Post-partum Necrosis of the Anterior Pituitary; Pathological and Clinical Aspects

BY

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IN a recent article (Sheehan[1]) it was shown, both from cases personally examined and from a review of the relevant literature, that (*a*) extensive ischaemic necrosis of the anterior pituitary is a not uncommon incidental finding at autopsy in women who die during the puerperium. The necrosis appears to be caused by collapse of the patient at delivery, due in the majority of cases to severe haemorrhage, but it cannot usually be recognized histologically until 14 hours or more post partum. (*b*) In patients who die of Simmonds's disease which originated from a delivery a long time previously, the pathological appearances of the anterior pituitary correspond to the healed stage of this necrosis. Where a history of the delivery is available it appears that the delivery was always complicated by collapse, usually due to haemorrhage.

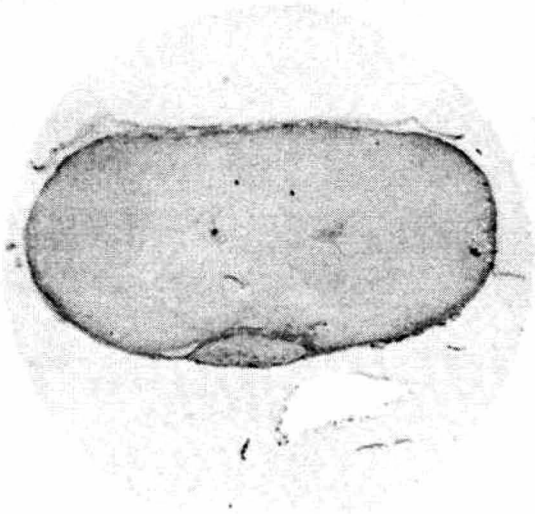
Pathology.

To illustrate the early stage, two new cases are described in which recent post-partum necrosis of the anterior pituitary was found at autopsy.

CASE 1. *Extensive necrosis due to haemorrhage and collapse at delivery. The case is complicated by a pre-existent myxoedema.* Aged 40 years, 8-para. A rather fat woman with scanty eyebrows and head hair, and a myxoedematous appearance of the face. Her last two pregnancies ended in abortion at 4 months; the other five were full-time spontaneous deliveries.

She was admitted at term after 36 hours in labour, disproportion due to the large size of the foetus being the cause of the delay. Two hours later a rupture occurred in the lower uterine segment with severe haemorrhage into the peritoneal cavity; the patient became desperately collapsed, quite unconscious, and

FIG. 1.
Necrosis of the entire anterior lobe of the pituitary.



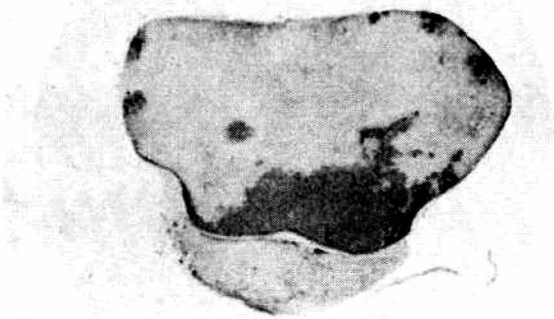


FIG. 2.
Necrosis of about two-thirds of the anterior lobe of the pituitary.
(Horizontal sections, ×5. The dark areas are live anterior lobe tissue; the pale areas are necrosed. The posterior lobe is seen at the bottom of the sections.)

moribund. Laparotomy and hysterectomy were performed at once, an anaesthetic not being required as the patient was so deeply unconscious, and two blood transfusions were given. Though the immediate prognosis appeared quite hopeless, the patient recovered from the operation. During the next three days she was placid and cheerful, but abdominal distension and vomiting then developed; the temperature varied between 99 and 100°F., and the pulse-rate between 120 and 135. At 6 days post-partum she suddenly became drowsy and died a few hours later.

At *autopsy* there was a localized pelvic peritonitis with a recent spread to the general peritoneum, and terminal hypostatic pneumonia. The anterior pituitary showed gross necrosis and, in addition, was rather larger than are most pituitaries 6 days after delivery. The thyroid gland was represented only by a small white mass of fibrous tissue, in which microscopic examination reveals scattered small islets of atrophic alveoli surrounded by accumulations of lymphocytes.

Histologically the anterior pituitary is almost completely necrosed; the only live parenchyma which remains is in two small areas under the capsule in front, and a narrow band along the edge in contact with the posterior lobe. The general appearances are shown in Fig. 1, though the areas of live tissue are too small to be recognizable in this section. Most of the necrosis appears to be several days old, and shows complete loss of nuclear staining in parenchyma and interstitial tissue; there is the usual retention of staining power by the granules in the acidophile cells. There are two ill-defined areas of less advanced necrosis near the centre of each half of the anterior pituitary just in front of the main arteries. In these areas the tissue appears somewhat oedematous and there is still a very faint haemalum staining of nuclear ghosts. Near the surface of the necrosis the capillary endothelium is intact and rather swollen though the parenchyma here shows advanced necrosis. There are no polymorphs in this region but more deeply, about 1 mm. beneath the surface of the necrosis, there is a band of degenerate polymorphs. Where the necrosed area abuts on live tissue the margin is quite sharp with no trace of any atrophy of the live acini and no accumulation of any lymphocytes or plasma cells. Four small sinuses near the surface of the necrosis on the left side contain fibrin thrombi which appear to be a few days old. The main artery in the left half of the gland shows extensive infiltration of its media by fibrin, but the artery is not thrombosed.

Remarks. This history of severe haemorrhage and collapse

at delivery is very typical; with such extreme collapse the chances that the pituitary will escape necrosis are very slight. Greater interest lies in the finding of a fresh pituitary necrosis in a patient with an old standing fibrosis of the thyroid gland. As the patient did not survive, the effect of subsequent absence of thyrotropic hormone on a thyroid with pre-existent fibrous atrophy remains a matter of speculation. But if she had recovered from the delivery there are obvious possibilities of a subsequent clinical or pathological misinterpretation of the case. This raises the question whether there may be multiple aetiological factors in certain cases of pluriglandular sclerosis (see Sourdel,[2] Falta,[3] and Boller and Goedel[4]). It may be noted here that clear evidence has not been found in the literature to indicate that hypothyroid patients have a particular tendency to haemorrhage or collapse at delivery.

The chief points of histological interest in the pituitary are the arterial lesion and the fact that at 6 days post partum no early stages of a zone of secondary atrophy can yet be found. The apparent age of the more advanced parts of the necrosis is in agreement with the view that the lesion began at about the time of delivery; the more recent parts of the necrosis may date from perhaps two days later.

CASE 2. *Large necrosis due to post-partum collapse which was partially obscured by eclamptic coma.* Aged 28 years, 2-para. At 32 weeks gestation the patient developed a hypertensive toxaemia which did not respond to treatment and developed into eclampsia at 37 weeks. She had a spontaneous delivery during the eclampsia; there were 7 fits in the 18 hours ante partum and 5 fits in the 4 hours post partum. During the period from 4 to 18 hours post partum she remained comatose with temperature of 100 to 101°F., but the pulse suddenly became very weak and rapid (about 150) and repeated injections of cardiac stimulants were required. After this she improved gradually for 2 days but then developed signs of broncho-pneumonia and died 3¼ days post partum.

At *autopsy* the typical lesions of eclampsia were found in the liver and kidneys and there was gross broncho-pneumonia in both lungs. The uterus showed some intramuscular and sub-peritoneal haemorrhages. The anterior pituitary showed a large necrosis.

Histologically the pituitary necrosis has a very patchy distribution, as is seen in Fig. 2. Much of it does not show any nuclear staining but there are some areas of less advanced necrosis, par-

ticularly near the front in the mid-line where the lesion appears to be of only about 1½ days' duration. The older parts of the necrosis have a slight even infiltration with polymorphs for a depth of about 1 mm. from the surface; the capillary endothelium near the surface remains healthy but is not so swollen as in the previous case. The areas of live parenchyma appear quite healthy. Several sinuses in various parts of the anterior lobe contain fibrin thrombi which appear to be 2 or 3 days old.

Remarks. The chief interest in this case concerns the condition at delivery. There was only slight blood loss, and the aetiological factor thus appears to have been purely post-partum collapse on a basis of eclampsia and slight accidental haemorrhage. The collapse occurred during the eclamptic coma and would have been hidden by it if the poor condition of the pulse had not been noticed.

Histologically there are no unusual features; the more advanced parts of the necrosis appear to be almost 3 days old.

Aetiology of the Necrosis.

The frequency with which the necrosis is found at autopsy and the actual size of the lesion bear a clear relation to the severity of the haemorrhage collapse at delivery. Table I shows

Table I.

Relation of frequency of occurrence and size of necrosis at autopsy to grade of haemorrhage collapse at delivery 14 hours to 30 days before death.

Size of necrosis	Grade of haemorrhage collapse					
	5	4	3	2	1	0
Complete or almost complete	4	1	—	—	—	—
Large	2	—	1	1	—	—
Medium	1	1	—	—	—	—
Small	—	—	—	—	2	—
None present	1	1	3	2	1	25

(The figures indicate the number of patients.)

the findings in a consecutive series of 46 full autopsies on patients dying later than 14 hours post partum. The severity of the haemorrhage collapse is graded numerically according to the method described below in the section dealing with the first follow-up. Grade 5 is the most severe. As it is not always possible to assess very trivial degrees of haemorrhage collapse, a few patients placed in grade 0 may really belong to grade 1; in 14 of these grade 0 cases there had been operative delivery,

anaesthesia, or eclampsia, but in none of them was any unusual bleeding or any collapse noted in the records. This point, however, hardly affects the significance of the Table.

Pituitary necroses were not found in 18 women dying before delivery nor in 24 women dying during the first 14 hours after delivery. Of these latter 24 patients, 6 had severe and 13 had fatal haemorrhage collapse, but death occurred too soon for any incipient necroses to become recognizable histologically.

It is of interest that the necrosis is found after haemorrhage collapse at delivery but not after haemorrhage collapse in the absence of pregnancy. For instance, there were not any cases reported in soldiers during the war. The association with delivery is to be related to the sudden change from the marked hypertrophy of the anterior pituitary during pregnancy to the rapid involution during the puerperium. At a normal delivery there is presumably a physiological reduction of the blood-flow to the anterior lobe; if in addition to this there is a severe general circulatory collapse, it is possible that the blood-flow to the anterior lobe may be so reduced that thrombosis occurs in the vessels of the lobe and leads to the ischaemic necrosis. This explanation is obviously quite speculative.

Table II shows that there is no recognizable relation between the occurrence of pituitary necrosis and the finding of sepsis or inflammation anywhere in the body at post-mortem. It is commonly accepted that post-partum necrosis of the anterior pituitary is due to embolism as a result of puerperal sepsis. The present findings are in disagreement with that view.

TABLE II.

Pathological findings in 46 women dying later than 14 hours post partum. Showing the lack of relation between pituitary necrosis and sepsis or inflammation.

	Total number of cases	Number with pituitary necrosis
All autopsies	46	13
No sepsis or inflammation whatever	11	3
Uterine sepsis	12	3
Peritonitis	11	4
Pneumonia	20	7
Other sepsis or inflammation (pyelitis, endocarditis, venous thrombosis, abscesses, etc.)	24	5

Clinical Aspects.

The conclusion that the pituitary necrosis is due to haemorrhage and collapse at delivery is based so far only on cases examined post-mortem; it should, however, be capable of confirmation by the clinical examination of patients who survive. Two lines of approach to this problem are available:

(*a*) To look for evidence of hypopituitarism in patients who have survived haemorrhage and/or collapse at delivery.

(*b*) To find whether there is a history of haemorrhage and/or collapse at delivery in patients who have evidence of hypopituitarism.

First Follow-up. Clinical Investigation of Patients some Years after a Delivery with Haemorrhage or Collapse.

For this study it was necessary to collect a group of patients who had had marked haemorrhage or collapse at delivery but had recovered, and about whom complete details of the delivery and puerperium were available. For this purpose the records of all such cases in the hospital during the years 1930 to 1936 were examined and, from these records, the grade of severity of each case was assessed according to the total number of marks which were given for haemorrhage and for collapse. These marks were allocated for each condition separately as shown in the following schedule.

Haemorrhage. One mark, severe haemorrhage; two marks, very severe haemorrhage, mucosae pale, patient restless and definitely requiring transfusion; three marks, extreme haemorrhage, sighing respirations, air hunger, patient exsanguinated and requiring immediate intravenous saline until a blood transfusion can be given.

Collapse. One mark, collapse, pulse-rate less than 140; two marks, severe collapse, pulse-rate over 140, patient may or may not be in obvious coma but remembers nothing afterwards; three marks, extreme collapse, pulse imperceptible, patient comatose, condition "grave" or "moribund".

This assessment from the two aspects gave a reasonably true estimate of the patient's general condition at or just after delivery, though cases of pure collapse without haemorrhage were perhaps assigned to a somewhat low grade.

The cases fell thus into 6 grades; the highest grade with 6 marks was very small and was incorporated with the rather larger grade 5. A follow-up was then undertaken of all patients

in grades 3, 4, and 5, of a large proportion of those in grades 1 and 2, and of a control series (grade 0) of multiparae who had not had any haemorrhage or collapse in their last delivery. Less than half the patients could be traced and examined, but there is not any reason to doubt that they are representative of the whole group. A routine clinical investigation of all these patients was made and, where any indications were present, careful physical examination and chemical studies were performed. In all, the actual follow-up consisted of 128 women who had had haemorrhage collapse at delivery and 64 women whose previous delivery had been normal.

General Symptomatology.

It is sufficient in this connexion to discuss only the clinical findings. These appear to have enough significance in themselves to be used as a basis for diagnosis, even without the support of the biochemical findings which will be reported in another paper. Apart from the question of lactation, the only symptoms to be considered here are those which date from, and have continued since, the significant delivery. No notice is taken of temporary symptoms during the 3 months following delivery when the patient was convalescing from the complicated labour and blood loss, nor of symptoms which date from before the delivery, nor of symptoms due primarily to obvious conditions such as anaemia, under-nutrition, neurosis or heart disease.

Table III.

Relation of individual symptoms to severity of haemorrhage collapse at delivery.

	Total cases	Grade of haemorrhage collapse					
		5	4	3	2	1	0
		12	29	30	31	26	64
Absence of mammary reaction	44	9	13	11	8	3	—
Menses absent or infrequent ...	32	11	12	5	4	—	—
Cold syndrome	25	5	12	6	2	—	—
Loss of body hair	11	3	4	2	2	—	—
Adiposity	21	2	4	5	3	—	7

(The figures in each column indicate the number of patients in that grade who show the particular symptom.)

The significant symptoms require a short description before the condition of the individual patient is summarized; the symptoms are absence of mammary reaction, absence or infrequency of menses, "cold syndrome", loss of body hair, and adiposity. The relation of these symptoms to the grade of haemorrhage collapse is shown in Table III.

Absence of Mammary Reaction.

This refers to the puerperium of the delivery in question. In these patients the breasts involuted at once after the delivery without any general or local treatment; there were not any signs of commencing lactation, not even slight swelling or discomfort, such as are normally present about the fourth day of the puerperium. Among the patients showing this symptom suckling was usually not attempted, as many were considered unfit or had had stillbirths, but this factor in itself does not inhibit the normal mammary reaction.

This symptom shows a frequency in direct proportion to the grade of haemorrhage collapse, and is presumably due to lack of secretion of the lactogenic hormone by the anterior pituitary. As it can only occur in the early puerperium it is an indication of pituitary insufficiency at that time only. Such insufficiency may be merely a temporary expression of the severe disturbance of the body in general due to the haemorrhage collapse which had just occurred in the patients studied. Nevertheless, in certain cases the symptom appears to be the first evidence of a permanent pituitary insufficiency.

Menses Absent or Infrequent.

This refers to a gross reduction or complete cessation of menstruation continuing for a long period or permanently after the delivery and sometimes associated with genital atrophy. Those cases are not included in which any general complicating factors can be found, such as irregularity of menstruation before the pregnancy or suckling the baby after the delivery, or where the menstrual disturbance could be related to the ordinary menopause or to any pelvic condition.

The patients classified as normal under this heading had menses beginning at 1 to 3 months post partum or, when the child was suckled, towards the end of lactation; the menstrua-

tion continued afterwards as usual except in two women who had some menorrhagia due to subinvolution.

The frequency of occurrence of partial or complete amenorrhoea shows a definite relation to the grade of haemorrhage collapse. The cases are discussed in more detail below; here it is sufficient to remark that the symptom is considered as a probable indication of a continuous under-production of gonadotropic hormone by the anterior pituitary. This is, of course, particularly the case when there is genital atrophy due to complete absence of oestrin activity.

Cold Syndrome.

This term is used here only as a conveniently short designation for a symptom-complex which dates from the delivery. The syndrome consists of: (1) Hypersensitivity to cold. The patient is unable to keep warm and sits close to the fire for most of the day. She wears extra clothing and has a marked dread of the winter. (2) Asthenia, shown by inability to do ordinary housework. (3) Apathy. The patient loses her spontaneous interests and can only be persuaded with difficulty to visit friends and entertainments. According to her relatives, "she just sits". She is suspicious of any form of medical examination. The voice becomes slow and monotonous. Libido is sometimes lost. (4) The weight may remain the same or may decrease by 15 to 25 pounds; marked emaciation is rare. In this connexion it should be explained that minor loss or gain of weight (less than 15 pounds, and not necessitating readjustment of clothing) is passed as normal.

This description is of a well-marked case, but the syndrome may be of varying degrees of severity. In milder cases certain of the symptoms may be slight or even absent (this applies particularly to the mental symptoms) and the condition could be classed as only an extreme 'general debility'. The more severe cases may have many of the appearances of myxoedema, or may give a clinical picture similar to that seen in fully developed Simmonds's disease.

The frequency of occurrence of the syndrome shows an obvious relation to the grade of haemorrhage collapse. In view of its sudden onset after the delivery and its association with other symptoms it may be regarded in these cases as a result of insufficient production of thyrotropic hormone, and possibly also of adrenotropic hormone, by the anterior pituitary.

Loss of Body Hair.

A few of the patients show this symptom. Complete loss of pubic hair is rare, particularly in the region of the labia, but loss of axillary hair is more common. Only marked alterations from the previous condition are recorded. Temporary thinning of head hair is a common occurrence after delivery, and will not be considered here.

Loss of body hair is closely related to the grade of haemorrhage collapse at the delivery and is probably an indication that the anterior pituitary is producing insufficient adrenotropic or gonadotropic hormone.

Adiposity.

Some women have a sudden increase in weight after a delivery, from 20 pounds to 40 or even 50 pounds. They develop the opposite of the 'cold syndrome' in that they enjoy cold weather, they are able to do their housework easily and are mentally bright, cheerful and co-operative. Only if the weight increase is very marked does the patient tend to feel rather lazy.

This symptom is not uncommon after any sort of delivery. It is no more frequent after haemorrhage or collapse than after normal deliveries, and does not appear to be due to any pituitary insufficiency. A satisfactory explanation for it cannot be offered here; in particular it does not show any significant relation to puerperal sepsis in the series under review. Its chief importance in the present connexion is that it may occur incidentally in women who also have symptoms suggesting pituitary insufficiency. When this happens it nearly always completely suppresses any 'cold syndrome' that might otherwise have been expected to develop, though it does not appear to influence the menstrual disturbance. The question of the relation of menstrual disturbances to change of weight is discussed by Kaboth,[5] though the obstetrical aspects are not considered.

Other Symptoms.

Certain other symptoms, which might have been expected from a study of the literature, were found less frequently or not at all.

Marked emaciation occurred in only 2 patients (grade 4 and 3) who lost 50 and 90 pounds weight respectively, and may be regarded as cases of 'pituitary cachexia.'

Premature ageing was seen in 6 patients (3 in grade 5, 2 in

grade 4, and 1 in grade 3). Their general appearance was that of women 20 years older.

Severe anaemia sufficient to be easily recognized on inspection of mucosae was present in 3 patients (grades 4, 2 and 1); these patients did not show any other marked symptoms. The question of the relation of anaemia to the pituitary and other glands is discussed by Snapper, Groen, Hunter and Witts.[6]

Anorexia was not found in a single case. This is in striking contrast to its almost invariable occurrence in the pseudo-Simmonds's disease which is referred to later.

Two further points are recorded in the discussion below and may be mentioned here. A case is noted as having had *pyrexia* if, during the puerperium, the temperature reached 100.4°F. on any occasion, whatever the cause. This point is taken into consideration in view of the reputed importance of puerperal sepsis as a cause of pituitary necrosis. In this connexion it is of interest that, of 9 patients who developed femoral phlebitis or pulmonary infarcts in the late puerperium, 1 was a grade 4 haemorrhage collapse, 1 a grade 3, while the other 7 were only in grades 1 and 2. These patients are now all in normal health, with the exception of the first, who has definite evidence of pituitary insufficiency.

Subsequent pregnancies have occurred in some of the patients, even in those with rather marked symptoms, but most of the patients have not had any further pregnancies. Sterility can, in certain cases, be caused by pituitary malfunction either by interference with ovarian activity or by the destruction of libido. A satisfactory conclusion cannot, however, be drawn from the incidence of those pregnancies which occur, as this incidence is also affected by two opposing but unmeasurable factors: (*a*) The causes of the haemorrhage and collapse are most frequent in multiparae. Multiparity often indicates that birth control is not practised, either for social or for religious reasons. These reasons usually remain as operative after a delivery with haemorrhage and collapse as they were before it. (*b*) A delivery which is nearly fatal from haemorrhage may cause so much fear of subsequent pregnancy that the patient abstains completely from coitus. In addition some of the patients have been sterilized at operation.

Classification of Patients.

The individual patients can be divided into certain groups on the basis of the symptoms just discussed. The relation of these

groups to the grade of haemorrhage collapse is shown in Table IV. The details about the incidence of certain general symptoms in each group are given in Table V.

Group A. Genital Atrophy. 8 *cases.*

All these patients have superinvolution of the uterus, atrophy of the cervix to the size of a small button, negative iodine reaction for glycogen in the vaginal mucosa, absence of acid or of Döderlein's bacilli in the vaginal secretion, and a shrunken senile vulva. They have absolute amenorrhoea without molimina, and subsequent pregnancy has never occurred. Flushings similar to those of the menopause have been very troublesome in several of the patients. These genital symptoms are presumably dependent on lack of oestrin.

One of these patients has lost about 90 pounds in weight and shows the clinical picture of Simmonds's disease, and one patient has developed into a full myxoedema. Mammary reaction was absent in all the patients; the majority have a well-developed cold syndrome, and many have lost body hair or show premature senility. The ages of the patients range from 23 to 38 years.

The relation of this group to severity of haemorrhage collapse is clear.

TABLE IV.

Relation of clinical classification of patients to severity of haemorrhage collapse at delivery.

Group			Grade of haemorrhage collapse					
			5	4	3	2	1	0
A	Genital atrophy	8	3	3	2	—	—	—
B	Menstrual disturbance	18	6	5	3	4	—	—
C	Menstrual disturbance with adiposity	6	2	4	—	—	—	—
D	Cold syndrome	9	—	5	4	—	—	—
E	Absence of mammary reaction	20	—	4	6	7	3	—
F	Adiposity	15	—	—	5	3	—	7
G	Normal	116	1	8	10	17	23	57
		Total cases	12	29	30	31	26	64

(The figures in each column indicate the number of patients in the group who had had haemorrhage collapse of that grade.)

TABLE V.

Incidence of certain general symptoms in the various groups.

	Classification of patients						
	A	B	C	D	E	F	G
Total cases	8	18	6	9	20	15	116
Absence of mammary reaction	8	9	5	1	20	—	—
Puerperal pyrexia	4	1	1	2	2	3	(9)
Cold syndrome:							
Severe	7	7	—	6	—	—	—
Moderate	—	2	—	3	—	—	—
Weight change:							
Loss 15 to 30 pounds	2	4	—	5	—	—	3
Loss 50 to 90 pounds	1	1	—	—	—	—	—
Gain 20 to 50 pounds	—	—	6	—	—	15	—
Body hair loss:							
Severe	5	2	—	—	—	—	—
Moderate	—	3	—	—	1	—	—
Premature ageing	4	3	—	—	—	—	—
Subsequent pregnancy	—	3	2	4	5	4	(15)

(The figures in each column indicate the number of patients in that group who showed the symptoms.)

Group B. Menstrual Disturbance. 18 *cases.*

Eight of these patients had amenorrhoea for 9 to 18 months post partum; menstruation then recommenced, but was only occasional and at irregular intervals of 2 to 9 months or more.

In 6 cases a similar occasional menstruation is present, but the initial amenorrhoea did not occur.

The other 4 patients had the initial long amenorrhoea; when the menstruation recommenced it was regular but exceedingly slight. Of these 4, 1 is only a borderline case as menstruation has now become almost normal in amount.

The patients in this group do not have superinvolution of the uterus or loss of iodine staining in the vagina; their genital tract is still under oestrin control despite the menstrual disturbance. The group shows a similar condition to group A, but in a much milder form. The same general symptoms are present, but with only half the relative frequency. The relation to severity of haemorrhage collapse is also seen in this group.

Group C. Menstrual Disturbance with Adiposity. 6 *cases.*

Three of these patients have complete amenorrhoea; 2 had

initial amenorrhoea (up to 17 months) with subsequent occasional menses at irregular intervals of about 3 or 4 months; the other has similar occasional menses, but had no initial amenorrhoea.

This group is separated from group B because all the patients show a marked gain in weight and, in association with this, are all in excellent health physically and mentally. None of the patients has any genital atrophy. There are only two general symptoms of interest; 2 patients have complete loss of libido and the majority had absence of mammary reaction.

The group shows a clear relation to the severity of haemorrhage collapse. The significance of this relation lies probably in the fact that a patient must primarily have menstrual disturbance in order to be included in this group. As explained in the discussion on symptomatology the adiposity appears to be unrelated to the haemorrhage collapse; it seems to be only a accidental concomitant which changes the general clinical picture. The menstrual disturbance is, however, just as marked as in group B.

Group D. Cold Syndrome without Menstrual Disturbance. 9 *cases.*

In this group menstruation is not affected; otherwise the patients show general symptoms similar to those in groups A and B, but usually not so marked.

There is a definite relation to severe haemorrhage collapse, but this is less evident, since most of the patients who have a cold syndrome have also an associated menstrual disturbance, and have therefore been included in groups A and B.

Group E. Absence of Mammary Reaction without subsequent Symptoms. 20 *cases.*

These patients are only excluded from the normal group because of the history of complete absence of breast activity in the puerperium; 4 of them have minor degrees of ill-health, but not sufficient to be considered significant in the present connexion.

There is some relation to haemorrhage collapse; none of the cases occur in grade 0. It should be noted that the other 23 cases without mammary reaction have already been classified in groups A, B, C and D; these groups include most of the severe cases of haemorrhage collapse.

Group F. Adiposity. 15 *cases.*

This group is only separated from the normal group for comparison with group C. There is not any relation to haemorrhage collapse, even taking group C into consideration.

Group G. Normal. 116 *cases.*

Three of these patients have menorrhagia due to subinvolution or fibroids; one has some irregularity of menses, but not sufficient to be considered a 'menstrual disturbance'; and two have minor degrees of ill-health. Otherwise the patients in this group have no symptoms dating from the delivery.

The bracketed figures in Table V for "puerperal pyrexia" and "subsequent pregnancies" in this group refer only to the 59 patients with a history of haemorrhage collapse. The other 57 cases are from the control series, in which the data on these two points are not strictly comparable and are therefore omitted.

This normal group shows an inverse relation to the severity of the haemorrhage collapse.

Additional Cases.

Four cases of rupture of the uterus which necessitated immediate hysterectomy have not been included in the series, as the diagnosis is naturally complicated by the removal of the uterus. The grade of haemorrhage collapse was 3 and 4 in these cases. During the puerperium all of them had absence of mammary reaction, but none had pyrexia. Complete amenorrhoea has, of course, continued since the delivery; 3 of the patients have a definite cold syndrome, but their weight is unchanged; the other patient is in good health.

Patients who have a severe haemorrhage and collapse at delivery usually become comatose. The question thus arises as to whether coma alone at delivery without any haemorrhage or collapse can lead to a subsequent pituitary insufficiency. To investigate this point a series of 29 cases of eclampsia was followed up at 1 to 3 years after delivery. None of these patients had had any haemorrhage or collapse at delivery, but all had had convulsions and coma. In no case were any symptoms found suggesting pituitary insufficiency. This series is also of interest in that it does not give any support to the view that toxaemia may predispose to pituitary insufficiency.

Discussion.

Significance of Symptoms.

In this follow-up, group A gives evidence of definite endocrine insufficiency, while groups B, C and D show lesser degrees of a similar condition. Groups E and F, on the other hand, have minor disturbances which can scarcely be classed with those in the previous groups. The endocrine insufficiency in groups A, B, C and D can be most satisfactorily explained on general physiological grounds as due to underfunction of the anterior pituitary. This pituitary underfunction is a permanent condition; it dates from a delivery complicated by haemorrhage collapse and is clearly related to the severity of the haemorrhage collapse. This clinical finding is obviously linked up with the pathological finding that the anterior pituitary often becomes necrosed after a delivery complicated by haemorrhage collapse, and that the frequency and size of these necroses are related to the severity of the haemorrhage collapse. The significance of the comparison is illustrated in Table VI, which shows: (*a*) The essential findings in this clinical follow-up. (*b*) A summary of the pathological findings discussed in the first part of this paper, but not including minute necroses which would not produce symptoms. Most of the percentages are calculated from figures too small to carry any individual weight, but their general trend is clearly the same in both series.

The most reasonable interpretation is that the patients in group A have gross healed necroses of the anterior pituitary, and that those in groups B, C and D have medium-sized healed necroses. It is, however, not possible to conclude definitely that healed pituitary necroses are present in all the patients in groups A, B, C and D and in none of the patients in groups E, F and G.

(*a*) Only two cases with "pituitary cachexia" were found. In many of the other patients the symptoms, on which a diagnosis of pituitary insufficiency was based, were often not very striking and could not be considered at all specific if it were not known that they began suddenly after a delivery with haemorrhage collapse. Care has been taken to obviate as far as possible the error, which is potentially inherent in any follow-up, of attributing too much significance to borderline symptoms. Nevertheless, it must be accepted that absolute proof of healed pituitary necrosis can only be obtained at post-mortem examination. For instance, in Case 2 of Usadel[7] there were doubtful symptoms following an

abortion, but at post-mortem examination the pituitary did not show any old lesion.

TABLE VI.

Showing the similarity of relation of pituitary necroses and of pituitary insufficiency to the grade of haemorrhage collapse.

CLINICAL.

Grade of haemorrhage collapse	Total cases	Pituitary underfunction; cases in groups A, B, C and D	Percentage
5	12	11	92
4	29	17	59
3	30	9	30
2	31	4	13
1	26	0	0
0	64	0	0

PATHOLOGICAL.

Grade of haemorrhage collapse	Total cases	Pituitary necroses; complete, large or medium-sized	Percentage
5	8	7	88
4	3	2	66
3	4	1	25
2	3	1	33
1	3	0	0
0	25	0	0

(*b*) On the other hand, it seems almost certain that a patient with a small pituitary necrosis will be free of symptoms and be passed as clinically normal. In animal experiments it is necessary to remove at least two-thirds of the anterior pituitary to produce recognizable malfunction. In human beings the diagnosis of malfunction is probably easier, as subjective symptoms can be ascertained and as menstruation can also be studied. It remains, however, a matter of conjecture whether a patient can lose half of the anterior pituitary and yet remain free from clinical symptoms. There are in the literature a few cases in which the symptoms corresponded to those of groups B or D in this follow-up and where the pituitary was finally examined at autopsy. The

anatomical information from these cases is complicated by two circumstances.

Firstly, it is not possible to say whether the remaining portion of healthy pituitary may have hypertrophied or atrophied since the original necrosis. Secondly, any illustration given is usually only one section of the pituitary; to form any satisfactory conception of the size of the healthy remnant of anterior pituitary it would be necessary to reconstruct the gland from serial sections. The estimates given in the following list are based on the fact that, in a mid-line section of the normal pituitary, the anterior lobe has about three times the area of the posterior lobe. These estimates are probably somewhat high because the necrosis usually spares the region in front of the posterior lobe and beneath the stalk; this region is included in the mid-line section which is usually photographed. The significant cases are :—

Jakob,[8] Case 2. Necrosis of anterior pituitary after a difficult delivery with post-partum haemorrhage at 36 years of age. Subsequent deliveries at 37 and 39 and a menstrual period at 41 years of age. Died at 41. At autopsy the anterior pituitary was represented by a few very small areas of live tissue and a band along the middle lobe. The illustration is not good enough for detailed measurements.

Sheehan,[1] Case 12. Necrosis of anterior pituitary at 37 years of age due to retained placenta with severe haemorrhage collapse. Pregnancy began 9 months later; she died at delivery owing to retained placenta and severe post-partum haemorrhage. At autopsy the live remnant of the anterior pituitary was 10 to 15 per cent of the normal.

Richter.[9] Necrosis of anterior pituitary at 32 years of age when she had a delivery followed by puerperal fever. Menstruation continued till 40 years of age. She died aged 62 years. At autopsy there were small groups of cells remaining alive in the anterior pituitary, but no illustration is given.

Heinrichs.[10] Necrosis of anterior pituitary at 33 years of age due to severe haemorrhage at her ninth delivery. She had a definite cold syndrome, but menstruation was regular for a time, then became infrequent and finally ceased at 35 years of age. She died aged 36 years. At autopsy the live remnant of the anterior pituitary was about 15 to 20 per cent of the normal.

Kaminski,[11] Case 2, and Reye and Scürmann.[12] Necrosis of anterior pituitary at 28 years of age due to retained placenta and uterine atony with severe haemorrhage and collapse. She had irregular menses during the next 3 years and then developed into a complete Simmonds's disease. She died aged 58 years. At autopsy there was practically no anterior pituitary tissue remaining, though the pars intermedia was still recognizable.

In the present follow-up there is a further point which is difficult to interpret satisfactorily. Any severe case, such as in

group A, shows most of the significant symptoms. In the lower groups, however, there is a curious dissociation; the patients can have any single symptom or any combination of symptoms. The explanation may be on various lines:—

(*a*) The part of the pituitary which escapes necrosis is not necessarily the same in all cases; different parts of the pituitary have different cell-ratios and may possibly have different functions.

(*b*) There may be variations of sensitivity of different endocrine glands to tropic hormones from the pituitary in different individuals.

(*c*) There may be basic variations in the activity of the different endocrine glands, either intrinsic or under the influence of non-pituitary tropic factors.

In the absence of any direct evidence, further speculation about this question does not appear of value.

Parity, Age and Obstetrical Complication.

Textbook descriptions of Simmonds's disease sometimes stress the common occurrence of the disease in old multiparae. In this follow-up the patients with symptoms of pituitary necroses were often rather elderly multiparae at the time of the significant delivery. This association appears, however, to be due only to the increasing frequency of haemorrhage and collapse with increasing parity and age. The relevant data are summarized in Table VII.

Table VII.

Relation of parity and age at time of significant delivery to occurrence of haemorrhage collapse and to subsequent development of pituitary insufficiency

	Percentages					
	Parity			Age		
	1	2 and 3	4 and over	15–24	25–29	30–45
Patients with pituitary insufficiency. Groups A, B, C and D—41 cases	12	27	61	22	20	58
All patients with haemorrhage collapse in this follow-up—128 cases	15	30	55	13	23	64
"Haemorrhage deaths" in this hospital—100 cases	16	19	65	8	25	67
General admissions to this hospital—350 cases	35	34	31	29	37	34

Table VIII shows that there is not any correlation in this follow-up between the actual cause of the haemorrhage collapse and the clinical evidence of pituitary necrosis. All the patients had deliveries at or near full time; a follow-up was not made of abortions or ectopic pregnancies.

TABLE VIII.

Showing that the actual cause of the haemorrhage collapse at delivery is not significant.

Cause of haemorrhage collapse	Total cases	Cases in groups A, B, C and D
Retained placenta	52	19
Accidental haemorrhage ...	37	10
Placenta praevia	25	8
Post-partum haemorrhage, or obstetric shock, or rupture of uterus	14	4

Second Follow-up. Investigation of Previous History of Patients with Symptoms Suggestive of Pituitary Insufficiency.

The last follow-up was limited to one direction; it gave data only as to how many patients, who had had haemorrhage collapse at delivery, subsequently developed pituitary insufficiency. A second follow-up was therefore made, approaching the problem from the opposite angle. Its purpose was to ascertain how many parous women with symptoms suggesting pituitary insufficiency had a history that these symptoms developed after a delivery, and whether or not this delivery was complicated by haemorrhage collapse.

As it was desired to study only those patients who had presumptive indications of pituitary insufficiency, no attempt was made to collect borderline cases. The primary criterion for inclusion in this follow-up was the occurrence of amenorrhoea or very infrequent menses without any obvious local or general explanation. The follow-up was limited to parous women, but selection was not made on the question of whether or not the symptoms dated from a delivery. Fifteen cases* with menstrual disturbance of this type were collected from several local hospitals.

* Thanks for assistance in collecting these 15 cases are due to the following: Drs. Crawford, Hart, Hendry, Hewitt, Hunter, MacIntyre, MacLennan, Morton, and Sharman.

They were first investigated clinically and then the history of the condition was elicited; as this history was obtained only from the patient herself it is often incomplete, but the details are sufficient for the present purpose. The cases are divided into groups A, B and C on exactly the same basis as in the previous follow-up; an idiopathic group is also included.

Group A. Genital Atrophy. 4 *cases.*

The first 2 cases may be described in some detail, as they give fairly typical pictures, the first of Simmonds's disease and the second of post-partum myxoedema.

Case 3. Aged 47 years, 3-para. Complete amenorrhoea and complete loss of pubic and axillary hair. Marked cold sensitivity and physical weakness almost to the state of being bedridden. Mental deterioration and great apathy with a negativistic attitude which prevented any investigation of the condition of the genitalia. Delusions had been present for the past 2 months. Slow speech with a peculiar accent, and tailing off to complete inaudibility towards the end of any sentence. Dry, pale skin; face wizened and haggard so that she looks more than 65 years of age. Some loss of weight but no emaciation. Basal metabolic rate −28 per cent, achlorhydria, anaemia.

All the symptoms began suddenly after the last delivery 11 years previously when she had a very severe haemorrhage and was dangerously ill.

Case 4, aged 37 years, 2-para. Complete amenorrhoea, superinvolution of the uterus and senile vulva but normal glycogen in vaginal mucosa. Loss of all axillary and pubic hair except over the labia. Absence of libido. Polydypsia and polyuria. Loss of about 25 pounds in weight within a year, since which she has slowly regained about 7 pounds weight. Waxy pallor of face. Occasional rheumatic swelling of knees, blood-pressure 90/65, achlorhydria, moderate anaemia. For the first 2 years she had in addition the following symptoms: marked cold sensitivity and muscular weakness, strikingly myxoedematous appearance of face, thick dry skin, mental torpor, slow speech, loss of head hair and eyebrows, basal metabolic rate −47 per cent. This last group of symptoms has been much ameliorated by thyroid treatment for the last 4 years, though she is still rather weak and unable to do housework.

All the symptoms began suddenly after her last delivery 6 years previously when she had a very severe post-partum haemorrhage due to retained placenta. She was unconscious for several hours. Mammary reaction was absent in the puerperium.

Case 5, aged 33 years, 5-para. Complete amenorrhoea, superinvolution of the uterus, absence of glycogen in vaginal epithelium, no acid or Döderlein bacilli in vaginal secretion, senile vulva. Marked loss of axillary and pubic hair. Severe cold syndrome but no loss of weight.

The symptoms began suddenly after a delivery 4 years previously; exact details about this are not available as she became unconscious during the third stage of labour and only recovered a long time after the placenta was delivered. There was no swelling of the breasts during the puerperium; she had symptoms suggesting a mild puerperal sepsis. Nine months after the delivery she had one slight uterine haemorrhage with pain.

Case 6, aged 28 years, 1-para. The condition of this patient is the same as Case 5 except that there is not any loss of body hair.

The symptoms began suddenly after a delivery 5 years previously when she had very severe haemorrhage due to placenta praevia.

Group B. Menstrual Disturbance. 3 *cases.*

In each of these cases the uterus is small, but the vaginal epithelium contains glycogen and the vaginal secretion is acid.

Case 7, aged 20 years, 2-para. Complete amenorrhoea, but she has recently had molimina. She has lost 30 pounds in weight but has no cold syndrome.

The symptoms began suddenly after a delivery one year previously when she had severe post-partum haemorrhage but did not become unconscious The breasts became swollen in the early puerperium.

Case 8, aged 36 years, 8-para. Amenorrhoea for 7 months followed by a return of regular menses and a further pregnancy. For the 12 months since this second delivery there has been complete amenorrhoea. She has a well-marked cold syndrome, a weight loss of 70 pounds, and some diarrhoea.

The symptoms began suddenly after a twin delivery 3 years previously when she had very marked post-partum haemorrhage. There was no mammary reaction in the puerperium. In the last delivery she had an accidental haemorrhage and was very seriously ill.

Case 9, aged 34 years, 1-para. Amenorrhoea for 4 years, followed by three slight menses, since which there has again been complete amenorrhoea (6 months). Otherwise well.

The symptoms began suddenly after a delivery 4¾ years previously when she had much haemorrhage due to a placenta praevia, and also post-partum haemorrhage.

Group C. Menstrual Disturbance with Adiposity. 6 *cases.*

In case 10 the uterus is normal in size; in case 15 it is enlarged owing to a polypus in its cavity; in the other cases the uterus is rather small. The vagina is normal in all.

Case 10, aged 25 years, 1-para. Occasional menses at intervals of 1 to 12 months: in all, 8 menses in 4 years. Her weight increased rapidly by 40 pounds, but otherwise she is quite well.

The symptoms began suddenly after a delivery 4 years previously when she had severe post-partum haemorrhage. She lactated for 2 months after the delivery.

Case 11, aged 23 years, 1-para. Complete amenorrhoea without molimina Rapid increase of 25 pounds in weight following delivery; otherwise well.

The symptoms began suddenly after a delivery 1 year previously when she says she had no haemorrhage or sepsis.

Case 12, aged 24 years, 2-para. Amenorrhoea for 17 months, then one menstrual period, and since then (35 months) amenorrhoea. Rapid increase of 30 pounds in weight following delivery. She felt rather lazy until recently but is otherwise quite well.

The symptoms began suddenly after a delivery 4½ years previously. Details about this delivery are lacking as she became unconscious during the third stage of labour and remembers nothing for several hours later. The temperature was normal during the puerperium, but there was not any mammary reaction.

Case 13, aged 29 years, 1-para. Amenorrhoea without molimina. Her weight has increased by 40 pounds and there is the unusual complaint of increased sensitivity to cold and some asthenia. Otherwise she is well.

The symptoms began suddenly after a difficult operative delivery with cervical incisions 2½ years previously when she had very severe haemorrhage. There was swelling of the breasts during the puerperium and possibly some pyrexia.

Case 14, aged 34 years, 13-para. Amenorrhoea without molimina. Rapid increase of 20 pounds in weight. Some asthenia and increased sensitivity to cold, but otherwise well.

The symptoms began suddenly after an abortion 1½ years previously when she had very severe haemorrhage and some sepsis.

Case 15, aged 30 years, 1-para. Menses at irregular intervals of 3 to 10 months but rather profuse, possibly as a result of the polypus. Rapid gain of 25 pounds weight, but otherwise quite well.

The symptoms began suddenly after a difficult forceps-delivery 6 years previously when she had severe post-partum haemorrhage. There was no mammary reaction during the puerperium.

Idiopathic Pseudo-menopause. 2 cases.

Case 16, aged 40 years, 3-para. At 32 years of age menstruation became slighter and less frequent, it decreased steadily for a year and then became a complete amenorrhoea.

There is no relation to any pregnancy; the three deliveries were normal

Case 17, aged 29 years, 1-para. Gradual diminution of menstruation for last 3 years; now almost complete amenorrhoea.

The symptoms are not related to the previous delivery, which was normal.

Discussion.

The clinical condition and history in cases 3 to 15 are in obvious agreement with those in Groups A, B and C in the first follow-up. It can be presumed that in these 13 cases a necrosis of the anterior pituitary occurred at the last delivery. It must be emphasized that in this follow-up the history of the significant delivery was provided only by the patient; information could not be obtained from anyone else present at the delivery in the anomalous case 11 or in cases 5 and 12. In these latter 2 cases the unconsciousness in the third stage of labour was probably due to post-partum haemorrhage from retained placenta.

Cases 16 and 17 are clearly examples of a quite unrelated condition; their menstrual disturbance was of gradual development and had no relation to delivery. The aetiology of this is not clear, but there is no evidence to indicate that it is due to any pituitary lesion. These two cases are included only to complete the record of the series investigated.

The number of cases in this follow-up is rather small for definite conclusions based on the series alone, but with the support of the findings in the first follow-up it seems reasonable to consider that symptoms of pituitary insufficiency in parous women are in many cases indicative of an old necrosis of the anterior pituitary due to haemorrhage collapse at delivery.

Literature.

Pathological.

A review has been given elsewhere (Sheehan[1]) of most of the reported cases in which there is autopsy proof of post-partum necrosis of the anterior pituitary, either recent or healed. References were also given to certain other pathological conditions which may show a superficial similarity to the post-partum lesion and must, therefore, be carefully differentiated from it. The following cases should be added to the lists given in that paper.

Typical Healed Post-partum Necroses Found at Autopsy.

Richter.[9] F.62, 6-para. Symptoms since last delivery 30 years before when she had puerperal fever. No other obstetric data.

Heinrichs.[10] F.36, 9-para. Symptoms since last delivery 3 years before, when she had severe haemorrhage.

Usadel.[7] Case 1. F.38, 1-para. Symptoms since the delivery 11 years before. The delivery was difficult and was accompanied by severe haemorrhage.

Gallavan and Steegman.[13] Case 1. F.51, 2-para. Symptoms since last delivery 5 years before. This delivery was difficult but no other information is given about it.

Gallavan and Steegman.[13] Case 2. F.60, 7-para. Symptoms since last delivery 28 years before, when she had toxaemia; no other obstetric data.

Bini.[14] F.47, 7-para. Symptoms since last delivery 19 years before, when she had ante-partum eclampsia. According to her sister the delivery was otherwise normal.

DOUBTFUL HEALED NECROSES.

Berblinger.[15] F.66. Massive connective tissue replacement of the front and sides of the anterior pituitary. Died of thyroid sarcoma. Obstetric history not given.

Boller and Goedel.[4] Case 1. F.51. Doubtful healed necrosis of anterior lobe with some fibrosis. Severe symptoms only for last year but menopause at 35 years of age. No obstetric history given.

Boller and Goedel.[4] Case 2. F.69, 3-para. Doubtful healed necrosis of anterior lobe. Severe symptoms only for last 2 years. No history of any relation of symptoms to delivery.

TRUE FIBROSIS OR GROSS SCARRING OF ANTERIOR PITUITARY.

These are entirely different pathological conditions and are unrelated to pregnancy.

Cagnetto.[16] Case 3, M.80; Case 5, M.41, syphilis; Case 6, M.72; Case 7, M.47; Case 8, M.33, syphilis; Case unnumbered, M.48, syphilis.

Faure-Beaulieux, Villaret and Sourdel.[17] M.58, syphilis.

von Monakow,[18] M.58. Fränkel,[19] M., syphilis. Parhon and Briesse,[20] insane patients. Dimmel,[21] M.28. Strauss and Globus,[22] F.53. Werthemann,[23] Case 3*b*. Nielsen,[24] two cases (?). Hantschmann,[25] M.35. Rössle,[26] M.26 and F.52.

RECENT NECROSIS OF ANTERIOR PITUITARY, NOT RELATED TO PREGNANCY.

Forlini,[27] diphtheria.

Clinical.

Though the aetiology has only been explained recently, the clinical aspects have been known and described for a century or more as superinvolution of the uterus (in contradistinction to lactation-atrophy), or as premature menopause, or as myxoedema developing after pregnancy with haemorrhage (see Hun and Prudden[28]), or more recently as Simmonds's disease. A review of the clinical aspects must inevitably be incomplete as an attempt cannot be made to survey all the cases reported in the older literature.

One very striking paper by A. R. Simpson[29] deserves, however, to be quoted. In reporting 22 cases of superinvolution of

the uterus, he noted that the most fruitful cause of superinvolution was the complication of the antecedent labour or abortion with a pronounced haemorrhage, sometimes unavoidable or accidental but more frequently in the third stage or post partum. In some of his patients there was amenorrhoea since the delivery; in others there was a menstrual discharge very slight in amount and short in duration or recurring at prolonged intervals. There was sometimes sterility or loss of libido. In some patients there was a marked diminution in the intellectual powers, or a thickness and hesitancy of utterance, or general drowsiness, or unsteadiness of gait, or in a few cases puerperal insanity. Most of the patients were thin and tabetic but in a few cases the patient was unusually stout. In one or two the appearance resembled that of sufferers from myxoedema, and one patient developed Addison's disease. J. Y. Simpson[30] had previously described the syndrome that develops in cases of post-partum superinvolution of the uterus; he noted the amenorrhoea and sterility, the loss of subcutaneous fat, the atrophy of breasts, the withering and wrinkling of skin and appearance of progeria, the depression and impaired activity of the mind, the anaemia, the general debility and the ease with which the patients became fatigued. Frommel[31] also remarked on the progeria and poor nutrition of many of his cases of superinvolution of the uterus. More recent discussions of post-partum pituitary insufficiency are given by Reye,[32] Nürnberger,[33] Seitz,[34] Reye,[35] Kehrer,[36] and Jumon.[37]

A summary is given below of reports in the modern literature of clinical cases in which a condition suggesting pituitary insufficiency followed a delivery. In a few of these cases the patient died but the pituitary was not examined; the other patients were still alive at the time the case was published. All of these cases appear to be examples of healed post-partum necroses of the anterior pituitary, though pathological proof is not available. Many of the more severe cases were diagnosed as Simmonds's disease, those with gross evidence of thyroid insufficiency were reported as myxoedema, while others with less marked general symptoms were reported as superinvolution of the uterus or post-partum emaciation. To avoid duplicating the descriptions, the cases are classified here in the same groups as the follow-up series; the classification is reasonably correct though in a few instances the information available is insufficient for absolute accuracy.

GROUP A.

Brissaud and Bauer.[38] F.29, 1-para. Symptoms since the delivery 9 years previously. Obstetric data, except that labour was premature, absent.

Goullioud and Poncin.[39]. F.37, 4-para. Symptoms since last delivery when she had severe haemorrhage and collapse.

Hertoghe.[40]. F.39. Symptoms since last delivery 2½ years previously Obstetric data absent.

Veil.[41] Case 1. F.38, 5-para. Symptoms since last delivery when she had severe haemorrhage.

Lichtwitz.[42] Case 3. F.41, 2-para. Symptoms since last delivery 16 years previously when she had puerperal pyrexia. Obstetric data absent.

Borchardt.[43] F.41, 5-para. Symptoms since last delivery 14 years previously when she had severe haemorrhage and puerperal pyrexia.

Reye.[32]. Case 3. F.36, 1-para. Symptoms since the delivery 4 years previously when she had very severe haemorrhage.

Suchier.[44] F.21. Symptoms since delivery 1 year before when there was manual removal of the placenta and severe haemorrhage.

Rowe and Lawrence.[45] F.35, 3-para. Symptoms since complicated labour 3 years previously.

Farquharson and Graham.[46] Case 1. F.40. Symptoms since delivery 8 years previously when she had puerperal pyrexia. Obstetric data absent.

Farquharson and Graham.[46] Case 3. F.38, 4-para. Symptoms since last delivery 10 years previously. The delivery was difficult but no other details are given.

Hoet.[47] Case 1. F.30, 2-para. Symptoms since last delivery. Obstetric data absent.

Clauberg.[48] Case 2. F.37, 1-para. Symptoms since the delivery 13 years previously. Obstetric data absent.

Schachter.[49]. F.28. Symptoms since last delivery when she had severe haemorrhage and collapse which necessitated blood transfusion.

Rau.[50] F.56, 3-para. Symptoms since last delivery 20 years previously. The labour is recorded as normal.

Snapper, Groen, Hunter and Witts.[6] Case 2. F.43, 3-para. Symptoms since last delivery 15 years previously. This was complicated by severe bleeding.

Ehrhardt and Kittel.[51] Case 9. F.28. Symptoms since a miscarriage for which curettage was required.

GROUP B.

Carli.[52] Case 3. F.26, 3-para. Symptoms since last delivery when she had severe haemorrhage.

Reye.[32] Case 2, and [54], Case 2. F.35, 6-para. Symptoms since last delivery 7 years previously when she had severe haemorrhage but no sepsis.

Reye.[53 and 54] Case 3. F.35, 2-para. Symptoms since last delivery 2 years previously when she had manual removal of the placenta and post-partum haemorrhage.

Curschmann.[55] Case 2. F.39, 9-para. Symptoms since last delivery 10 months previously. Obstetric data absent.

Constantini.[56] F.54, 8-para. Symptoms since last delivery 20 years previously when she had severe haemorrhage.

Hürthle.[57] Four cases following delivery.

Seitz.[34] F.23. Symptoms since delivery when she had some post-partum haemorrhage.

Guggisberg.[58] F. 26, 3-para. Symptoms since last delivery which was normal.

Wilson.[59] Case 2. F.37. Symptoms since delivery.

Wilson.[59] Case 1. F.29. Doubtful case following normal delivery.

Gardiner-Hill and Smith.[60] Table VII, case 2. F.52. Doubtful case. Amenorrhoea since delivery 14 years before. Obstetric data absent.

Ehrhardt.[61] F.35. Doubtful case following operation for ectopic pregnancy 14 years previously.

Group D.

Curschmann.[62] Case 2 and [55] Case 1. F. 27, 1-para. Symptoms since the delivery. Obstetric data absent.

Lucke.[62a] F.40, 4-para. Symptoms since last delivery which was an abortion with sepsis.

Discussion.

In the above lists, together with the lists given previously (Sheehan, 1937), there are records of 27 cases with pathological evidence of healed post-partum necrosis of the anterior pituitary and of 34 cases with clinical evidence of the same condition. It will be noted that only 25 have a history of haemorrhage collapse at delivery. The comparative rarity with which this obstetrical condition is recorded is not of very great significance. Obstetric histories are often not given or are imperfect; as a result of the original theory as to aetiology, authors have usually paid more attention to eliciting a history of any puerperal sepsis than of any haemorrhage or collapse at delivery. In the cases of Bini, Rau, Guggisberg and Wilson the labour is reported as normal; these 4 cases would be of greater importance if a definite statement were made that haemorrhage or collapse had not occurred. There is not, however, any evidence that a detailed investigation of this point was made; delivery took place very many years previously, and information is lacking as to whether the history of the delivery was obtained from a reliable source.

Differential Diagnosis.

Clinical evidence of pituitary insufficiency may be due to various causes:

(*a*) Surgical hypophysectomy, as in the cases described by Moricard[63] and Eldon.[64]

(*b*) Post-partum necrosis of the anterior pituitary as discussed in this paper.

(*c*) Scarring or fibrosis of the anterior pituitary, due in many cases to syphilis or trauma.

(*d* Tumours, cysts or granulomata in the pituitary. These sometimes give evidence of pressure on neighbouring structures, e.g. diabetes insipidus. Occasionally, in these cases, symptoms either of underfunction or of overfunction of the anterior pituitary may become prominent during or after pregnancy. If underfunction develops it may be due to an associated post-partum necrosis, but such a diagnosis is naturally very uncertain. Cases of interest in this connexion are described by Lichtwitz,[12] Case 2, Keilmann,[65] Lévi,[66] Winter,[67] Khavine,[68] Reckmann,[69] and Snapper, Groen, Hunter and Witts,[6] Case 3. The case of Lichtwitz is discussed critically by Reiche.[70]

(*e*) Functional disturbances. In recent years numerous reports have been published of cases clinically diagnosed as Simmonds's disease in which there is no evidence suggesting any organic pituitary lesions of the types mentioned above. In a few of these cases the symptoms point strongly to a true pituitary insufficiency; in some cases the diagnosis of Simmonds's disease appears to be merely a label for cachexia of unknown origin; in most of the cases the diagnosis is based only on the general endocrine disturbance that develops in the course of anorexia nervosa (see Ryle,[71] Berkmann[72]). Commonly the patient is an unmarried woman about 15 to 25 years of age; the primary symptoms are usually psychic disturbance and anorexia followed by emaciation; there is often an associated amenorrhoea and lowering of the basal metabolic rate. A cure can be obtained by various treatments ranging from psychotherapy to the subcutaneous implantation of an animal pituitary.

Purely functional insufficiency of the anterior pituitary is an obvious and important possibility in endocrine pathology, but the clinical diagnosis should be very circumspect. A similar attitude is required when a patient, who had symptoms which might possibly suggest a pituitary insufficiency, is found at post-mortem not to have any gross lesion of the pituitary, any histological change described being only cytological. While cytology is clearly of fundamental importance in the study of function, its interpretation is not easy in dead tissues in view of the possible occurrence of purely terminal cellular disturbance or of post-mortem autolysis. Cases in which the pituitary did not show any

gross lesions are recorded by Popper,[73] Azerad,[74] de Gennes, Delarue and Rogé,[75] Kylin,[76] Case 22, and Hubschmann.[77]

The whole subject of possible functional pituitary insufficiency is of great interest, but it must be sharply distinguished from true organic insufficiency. The recent literature on the subject is noted in the Appendix. This list includes many cases reported as Simmonds's disease without any satisfactory evidence that the pituitary was affected, a few cases in which the diagnosis appears justified but the aetiology is obscure, and discussions as to whether or not the anterior pituitary plays any role in anorexia nervosa.

Summary.

Post-partum ischaemic necrosis of the anterior pituitary is of relatively frequent occurrence. It is caused by collapse of the patient, usually as a result of haemorrhage, at or about the time of delivery. It can be found pathologically in its early stage if the patient dies in the puerperium, or in its healed stage if death occurs some years later. If the patient survives the puerperium, clinical evidence of pituitary insufficiency may develop subsequently; this can be of any degree of severity from general debility to superinvolution of the uterus or, in its most extreme form, to the cachexia known as Simmonds's disease.

Two cases of the early stages of the necrosis are described. This condition has been found at post-mortem in 13 out of 46 women who died in the puerperium later than 14 hours after delivery. There is a definite relation between the frequency and size of the necroses and the severity of the haemorrhage collapse.

A follow-up of 128 patients who had had various degrees of haemorrhage collapse at delivery some years previously showed that in 41 cases there were symptoms suggesting pituitary insufficiency which dated from the delivery. There is a definite relation between the frequency and severity of the present symptoms and the severity of the haemorrhage collapse at the delivery. It is concluded that, in the 41 cases, the symptoms are due to healed post-partum necroses and are proportionate in severity to the extent of these necroses (see Table VI).

A reverse follow-up of 15 parous women who had symptoms suggesting pituitary insufficiency showed that in 13 of them the condition dated from a delivery in which there was severe haemorrhage collapse. It is concluded that in these 13 cases the symptoms are due to healed post-partum necroses.

The relevant literature is reviewed.

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