

reaction to his external environment is probably dependent on the ratio of acetyl choline to adrenalin resulting from hypothalamic stimulation. As the responses to environment differ in different people, so do the relative quantities of adrenalin and acetyl choline vary. Some will produce greater quantities of adrenalin than normal, and thus the bleeding phase of the menstrual cycle will cease. Others will be scarcely affected by a change of environment, and thus the menstrual cycle will remain normal.

Similarly, we may be able to explain irregularity, increase or decrease of the menstrual flow, as resulting from an increase or decrease of the adrenalin - acetyl choline ratio in the blood stream. However, other factors, such as organic disease of the uterus and ovaries, for example, metropathia, haemorrhagica, fibromyoma, carcinoma, etc., can be brought in to explain these irregularities.

Epimenorrhoea is dependent on an increased activity of the ovaries, which ovulate too frequently. This is probably due to a speeding up of the frequency of the discharge from the hypothalamus.

It is self evident, therefore, that the hypophysis cannot now be regarded as the "leader of the endocrine orchestra". It only plays the part of the "second fiddle", probably to the autonomic nervous system, represented in the hypothalamus.

Perhaps the subject would be better expressed in the following diagram :-

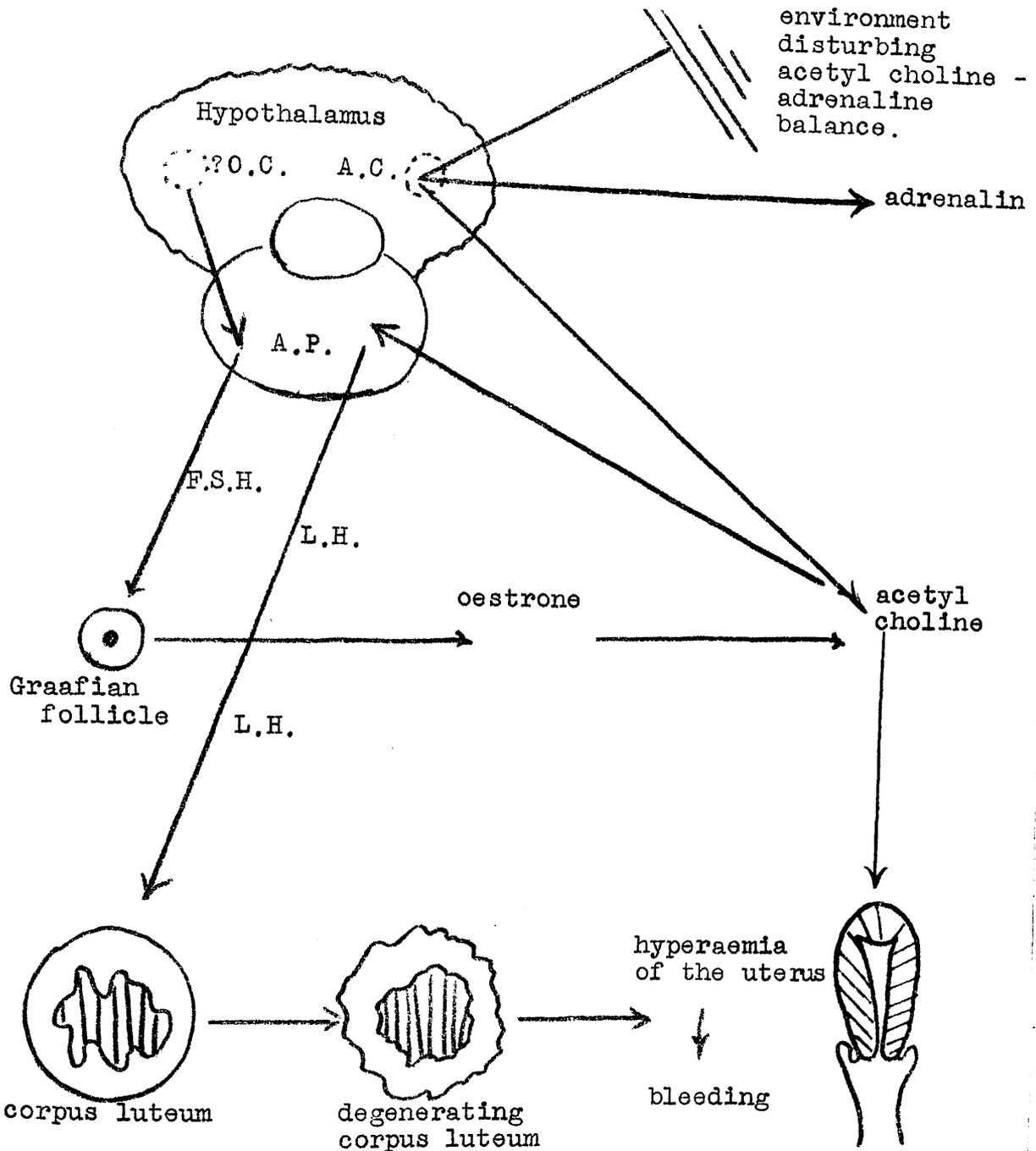


Fig. 3. ? Centre for ovulation in the hypothalamus (O.C.) rhythmically activates the anterior pituitary gland (A.P.) to produce the follicle stimulating hormone F.S.H. resulting in the production of oestrogen and acetyl choline. The latter acts on the A.P. to produce luteinising hormone (L.H.) and hyperaemia of the uterus. Bleeding occurs as a result of hyperaemia and degeneration of the corpus luteum. Acetyl choline - adrenaline balance can be disturbed by External Environment.

This section of the work can probably be concluded no better than by quoting the words of Foster Kennedy⁴⁴ in an extremely well balanced and philosophical article on the hypothalamus as a pace maker of metabolic and emotional rhythm.

"The supreme mystery lies in the commonplace phenomena so exquisitely maintained that they excite almost no attention. The regularity of the rhythm of breathing, the constancy of the pulse rate, the exact maintenance of body temperature, the beautiful balance of intake and output of fluid, the cycle of sleep, the integrity of body weight and the periodicity of the menstrual rhythm and this integrating mechanism of the diffusely working sympathetic and discreetly working parasympathetic systems are linked and perhaps activated by hormone messengers, chiefly from the hypophysis, but stimulated and controlled through the subthalamus to the thalamus and thence to the prefrontal cortex

"Further, in an area where the sympathetic and parasympathetic functions are both represented in their enormous variety we discover stimulating clinical patterns of dysfunction not ordinarily associated in our minds. For instance, we readily accept amenorrhoea as part of the picture of abnormal obesity in women. We somehow see immediately that the same lesion has produced both of these two symptoms, but we do not readily see that the

fluctuations in body weight, the sleeplessness and the amenorrhoea of a young woman with cyclothemia are caused by the same lesion that produced her recurrent manic behaviour and mood. Indeed we ask ourselves 'Did the suppression of the menses cause her mental breakdown?' Instead of perceiving the probability that the breakdown in the rhythm of her menses has been produced by the same abnormality in structure and function that has caused the break in the rhythm of her emotional life."

SUMMARY AND CONCLUSIONS.

1. A modification of a present classification of amenorrhoea is suggested - on a clinico-pathological basis, rather than on the time of onset of amenorrhoea.
2. A short historical review of delayed menstruation, or, *Kriegsamenorrhöe*, as it was then called by the German workers, is then given. The general consensus of opinion in German medical circles up to about 1928 was that the causes of *Kriegsamenorrhöe* in the order of their importance are: (1) Protein deficiency in the diet. (2) Increased work. (3) Psychological and emotional stress.
3. The incidence of delayed menstruation, on entry to service, in 2,312 airwomen between 1939 and 1943 is tabulated.
4. The relationship between delayed menstruation and

occupation was investigated, and it was found that the greatest number of cases occurred in those with a sedentary occupation.

5. The diets of a number of stations with cases of delayed menstruation were examined and no protein deficiency was found.
6. 150 normal girls were weighed, and over 90% had put on weight since entry to service, but airwomen with amenorrhoea put on more weight than would be expected in the average normal girl.
7. Four cases of delayed menstruation were treated with carbaminocholine chloride and two of the cases menstruated in 17 and 96 hours, one menstruated in 35 days, and one menstruated with a placebo. No definite conclusions can be drawn, owing to the small number of cases treated, but it appears that carbaminocholine is a useful form of therapy and is worthy of further clinical trial.
8. Two normal controls were unaffected by treatment with carbaminocholine chloride.
9. Three cases of pregnancy were treated with carbaminocholine chloride, a total of 9 to 12 tablets (0.018 - 0.024 gm. active drug) in each case was administered. No disturbance of pregnancy occurred. As a test for pregnancy, however, carbaminocholine cannot be regarded as efficient as the Zondek-Aschheim test

owing to the number of cases of delayed menstruation in whom precipitation of the period does not occur in spite of treatment.

10. The control of the menstrual cycle and the probable mechanism of production of delay is discussed. It is suggested that rhythmic impulses, either neural or neuro-humoral, from the hypothalamus stimulate the anterior pituitary gland to produce its gonadotropic hormones rhythmically, thus effecting a definite rhythm in the menstrual cycle. Disturbance of the rhythm or delay in onset of the bleeding phase can be caused by a change of environment, which affects hypothalamus and disturbs the balance of adrenalin to acetyl choline in the circulation. This brings about a relative deficiency of acetyl choline. Re-establishment of the menstrual cycle can occur by replacing the acetyl choline content of the body.
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