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SIMMONDS' DISEASE-OBSTETRICAL SHOCK
AND POST-PARTUM NECROSIS OF
THE ANTERIOR PITUITARY

BY

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INTRODUCTION

Since the time of Galen, who first described the pituitary gland as the "phlegmatic glandule", considerable consternation has existed as to its precise function in the human body. Today doubt still prevails in regard to the part that the gland plays in various physiological and pathological processes in the body.

The topic of this paper is intimately concerned with a malfunction of this gland; one that is not conclusively established, and one that has not been considered to any great extent in the past. The condition is known as Simmonds' disease or pituitary cachexia, a condition of deficiency of secretion of the anterior lobe of the gland, in which there is an associated syndrome of extreme loss of weight, loss of hair, frequent history of obstetrical complication, etc. This is in contradistinction to the usual picture observed in an anterior lobe deficiency, in which obesity predominates the picture.

In the more recent literature Sheehan and Murdoch, (66), (65), (64), and (63), of the Research Department of the Glasgow Royal Maternity and Woman's Hospital have described a condition called "post-partum necrosis of the anterior pituitary." This was observed by a series of post mortem examinations of women dying in the immediate puerperium of collapse, hemorrhage, sepsis, etc. In these women a definite lesion of the anterior lobe of the pituitary was observed, an ischemic necrosis, that could be more or less definitely proven to have originated at approximately the time of delivery. Furthermore, a number of these cases that exhibited a difficult, complicated labor and recovered

also presented in their puerperium a group of symptoms that were similar, and closely allied to the condition known as Simmonds' disease.

It is the object of this paper to present as complete a review of Simmonds' disease that can be permitted in this short space, and to arrive at some conclusion as to its relationship to post-partum necrosis of the anterior pituitary and to obstetrical shock. Obstetrical shock will be considered only to the extent of establishing a more definite conception as to the meaning of the term.

Inasmuch as this topic has an endocrine basis, any detailed description of the physiology of the gland will be avoided, as this would entail a description about which, the literature is voluminous and the conclusions in a great number of cases as yet are not definitely established.

HISTORY AND DEFINITION

Galen who was the first man known to describe the pituitary gland, described it as the "phlegmatic glandule", and attributed to it the function of "collecting the excrementous slime formed by the brain and passing it on through the "rete mirabile", which was later described by Willis as the vascular circle to the nasal passages. (Cited by Turner) (76)

From this time, various men have theorized as to the function of this gland. Bordeau gave the first intimation of internal secretion in 1835 and Claude Bernard furnished studies of hepatic glycogen. Brown-Sequard also furnished further evidence in their theory that the cells of the gland secreted a substance which might influence other cells independently of the nervous system. (76)

Previously in 1884 Fritsche and Klebs had recorded an enlargement of the pituitary body in a case of giantism, and Muikowski, in 1884 suggested that the pituitary might be related to acromegaly. Tamburini in 1894 reported the first series of cases showing that enlargement of the hypophysis was of etiological significance in cases of pathological overgrowth. Subsequent clinical and post-mortem examinations soon proved that over-functioning of the pituitary leads to giantism and acromegaly. The effects of insufficiency of the gland, however, remained obscure until the experimental work done by Paulesco in 1907, in which was demonstrated that removal of the pituitary of dogs was followed by a train of symptoms, characterized by

weakness, loss of weight and death -- a condition to which the name "cachexia hypophyseopriva", was given. (13)

In 1914 Simmonds, (69) a German pathologist described the first clinical case exhibiting the syndrome observed in Paulesco's experimental animals, and confirmed it by autopsy. The syndrome of symptoms that is today described as Simmonds' disease did not come into this name until 1922, when it was so called by Lichtwitz, although the condition was first pointed out by Simmonds, whose name it today carries. Simmonds who first described the clinical picture in 1914, first called it "cachexia with fatal termination."(69) The various concepts of the fundamental nature of the disease is illustrated by the names given to the condition by different authors at the time when the condition was first described. In 1924 Colden named it "dystrophia cachectogenitalis", indicating a relationship to the syndrome of Frohlich. Colden was unaware at the time when he named it this that Zondek had already used this term. Urechia suggested "cachexia tuberienne", to show that the region of the tuber cinereum, rather than the hypophysis is primarily involved. Bauer combining previous notions used the term, "hypophysare-nervose-cachexie."(68)

It is obvious that the clinical picture existed before 1914, when it was first described by Simmonds, although the credit for the first clinical case of pituitary cachexia belongs to Nonne, who, knowing of Simmonds' reports recognized a case in 1919, which was later confirmed by Simmonds at autopsy. Such men as Wagner, Formanek, Marburg and Falta, apparently did not realize that a distinct clinical picture was associated with atrophy of

the pituitary gland, as no mention is made in their writings, and no typical findings have been recorded. (68)

American writers completely ignored the disease, as it is not even mentioned in the reviews of Abrahamson, (1), Englebach, (21), Tierney, (75), Frazier, (25), Eidelsberg, (20), or Rowe and Lawrence. The latter with a series of over four hundred cases did not record one with cachexia. They stated that, underweight was found chiefly in adolescents showing the Levi-Lorain type of disturbance and seldom amounted to more than 20%, the maximum recorded being 30%. The report of Good and Newman, (25) is the only case recorded in the English literature up til 1929.

Graham and Farquharson, (29) reported the first case in the American literature in 1931, and stimulated an interest that has resulted in some important observations as to the cause and therapy.

Since this time a number of cases have been reported in the literature, mention of which will subsequently be made in this paper.

Due to the fact that Simmonds' disease is a more or less obscure, and seldom mentioned entity, and the criteria by which a diagnosis can definitely be made is rather uncertain, a few words by way of definition should be considered.

Simmonds' disease according to Silver, (68) may be defined as a clinical state; most common in women, characterized by progressive extreme emaciation, premature aging, wrinkling of the facial skin, loss of pubic and axillary hair, dental caries and loss of libido and sexual function, accompanied by a depression

of the basal metabolic rate.

May and Roberts, (43) state that Simmonds' disease may be considered a malady characterized by emaciation, amenorrhea in females, and hypogenitalism in males, arterial hypotension, hypoglycemia and lowered basal metabolic rate.

Simmonds' disease according to Davis and Postle, (16) is a clinical syndrome resulting from destruction of the anterior lobe of the pituitary gland. "It is characterized by an extreme emaciation and the appearance of premature senility. It is usually accompanied by symptoms of psychic disturbance."

Futcher, (26) in a review of the entire group of pituitary disturbances, classes Simmonds' disease in the group of hypopituitaries, of which there is three; Frohlich's syndrome, or dystrophia adiposogenitalis, (this constitutes the most frequent type of pituitary insufficiency); pituitary obesity in adults, (including Dercum's disease or adiposis dolorosa); and lastly, Simmonds' disease or pituitary cachexia. The first two are probably due to chromophobe adenomas of the adenohypophysis or the supra-cellular region.

Steinnitz states that hypophyseal cachexia is generally attributed to a severe disturbance of the pituitary gland by a tumor, lues, thrombosis or embolism of this organ, while Reye says that in the classical hypophyseal cachexia, it is a disease of women due to atrophy of the anterior lobe of the pituitary after confinement.

Neilsen, (49) states that according to Bostroem, hypophyseal cachexia is divided into three groups, as follows: 1) Actual

cachexia hypophyseopriva, which is caused by essential atrophy of the anterior lobe of the hypophysis, and which bears the name Simmonds' disease, 2) Symptomatic hypophyseal cachexia, where the anterior lobe of the hypophysis is destroyed by a tumor, gumma, abscess or tuberculosis. When the affection is localized exclusively in the anterior lobe, symptomatic hypophyseal cachexia may resemble Simmonds' disease, 3) Hypophyseal cachexia caused by atrophy of the anterior lobe of the hypophysis, not as a separate disease, but as a link in a pluriglandular insufficiency.

INCIDENCE

It would be presumptuous for anyone to more than speculate as the frequency of occurrence of Simmonds' disease, as it has been considered so lightly in the past literature, and facts relevant to it, such as etiology, diagnosis, and treatment are as yet not definitely established.

By some men it is considered an extremely rare condition, and by others, one that occurs quite frequently, but is seldom diagnosed.

Although his figures are small and would allow nothing but a tentative conclusion, Sheehan, (66) makes the following statement: "The pituitaries we have examined at autopsies represent the deaths for about $1\frac{1}{2}$ years at the Glasgow Royal Maternity and Woman's Hospital and the main follow-up patients represent the recoveries from severe hemorrhage and collapse for about $2\frac{1}{2}$ years at the hospital. From these we can make some sort of estimate of what happens each year at this hospital according to the following table":

81 Cases of Severe Hemorrhage Collapse Each Year	
a. 15 deaths under 14 hours post-partum-----	
Pre-necrosis of pituitary-----	12 cases
No lesion-----	3 cases
b. 16 deaths over 14 hours post-partum	
Necrosis of pituitary-----	10 cases
No lesion-----	6 cases
c. 50 Recoveries	
Marked pituitary dysfunction-----	3 cases
Moderate " "-----	12 cases
No symptoms-----	35 cases

The figures for the deaths before 14 hours post-partum are only in the nature of good guesses about what we might have found

if these patients had lived another day or two. The remaining figures are based on actual finding. Some calculation can be done about the last series. The Maternity Hospital of Glasgow deals with about 49% of the Glasgow births and has about 35% of the total maternal mortality of the town. Approximately one-half of the cases of severe hemorrhage are taken into this hospital. According to this about 30 non-fatal pituitary necrosis occur each year. Of these the women are of about an age when their life expectation is thirty to forty years, so there are probably living about 180 women with large pituitary healed necroses out of a total population of rather over a million.

Falta in 1915 presented 11 cases which he called "multiple ductless glandular sclerosis." (Cited from Silver)

Calder, (13) in 1932 admitted 70 cases, while Silver, (68) accepted only 41 cases in 1933. Silver also states: "In addition to the advanced obvious cases, attention should be directed to mild, abortive forms that masquerade under such diagnoses as arterio-sclerotic cachexia, syphilitic cachexia and latent tuberculosis."

Prior to this time in 1929 Frazier, (25) reports 15 cases from 1914 to 1928, ten of which were in males, 5 in females, and all cases in females being caused by cysts or tumor, with no consideration of history from an obstetrical standpoint. (probably all surgical cases showing evidence of tumor).

Hurthlr, (37) maintains that hypophyseal cachexia is not as rare as is generally believed, and Schupbach says that the disease is also more frequent than is recognized.

Hawkinson, (32) also agrees with Hurthlr and maintains that it is more common than is generally realized.

On the other hand Greene,(30) states that Simmonds' disease is a rare condition, and that the diagnosis is admittedly difficult.

Up until 1935 Weinstein, (77) states that only 7 cases had been reported in the English literature that were proven by autopsy.

Plummer and Jaeger,(53) believed that the condition occurs more frequently in women than men, especially in women after repeated labors. They further state that advanced cases are not difficult to diagnosis but the question arises, "as to its existence in milder forms that may easily be mistaken for similar conditions."

Sheehan,(66) also states that Simmonds' disease affects both sexes but is more common in women than men, and gives the following figures:

	Male	Female
Tumors and Cysts-----	5	6
Granulomata and inflammation-----	3	3
Scarring, fibrosis and atrophy-----	13	40

The last group of scarring, fibrosis and atrophy can furthermore be shown to have a definite sex distribution:

	Male	Total	Post-partum
Gross Scarring -----	6	5	0
True fibrosis-----	7	8	0
Massive focal atrophy-----	0	27	21

It can be noted from the above figures that whereas gross scarring or true fibrosis shows about an equal incidence in men and women, this condition of massive focal atrophy occurs only in women. It is nearly always of post-partum origin.

Further difference of opinion is given by Rea and Hoover, (57) who state in 1938 that in the German literature there were reports of slightly over 50 cases in 1933, and in the English literature reports of 7 cases, 3 of which were verified by autopsy.

From the above mentioned facts by the various authors it may be concluded that the condition called Simmonds' disease occurs more frequently than was formerly supposed. It occurs more often in women than men, and a history of post-partum complication, such as hemorrhage, collapse, sepsis, etc., is frequently in evidence.

ETIOLOGY

The etiology like the incidence is not known, and only speculation can be made as to the cause of this condition, and the mechanism by which it is produced.

Simmonds who originally described pituitary cachexia, thought that the cause of the anterior pituitary necrosis was by septic emboli. This was based upon the fact that sepsis was quite often associated with the disease, (as observed by Simmonds).

That anterior pituitary insufficiency is responsible for the syndrome called Simmonds' disease was shown by Paulesco, and also by Mahoney, (42) who performed a number of experiments with hypophysectomized puppies. These puppies subjected to a hypophysectomy died of so-called "cachexia hypophyseopriva", which ultimately lead to death in hypoglycemic coma, which is often observed as the terminal state of Simmonds' disease in humans.

May and Roberts, (43) state that pregnancy appears to be the chief etiological factor. A predisposition probably exists, but tumors, syphilis, tuberculosis and infections are apparently not causal agents.

Neilsen, (49) agrees with May and Roberts and states that the disease usually occurs as a sequel to childbirth in which hemorrhage and profuse loss of blood occurred.

Hawkinson, (32) believes that the syndrome may be caused by transitory functional disorders of the anterior pituitary as well as by neoplastic involvement. He also mentions that the disease has been noted in several cases following repeated labors, especially when they are accompanied by hemorrhage.

Escamilla and Lisser, (22) state that the disease may occur in either sex at any age, but is more frequently found in females during those age periods when pituitary integrity is in greatest demand, as at puberty, during the menopause, or after many pregnancies.

Davis and Postle, (16) state that, "anything which causes destruction of the anterior pituitary may be an etiological factor. The following may operate in such a manner as to bring about this pathology; Tumor or cyst of the gland itself, or tumor or cyst of adjacent structures compressing it; tuberculous and syphilitic infections; embolic or thrombotic occlusion of the arteries supplying the hypophysis; simple fibrosis, or functional exhaustion."

Silver in a review of the literature gives the opinions and reports of the following men;

Merkel demonstrated the pituitary gland in a case of sepsis, in which seven-eighths of the anterior lobe was destroyed, while the posterior lobe remained intact.

Schlagenhauser observed tuberculosis of the pituitary with destruction, and a clinical picture of Simmonds' disease in 1916.

Cyran showed that symptoms of pituitary insufficiency may follow fractures of the skull with hemorrhage about the mid-brain.

Schaeffer in 1919 reported a case of Simmonds' disease in which tuberculosis or syphilis were apparently the causative factor.

Tumors, primary and secondary, of the hypophysis with Simmonds' disease have been reported by Simmonds, Lang, Honlinger, Striker, Menetti, Mogilnitzky, and Frazier.

von Monakow and Pribram, report a post-inflammatory destruction of undetermined origin as a causative factor.

Von Gerloczy reported the appearance of cachexia with anemia in a pituitary dwarf who had been subjected to intensive radiation of the hypophyseal region.

Metastatic abscess was noted by Jungmann, and Hirsch and Berberich reported a case due to destruction of the gland by hemorrhage.

Reye expressed the belief that pituitary atrophy is secondary more commonly to thrombosis than to embolism, especially in cases without definite sepsis. Another thing that opposed the embolic idea, was the absence of embolic phenomena in other organs of the body that ordinarily would not have been spared.

Maresch agrees with a number of other investigators, by calling attention to the fact that the appearance of hypophyseal cachexia is common after repeated labors, particularly if they follow in close succession, and suggested a functional exhaustion of the gland as a cause for the syndrome. (Cited from Silver) (68)

Englebach, (21) believes that since cases with complete recovery following replacement therapy have been reported, such cases are probably due to a transitional functional disorder of the gland.

Riecker and Curtis,(59) in a review of 24 cases finds partial or complete destruction of the anterior lobe in all cases examined. They report the destruction due to puerperal sepsis(septic emboli) in 9 cases, lues in 5, cysts in 4, tuberculosis in 2, and etiology unknown in 2 cases.

Rea and Hoover,(57) further state that from the fact that pluriglandular therapy has been shown to be of value in some cases, the fundamental cause underlying the condition is pluriglandular, and also suggest that the beginning of menses, and pregnancy phases of sexual life may easily precipitate an inactive endocrine abnormality. They also raise the question of whether or not Simmonds' disease is due to hypopituitarism alone.

Sheehan,(66) makes the following statement concerning post-partum necrosis of the pituitary, which might be of value in enlightening the question of the etiology of Simmonds' disease: "Massive necrosis of the anterior pituitary is a relatively frequent finding in patients who die during the puerperium, after a delivery complicated by collapse or severe hemorrhage. Patients with such a necrosis who survive the puerperium are left with a shrunken and scarred gland and they develop a clinical syndrome the main symptoms of which are either comparable or indistinguishable from the syndrome of Simmonds' disease." Sheehan further states: " Hemorrhage and/or collapse were present in all of our cases with pituitary necrosis though it was present at delivery in only half of our

total cases dying in the puerperium. The hemorrhage and collapse at delivery were usually due to the standard causes. The most reasonable explanation of this association appears to be along the following lines. Normally, as is well known, the anterior pituitary hypertrophies during pregnancy to two or three times its normal size. In the puerperium it involutes rapidly. Presumably there is in all normal deliveries a sudden reduction of blood flow to the anterior pituitary. If added to this normal reduction, a general circulatory collapse is initiated, the blood flow to the pituitary for a short time may be reduced almost to nothing. If this happens there is danger of thrombosis occurring in the sinuses, and this causes a permanent arrest of blood flow, leading to necrosis of the tissue. This explanation is of course speculative, but offers a better explanation than any other given at the present time.

Calder, (13) in a review of all the cases coming under his observation agrees with the views of Reye and Silver that the necrosis is caused by thrombosis rather than embolism, and makes the following statements concerning the relationship of sex, pregnancy, tuberculosis, syphilis, and tumors to Simmonds' disease: "Of 70 cases reviewed, 47 occurred in women, 18 in males, and 5 in patients whose sex is not recorded in case reports. Since females are affected much more frequently than males it is important to determine whether pregnancy is of etiological significance in the production of this syndrome. Of the 47 cases occurring in females 20 seem definitely to have developed as the result of pregnancy, while in 18 of these

cases factors other than pregnancy seem to have initiated the process. The reports in the literature of tuberculosis of the hypophysis are not unusual, but of the 70 cases reviewed by Calder, only that of Schlangenhauer showed pathological findings that could definitely be attributed to tuberculosis. Syphilis as a cause of hypophyseal destruction is likewise rare, and Reye's case is based upon clinical evidence only. Redlick recently emphasized the fact that tumors and cysts may be of sufficient extent to cause the syndrome described. Nine of the cases reviewed by Calder were apparently caused by tumors and cysts. Finally as a less frequent cause of destruction of the anterior lobe of the pituitary, von Monakow's case of acute inflammation, and Reinhardt's cases of fracture of the base of the skull may be mentioned, but not considered further."

A consideration of the pathology of Simmonds' disease must of necessity include two divisions, that concerning the local pathology of the pituitary itself, and the general changes observed throughout the other organs and glands of the body.

LOCAL PATHOLOGY

Gaubner in a review of the literature prior to 1925 was able to find six cases in which various destructive processes were found in the hypophysis, and which antedated those of Simmonds. However, previous to Simmonds' report it had not been recognized that the hypophysis was primarily at fault.

Pathologically all cases of Simmonds' disease have been characterized without exception by destruction of the anterior lobe of the hypophysis. In Simmonds' original case the onset of symptoms coincided with puerperal sepsis, and although at the time of necropsy the anterior lobe showed only scar tissue replacement, he assumed that the origin of the disturbance could be ascribed to bacterial emboli swept into the region of the anterior pituitary at the time of the puerperal sepsis. The anatomical basis for such an assumption was elaborated by Simmonds in 1914, when he pointed out that the arteries of the anterior lobe, in contradistinction to those of the posterior lobe are end-arteries. Embolic processes in the hypophysis, he maintained, are not at all rare, and occur in both lobes; but whereas these in the posterior lobe give rise, if

infected, only to small abscesses, those in the anterior lobe producing^e necessarily infected anemic infarcts, resulting in marked destruction of tissue.

Nielsen, (49) believes that the atrophy of the anterior lobe of the hypophysis, is due presumably to an embolic or thrombotic process, with secondary fibrous damage or contraction of scar tissue.

Sheehan, (63) in a discussion of the age and histology of the lesions found in the anterior pituitary glands of women examined dying in the puerperium, ~~found~~ the following to be true: "There was noted a tendency for the necrosis to affect essentially the antero-inferior part of the anterior lobe and spare the thin subcapsular zone and the angle in front of the stalk. The case reported by Merkel is of importance in showing that the posterior lobe can also be involved. Of the five cases (reviewed by Sheehan in this article) where histological details were available, one (Giornelli) would appear to have begun in relation to the hemorrhage before Caesarean section, but the other four (Schallock, Simmonds, Merkel, and Verga), are compatible with the view that the lesion began about the time of delivery"

As far as the local pathology of the pituitary is concerned, it is very consistently noted throughout the literature where necropsy reports are available. Atrophy, fibrosis, or new growths, are generally the terms used by the majority of investigators making a pathological report on a case of Simmonds'

disease.

The most valuable contribution to further knowledge of the pathology of the anterior pituitary in this condition has been given to us by Sheehan and Murdoch, who have made extensive studies, with follow-up investigations upon patients when available. The results of their work has already been mentioned in this paper in the section devoted to incidence, and will again be reiterated in a discussion of post-partum necrosis of the anterior pituitary.

GENERAL PATHOLOGY

Under this topic will be considered the findings at autopsy in other organs and glands of the body, in a typical Simmonds' disease.

Inasmuch as the two distinct syndromes, "cachexia hypophyseopriva", and "dystrophia adiposo-genitalis", are seen clinically as the result of pituitary disease, it is important to determine whether they are both induced by disturbances of the pituitary per se, or are caused by pathological changes in separate anatomical units. This fact was enlightened by Smith, (70) who by the use of a very ingenious operative procedure adduced decisive proof for the assumption that the two conditions are dependent upon totally different processes. He found that lesions of the hypothalamic region (tuber cinereum) of rats give rise to a syndrome characterized by extreme obesity and atrophy of the genital system, without any demonstrable change in thyroid or suprarenal cortex. Ablation of the anterior

lobe of the pituitary on the other hand gave rise to an invariable syndrome, the main features of which were an almost complete inhibition of growth in the adult; atrophy of the genital system with loss of libido ~~sexualis~~; immediate cessation of sexual cycles in the female; atrophy of the thyroid, parathyroids and suprarenal cortex; and a general physical impairment characterized by lowered resistance to operative procedures, loss of appetite, weakness, and a flabbiness that readily distinguished the hypophysectomized from the normal animal. Smiths' researches, therefore, furnished a well founded experimental basis for the clinical ^{Syndrome} described by Simmonds.

Calder gives the following res^ume of the changes found in organs other than the hypophysis: "The changes in the integument, thickening and loss of luster of the skin, falling of hair and teeth, and trophic changes in the nails, are constantly mentioned in remarks by other investigators. Conspicuous changes also occur in other glands of internal secretion. Macroscopically, the thyroid, parathyroids, suprarenal cortex, the reproductive glands are markedly decreased in size, and microscopically this decrease in size is seen to be due to an actual atrophy of the glandular structure. In addition, there are regressive changes in all the abdominal viscera, so that the liver, spleen and kidneys and pancreas are much smaller than normal. To emphasize the importance of pituitary insufficiency in this condition Simmonds has used the term splanchnomegaly^{icria}, which is in contrast to splanchnomegaly which accompanies overfunctioning of this gland."

Gunther and Corville,(31) state that in the 42 cases of Silver the thyroid was atrophic in 11 cases, adrenals in 8 cases, and the gonads in 5 (testis 4, ovary 1).

Davis and Postle,)16) in regard to general changes state the following: "The pathology is, without exception destruction of the anterior lobe of the pituitary gland, associated with atrophy and fibrosis of all viscera, especially the thyroid, gonadal, and adrenal glands."

P.E.Smith,(70) has given conclusive evidence of relation between the thyroid and pituitary gland. He showed that one of the results of removal of the anterior pituitary was a decrease in the weight of the thyroid and that histologically there was marked flattening of the epithelium. Moreover, that this decrease in size of the thyroid was due to pituitary insufficiency was proved by the fact that transplants of pituitary produced reparative phenomena in the thyroid so that it appeared structurally normal.

R.C.Moehlig,(46) reports that the supra-renal cortex is hypoplastic with absence of the pituitary body. Many of the symptoms of Simmonds' disease, notably the low blood pressure, subnormal temperature, weakness, and trophic changes in the skin and nails, resemble those of Addisons' disease. The two diseases differ mainly in that pigmentation of the skin occurs in one and not the other. The question whether symptoms of hypotension and asthenia observed in Simmonds' disease are attributable directly to the pituitary or to

secondary involvement of the suprarenal cortex is not definitely settled as yet.

Along with the general atrophy in the other organs, atrophy of the pancreas has been noted, both grossly and microscopically. In addition to this, hypoglycemia, increased tolerance to insulin, and in some cases a diabetic sugar tolerance curve has been noted clinically.

Also, without exception the cases reported every where are marked by cessation of menses in the female, and in the male and female both by impotence and loss of libido. Smith, (70) again has shown experimental evidence that loss of the anterior pituitary causes atrophy of the genital tract, loss of libido, and impotence in rats with anterior lobe ablated. Zondek and Aschheim also provided further evidence of this fact.

Relation of the anterior pituitary to the so-called "pluriglandular syndrome", is mentioned by Barker, who speaks of: "a thyreo-testicular-hypophyseal-suprarenal syndrome, which at necropsy shows sclerosis of the various endocrine organs. It has not been considered a clinical entity as yet."

As far as relation to the higher nerve centers, experimental work is as yet inadequate, although anatomical juxtaposition makes their relationship seem plausible.

In order to interpret the symptomatology of any endocrine disturbance it is necessary to remember that the glands of internal secretion are mutually interdependent, and that injury to one may lead to secondary changes, functional in some and anatomical in others. The endocrine system, moreover consists of a series of checks and balances, of pressors and depressors, the proper coordination of which is necessary for normal hormonal activity; and it therefore follows that symptoms may be produced not only by the absence of a given hormone but perhaps also by the release of a second hormone to which the first is normally antagonistic. This is especially true of the pituitary, as it elaborates not a single hormone but several having a side variety of physiological effects. Bugby, Simond and Grimes list eleven separate effects of various extracts of this structure. (Cited by Calder) (13)

The symptoms generally speaking may be divided into three groups: 1. A withered skin, falling out of hair of scalp and of body, 2. Emaciation associated with complete lack of appetite and also trophic disturbances, and 3. Disturbances of the genital sphere, especially amenorrhea, which is usually the first symptom noted.

Sheehan, (66) describes a fully developed case and groups the symptoms roughly according to what we know about the physiology of the gland:

- 1) There is no change of growth, as the person is nearly always and adult.

- 2) There is atrophy of the gonads. In women there is sub-involution of the uterus due to an absence of estrin production and complete amenorrhea. Often there is loss of pubic hair and axillary hair; this may not be purely pituitary, but possibly a secondary effect via the suprarenals.
- 3) There are symptoms suggesting myxedema in a mild form, apathy with a low BMR. The temperature is low and associated with sensitivity to cold.
- 4) Symptoms suggesting Addison's disease in a mild form are present, muscular weakness, low blood pressure, disturbances in chloride metabolism, and diarrhea.
- 5) There is marked emaciation called pituitary cachexia.
- 6) The opposite of diabetes mellitus appears, namely, attacks of hypoglycemia, increased sugar tolerance, and increased sensitivity to insulin.
- 7) A loss of elasticity and wrinkling of the skin develops, associated with drying up of tissues, loss of teeth, anemia and mental disturbances, namely apathy or confusion. All these symptoms together give an appearance of premature senility.
- 8) Finally the patient dies, either in coma, or in hypoglycemia, or some intercurrent infection. At post-mortem examination there is found a lesion of the anterior pituitary gland with fibrosis or atrophy of the other ductless glands and atrophy of internal organs.

Reger and Cuttle, (58) make the following statement concerning cachexia hypophyseopriva: "The onset is usually

insidious, usually the third or fourth decade, and occurs chiefly in women, the picture being characterized by marked emaciation, precocious senescence, gastro-intestinal distress, loss of secondary sex characteristics, and intense debility. In addition, hypothermia, bradycardia accompanied by hypotension, a reduced metabolic rate and diminished salt and water excretion are present with death terminating the syndrome. There may be marked somnolence, diminished mental powers and tendency to melancholia."

Richardson, (60) states that although a number of cases have been reported that were confirmed by autopsy, an experimental counterpart established, and the picture apparently well established,-- the condition is still hard to recognize and the diagnosis always more or less uncertain. This is because most if not all the symptoms characteristic of Simmonds' disease can be produced by simple inanition. The emaciation, appearance of age, amenorrhea, gonadal atrophy, dental caries, splanchnomicria, and depressed basal metabolic rate may be all interpreted as the result of starvation. There is not any reason to doubt the existence of Simmonds' disease as a clinical and pathological entity but the means for making an accurate diagnosis are yet to be discovered. As a minimum standard for diagnosis of Simmonds' disease or acquired insufficiency of the anterior pituitary, the following is required according to Richardson:

1. Emaciation and gonadal insufficiency in the absence of constitutional disease.

2. The absence of a neurosis sufficient to account for the emaciation, or
3. Successful treatment of the neurosis, if present.
4. Treatment by nursing care, high caloric diet and vitamin supplement.

Greene,(30) in the Iowa State Medical Journal in 1937 states that the diagnosis of pituitary cahcexia is admittedly difficult, and gives the following reasons for stating this:

" It may be simulated by malnutrition. It may be easy to exclude the cachexia due to neoplasm, chronic infection, etc., but that which develops from psychoneurosis (Anorexia nervosa for instance) and gastro-enteric symptoms may be difficult. The gonadal atrophy may be of inestimatable value in making the diagnosis."

Addisons' disease may also cause confusion, but the principle factor of differentiation in this case is the peculiar skin pigmentation characteristic of Addisons' disease.

In addition to the symptoms already mentioned, which are stated repeatedly in the literature, Zondek pointed out that the ability of the patients to excrete water and salt is often embarrassed. One liter of water or 10 grams of sodium chloride is given and their excretion studied. Normally, the water should be excreted in four hours and the salt in twenty-four. In Simmonds' disease there is usually a marked retention of both salt and water.

Another finding that is reported by Silver,(68) and is

found repeatedly in the other cases reported, is the evidence of a gastric achlorhydria.

Two cases by Barr,(9) studied as to the blood chemistry showed the following findings: "Definite gain in weight and general condition and marked storage of nitrogen, sulfur, calcium, and phosphorus without specific treatment. Magnesium was lost during periods of control, while other elements were stored to a considerable extent. When cortico-adrenal extract was given and a resultant rise in the blood pressure occurred, a reversion of the negative magnesium balance to a positive balance, and increased retention of calcium resulted.

Silver,(68) makes the following statement concerning the differential diagnosis of Simmonds' disease: "The diagnosis of pituitary cachexia depends, to a large extent on the absence of any of the other more common causes of extreme loss of weight. If one can discover another adequate explanation for the cachexia, the diagnosis of Simmonds' disease should be made only with extreme reserve. However, in the cachexias secondary to tuberculosis, carcinoma or other conditions one does not find the recession of the secondary sex characteristics that is so marked in Simmonds' disease. Cachexia with the loss of pubic and axillary hair, especially if combined with atrophic genitalia and gonads and loss of sexual power, should attract attention to the pituitary gland as the possible source of the syndrome. It is noted that the loss of hair in the axilla and on the pubis is uncommon in the usual cachexias."

All authors note that the disease must be differentiated from the pluriglandular insufficiency of Claude and Gougerot, or the pluriglandular sclerosis of Falta. At times this distinction may be impossible clinically, but the condition can usually be separated, although in some cases the diagnosis will rest with the pathologist. In separating cachexias of pituitary origin the basal metabolic rate is often of great value. Depression of the metabolism is often noted and reported in Simmonds' disease. This finding is of particular significance because in almost all other cachexias, especially those due to carcinoma and tuberculosis, the basal metabolic rate is usually elevated above the normal.

In short, one should suspect hypophyseal cachexia in every case of marked loss of weight. If careful clinical, roentgen, and laboratory examinations reveal no other cause for the emaciation, one should suspect a cachexia of pituitary origin. The onset of symptoms after a complicated labor, loss of pubic hair, loss of teeth, especially without caries, anemia with eosinophilia, hypotension, bradycardia, hypothermia, achylia gastrica, depression of the basal metabolic rate and loss of appetite, with a loss of specific dynamic action of proteins are all to be looked for and considered in making the diagnosis of Simmonds' disease.

Treatment of Simmonds' disease has in the majority of cases been very inadequate, and as a whole unsuccessful. In view of the maze of symptoms and findings related to other portions of the body, other than the pituitary, both single and pluriglandular therapy has been tried, with varying degrees of success. The irregular clinical course also makes the evaluation of any one form of treatment difficult.

In his original description Simmonds pointed out that replacement therapy with the anterior lobe of the pituitary was indicated and should be tried.(68) Replacement therapy, in the form of prephyson, yielded excellent results in the hands of Reye, Zondek, and Lichtwitz, but the results for this disease in the manner that one regards thyroid extract in the treatment of myxedema, are not conclusive enough to enable one to speak of a specific for the disease.

Calder,(13), Hawkinson,(32), Striker,(74), and Brougher,(12), also report favorable results from the use of anterior lobe extract.

Although the diagnosis is doubtful from the report given, O.Stastny, (71) in 1918 reports a case of hypopituitarism with emaciation, in which improvement was made on an extract of the whole gland.

May and Roberts,(43) make the following statement concerning treatment: "Specific therapy is essential, and fresh total pituitary extracts should be given in large doses. Other glandular therapy(genital, thyroid, suprarenal extracts) may be employed as adjuvants. Medicaments such as arsenic, strychnine,

and phosphoric acid have proved of no avail."

McGovern, (44) reports an advanced case in which some improvement was made and patient could lay off of treatment for two weeks without symptoms reappearing.

The following men mention pluriglandular methods of treatment, and as a whole do not report as favorable results as the men employing the use of an extract of the anterior lobe alone, given subcutaneously or intramuscularly.

Aldrich,(4) started treatment with thyroid extract, then substituted antuitrin (P & D). The patient failed to gain on this, so the thyroid was removed and the antuitrin alone given. On this the patient finally started to gain and eventually reached the point where she was gaining one to one and one-half pounds per day. Upon arriving at normal weight, the patient was sent home on a maintenance dose of 2 cc. of antuitrin ten days each month. Her menses were never reestablished.

Moehlig,(47) reports a case where, antuitrin, obstetrical pituitrin, and thyroid were used, with no results, but continued emaciation. Also another case in which antuitrin S, suprarenal cortex (Eschatin), insulin alone with glucose, pituitary tablets, cod-liver oil, sunlight, high caloric diet with forced feedings, led only to the patients death seventeen months after the onset of symptoms.

As far as dosage is concerned in administering the pituitary extracts, K.Herman,(33) says: "No fixed rules can be laid down as far as dosage is concerned. It is impossible to say whether

100 rat units, or 200-300 units a day will be required. The proper amount of the hormone is that amount of the hormone on which a gain is demonstrated." Herman reports three cases with improvement on replacement therapy.

Brougher's case (12) shows improvement with anterior lobe extract 1 cc. (P & D), two times a week, has already been mentioned.

Sticks,(73) reports a case with improvement upon anterior pituitary extract, and Parker,(50) gave antuitrin lcc. at 2-5 day intervals along with 5-15 grains of anterior lobe extract t.i.d., and his case showed improvement.

Rea and Hoover's case,(57) showed extraordinary good results with anterior pituitary extract, insulin and glucose.

Hawkinson,(32) gave his patient Follutein (Squibb), every other day in doses of 50 rat units, desiccated thyroid one-half grain t.i.d., without improvement. Removing the thyroid the patient started to gain weight and rapidly returned to normal. Hawkinson further states that extracts of the whole gland have been of more value in the treatment of Simmonds' disease.

Thyroidein tablets, and dried anterior lobe extract by mouth was tried by Rau,(55), and some temporary improvement noticed. However, the patient later regressed and did not improve.

Greene,(30) says: "that in addition to a high caloric diet, with adequate vitamins, force feedings, rest and exercise,-- that anterior lobe extract should be given intramuscularly or subcutaneously, as the oral administration of the extract does

not elicit results." This is in accordance with cases reported with improvement by this author.

Summarizing an article by Sheehan, (65), in 1938, the following conclusions were made: "In patients who have had post-partum necrosis of the anterior pituitary--a subsequent pregnancy is possible if atrophy of the genital tract has not taken place. Such a pregnancy usually brings about improvement or even complete cures. If, however, delivery is accompanied by hemorrhage or collapse the improvement is partly or entirely lost." The practicability of such a measure as mentioned above would of course be questioned, and as the data gathered up to date is inadequate and incomplete; but it will have to be considered as rather convincing evidence is presented by the author, although his figures are small.

A detailed consideration of obstetrical shock will not be considered as it is a subject in itself, and one that is not clearly understood. The principle purpose is to attempt in very few words to establish a more definite conception of the term, so that its use in previous and subsequent parts of this paper will be more clearly understood.

Bernard Mann, (41) states that obstetrical shock implies a condition occurring in parturient women akin to that seen in surgical shock, but does not refer to the transient exhaustion usually accompanying delivery, but to definite collapse with a circulatory and respiratory dearrangement.

Moore, (48) considers obstetrical shock, or surgical shock as a definite entity although it may originate from different sources, and thinks that the mechanism is one of toxemia.

Blalock, (7) divides shock into three main groups, those originating from a hemogenic source, such as hemorrhage, loss of fluids, blood plasma, etc., neurogenic source, in which a reflex of some nature originating in the central nervous system contributes to the condition; and to a vasogenic source, in which there is a change in the character of the vessels and heart conveying blood to the various portions of the body.

In considering obstetrical shock, hemorrhage must be differentiated, as it is one of the most important factors in producing obstetrical shock (or predisposing factor), and can be differentiated principally from the fact that in the condition considered as obstetrical shock the patient is conscious, but

does not as a rule respond to external stimuli, (assuming an attitude of disregard for everyone and everything about them), while in shock produced by hemorrhage alone, the patient is wide awake, restless, and struggling for air.

Obstetrical shock as far as frequency of occurrence is concerned is almost a rarity. McIllroy, (45) in reporting 9468 confinement cases with a mortality rate of 2.7 per 1000, gives the following analysis of the causes of death:

6	cases	of	death	from	obstetrical	shock
4	"	"	"	"	hemorrhage	
6	"	"	"	"	sepsis	
2	"	"	"	"	embolus	
4	"	"	"	"	eclampsia, toxemia	
1	"	"	"	"	broncho-pneumonia	
1	"	"	"	"	acute appendicitis	

Akerman, (3) reports 39 fatalities among 10,000 cases, and attributes death in six of these to obstetrical shock. In 2323 confinements of the Maternity Center Association of New York City, shock was responsible for 3 out of 5 maternal deaths.

From these few figures it can readily be seen that the condition is one that does not frequently occur. This fact is of importance in considering the relationship of obstetrical shock to Simmonds' disease and post-partum necrosis of the anterior pituitary, and would lend additional knowledge as to their frequency of occurrence, considering them as possible sequelae of obstetrical shock.

Discolle, (19) states that shock is a complication which increases the risk of pregnancy and labor. Many times its onset is unrecognized, and when it is, the complete picture is as a rule present. Normal labor, toxemia and hemorrhage all play a

part as predisposing causes of obstetrical shock. All the factors that have been found to predispose to shock are found in normal labor. A long arduous labor with anxiety, and fear, vomiting, profuse perspiration, and excessive respiratory effort result in loss of body fluids, profound fatigue, and lowered alkali reserve. Normal labor also accompanied by relative retention of nitrogenous substances, acidosis, low carbon dioxide combining power of the blood. Toxemia presents a more drastic alteration of blood constituents, and the decrease in the carbon dioxide tension being of particular noteworthy attention. Hemorrhage, with its various causes composes the chief predisposing cause. To these complications may be added the supplementary hazard of the anaesthesia. Anaesthesia is accompanied by typical circulatory changes; a primary vasodilatation with a fall in blood pressure, a secondary vasoconstriction and an ultimate restoration of blood pressure to normal.

The symptoms and etiology of obstetrical shock is further discussed by Discolle. Though the appearance of deep shock is infrequent, the lower alkali reserve, the increased exertion, hemorrhage, and deep anaesthesia, necessarily in prolonged obstetrical operations, form a combination that may precipitate this condition. Discolle in describing a case of shock says: "The pallor of the cool, damp skin, the unquenchable thirst, jerky respiratory effort, restlessness, weak fluttering pulse, the eventual unconsciousness are well known symptoms but too often the diagnosis of shock is not made until the picture

is complete." The etiology of obstetrical shock like that of surgical shock is complex. When the blood pressure has fallen to 80 mm of mercury, or below, the alkali reserve depreciates very rapidly, and a synchronous decrease in the metabolic rate occurs. When the blood pressure drops to a fourth or fifth of its normal volume, the red blood corpuscles stagnate in the capillaries and begin extruding through the vessel walls. At that time, the blood volume and blood plasma are so reduced that the supply of oxygen to the tissues is retarded and ultimately arrested. In shock the vasoconstrictor reflex, which normally compensates for the fall of blood pressure is damaged, so that the downward trend of pressure continues. Concensus of opinion is that, loss of circulatory fluids and oxygen are the principle factors of etiological significance.

H.M.Phillips, (51) makes the following statement concerning obstetrical shock: "From the point of view of treatment, and especially preventative treatment, it is necessary to elaborate the question of causation. Besides the essential initiating causes produced by trauma, the primary reflex vasodilatation, and the secondary poisoning, there are other predisposing conditions or complication factors." They are:

1. Body fatigue from prolonged muscular exertion
2. Cold from exposure
3. Deprivation of food and water
4. Sweating
5. Hemorrhage
6. Anaesthetics
7. Toxemias of pregnancy
8. Infection
9. Emotion

It would possible have been better to have used the term

"obstetrical accident" rather than the term shock, using the former term as inclusive of shock, hemorrhage, sepsis, toxemia or whatever other factors are instrumental or associated with the principle theme of this paper, Simmonds' disease.

Very little has been written upon destructive lesions of the pituitary, associated with post-partum death; as a matter of fact in the majority of hospitals where a great number of autopsies are performed, it would not be thought necessary nor indicated to do an examination of the contents of the skull upon a women dying of post-partum hemorrhage or collapse. Sheehan and Murdoch, however, have performed a large number of autopsies upon women dying in the immediate puerperium, with especial emphasis laid upon their obstetrical histories. They have also very diligently made a number of survey follow-ups, investigating patients some years after hemorrhage collapse at delivery, and follow-up investigations of patients with symptoms suggestive of pituitary insufficiency. In addition to this they have collected data, that adds support to the etiology of the condition, and have shown that the degree of severity of the hemorrhage determines the severity of symptoms; that septic and inflammatory conditions elsewhere in the body have not relationship, and that the actual cause of the hemorrhage collapse is not of any significance. These pertinent facts have been brought out by these two men alone, and although their results are very conclusive, they have not been verified by any other investigators.

A detailed description of the etiology of post-partum necrosis of the anterior pituitary is unnecessary as it is incorporated in a discussion of the etiology of Simmonds' disease in previous pages of this paper.

In the first follow-up investigation of patients some years after hemorrhage collapse, the following figures were collected, showing the relation of individual symptoms to the severity of hemorrhage collapse, (at delivery).

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

(In the above table grade 5 represents the most severe degree of hemorrhage collapse).

It can readily be seen that in the above chart that the greater the degree of hemorrhage collapse, the greater the frequency of symptoms, and the greater number of them in evidence.

In a second follow-up in the other direction, the history of patients with symptoms suggestive of pituitary insufficiency is considered. In this group investigated it was presumed that in 13 of them a necrosis of the anterior pituitary occurred at delivery, as all give a significant history to that effect. The number of cases is small for definite conclusions but with the support of the findings in the first follow-up it seems plausible 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 hemorrhage collapse at delivery.

It has also been shown by Sheehan and Murdoch that the degree of severity of the hemorrhage determines the severity of symptoms. These facts are shown in the following table:

Group	Total Cases	Grade of hemorrhage					
		5	4	3	2	1	0
A. Genital atrophy	9	3	3	3	0	0	0
B. Menstrual disturbance	18	6	5	2	4	0	0
C. Menstrual disturbance with adiposity	6	2	4	0	0	0	0
D. Cold syndrome	9	00	50	44	0	0	0
E. Absence of mammary reaction	20	0	4	6	7	3	0
F. Adiposity	15	0	0	5	3	0	7
G. Normal	116	0	8	10	17	23	57

(In the above table the degree of hemorrhage collapse is indicated by the numbers, 5, being the most severe.)

It is evident from the above table that the severity of symptoms is determined by the degree of severity of the hemorrhage collapse. Also in the above groups according to the symptoms produced, it can readily be seen that group A shows definite evidence of endocrine underfunction, group B, C, and D show it but to a lesser degree, and groups E and F can scarcely be classified with the other groups.

That sepsis or inflammation anywhere in the body is not related to post-partum necrosis of the anterior pituitary will be shown in the following table. It was commonly accepted previously (Simmonds), that post-partum necrosis was due to embolism as a result of puerperal sepsis, but at the present, findings do not agree with that view. In the next chart the numbers indicate the number of patients.

(Chart shown on next page)

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

From the above chart it can be seen that no relationship is evident between sepsis and inflammation elsewhere in the body and the incidence of post-partum necrosis of the pituitary.

Furthermore, as has already been mentioned, the actual cause of the hemorrhage collapse at delivery is not significant, This is shown in the accompanying table:

Cause of Hemorrhage Collapse	Total Cases	Cases in groups A-B-C-and D
Retained placenta	52	19
Accidental hemorrhage	37	10
Placenta previa	25	8
Post-partum hemorrhage, or obstetrical shock, or rupture of the uterus	14	4

(By cases in group A,B,C, and D is meant the groups previously mentioned, A, genital atrophy, B, Menstrual disturbance, etc.)

The frequency with which necrosis of the anterior pituitary is found at autopsy and the actual size of the lesion bear a clear relation to the severity of hemorrhage collapse, that occurs at delivery. The following table substantiates this:

Size of Necrosis	Grade of hemorrhage collapse					
	5	4	3	2	1	0
Complete or almost complete	4	1	0	0	0	0
Large	2	0	1	1	0	0
Medium	1	1	0	0	0	0
Small	0	0	0	0	2	0
None	1	1	3	2	1	25

(In the above table the figures indicate the number of patients and the grade of hemorrhage collapse 5 is the most severe)

Of the 46 autopsies on patients dying later than 14 hours post-partum it is sometimes difficult to grade the degree of hemorrhage especially in group 1 and 0, but in grade 0 none of them had any unusual bleeding or collapse noted in the records.

Sheehan, (64) makes the following statement in the British Journal of Obstetrics and Gynecology: "In a recent article (Sheehan) it was shown, both from cases personally examined and from a review of the relevant literature, that, a) Extensive ischemic necrosis of the anterior pituitary is not an uncommon incidental finding at autopsy in women dying in the puerperium. The necrosis appears to be caused by collapse of the patient at delivery, due in the majority of cases to severe hemorrhage, but it cannot usually be recognized histologically until 14 hours post-partum, or later, b) In patients who die of Simmonds' disease which originated from a delivery a long time previously, the pathological appearances of the anterior pituitary corresponds to the healed stage of this necrosis. Where a history of delivery is available it appears that the delivery was always complicated by collapse, usually due to hemorrhage."

The before mentioned facts of Sheehan are substantiated by the following table, which shows the relation of the age of the lesion to the changes observed microscopically:

(Table shown on next page)

Case	Interval between delivery and death	State of parenchyma nuclei in necrotic area	Poly infil	2nd atroph and lymph infiltr.
I	14 hours	Pyknosis	None	None
II	1 day	Early lysis	"	"
III	1 $\frac{1}{2}$ "	Late "	Slight	"
IV	1 $\frac{3}{4}$ "	Faint stain	"	"
V	(2 $\frac{1}{2}$) 3 $\frac{1}{2}$ "	Almost unstained	Fair	"
VI	2 $\frac{1}{2}$ "	Unstained	Slight	"
VII	4 $\frac{1}{2}$ "	"	Moderate	"
VIII	10 "	"	Gross	"
IX	12 "	"	None	"
X	30 "	"	Gross	Moderate

The above table gives an idea as to the age of the lesions in the respective cases. This apparent age of the lesion is judged essentially from the haemalum staining of the parenchyma nuclei in the necrosis; on the stage of necrosis upon the cytoplasm of these cells and on the reaction around the margin of the lesion. Post-mortem autolysis does not complicate the issue; this was studied both by correlation of the lesions with the time of autopsy after death and by comparison of the necrosed and healthy areas in the same gland. The main findings as to the age of the lesion are shown in the previously mentioned chart. In all these cases the necrosis appeared to date from the time of delivery, with the exception of case V, which appeared to date from the time of removal of the placenta.

Further mention of the pathology of post-partum necrosis of the anterior pituitary is made by Sheehan in another article, (66): "Histologically the necroses in the early stages has a sharp margin. The nuclei become small and pyknotic and the cells retain their granules and stain normally. When the necrosis is about a day old the nuclei lose their staining power and in another day or two are hardly recognizable. The endothelial cells near the periphery of the necrosis usually remain intact,

but become necrosed toward the center. Thus, at two or three days old the tissue appears like an ordinary coagulative necrosis with the hypical appearance of an infarct. There are usually a few sinuses containing fibrinous thrombi near the periphery of the necrosed area. At about three days old polymorphs infiltrate the necrosis from the periphery. When seven days old a peculiar condition develops around the area of necrosis. It would naturally be expected that fibrosis would occur around the necrosed area producing encapsulation; instead of this there develops a secondary atrophy of the alveoli just around the necrosis. The alveoli contain large cells which are rounded off and free; they may be phagocytic or they may be developed from the actual parenchyma cells. These atrophic alveoli then lose all their nuclei and cells and the interstitial tissues become collapsed together to form a loose network in which can be seen occasional little accumulation of lymphocytes. The actual necrosed area probably undergoes a somewhat similar change, so that finally the whole necrotic and atrophic zones together are represented only by the condensed stroma. The parenchyma which is left alive remains quite normal in appearance and shows no fibrosis or encapsulation; it abuts by a sharp margin on the area of condensed stroma."

In summarizing the papers of Sheehan and Murdoch, the following points might be considered of importance:

In before mentioned lists there are records of 27 cases with pathological evidence of healed post-partum lesions of

the anterior pituitary and 34 cases with clinical evidence of the same condition. It will be noted that only 25 have a history of hemorrhage collapse at delivery. The comparative rarity of recording the obstetrical condition is of no significance.

Post-partum necrosis of the anterior pituitary is a relative frequent occurrence. It is caused by collapse of the patient, usually by hemorrhage, at or about the time of delivery. It can be found pathologically in its healed state if the patient survives the puerperium, or in its healed stage if death occurs some years later. If the patient survives the puerperium clinical evidence of the 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 cachexia known as Simmonds' disease.

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

A reverse follow-up of 15 parous women who had symptoms suggestive of pituitary insufficiency showed that in 13 of them the condition dated from a delivery in which there was severe

hemorrhage collapse. It is concluded that in these 13 cases the symptoms are due to healed post-partum necroses.

RESUME OF CASE REPORTS OF CASES
WITH A HISTORY RELEVANT TO
OBSTETRICS

The first case report is one obtained from the records of the University of Nebraska, College of Medicine. Although it is not definitely a case of Simmonds' disease, as the records are incomplete, and the case represents one of recovery, however, clinically it can probably be considered such.

The patient, a white unmarried female, age 29 entered the University Hospital 5-16-33, complaining of:

Weakness, stupor and tired feeling, sleepiness, and inability to do work, of a duration of one year.

Genito-Urinary History- Periods began at 14, regular flow for four days, became pregnant at age 18, never had any signs of toxemia. Near term, was in street car accident, immediately went into labor, and was delivered with a profuse post-partum hemorrhage following delivery. Patient had seven weeks of convalescence which were accompanied by fever, and pubic and axillary hair fell out.

Patient did not menstruate after delivery, and teeth gradually decayed, and eyebrows became sparse.

Physical examination-- Patient, an extremely pale, subicteric appearing female, with sparse eyebrows. Thyroid barely palpable, skin dry, heart slow, abdomen smooth, firm and not tender. Pubic and axillary hair absent. Pelvis examined shows an atrophic uterus and small atrophic ovaries. Progress and laboratory notes of no significance, except the BMR, which ranged from -27 to -39.

In a resume of Silver's cases, a total of 13 can be found that give a history of pregnancy with complications prior to the onset of symptoms. 13 out of 41 in this one group reviewed are substantiated with pathological findings. In another series of clinical cases, seven out of nineteen are cited with a history of obstetrical complication, but no necropsy findings are available.

In another review of the literature by Calder in which 70 cases are reviewed ^{twenty} ~~eleven~~ give a very definite history of onset of symptoms following a complicated pregnancy or puerperium.

And from the current literature (cases that have been reported since the reviews of the literature by Silver and Calder) up to the present time, out of 37 cases picked eight give a history of complicated pregnancy, attended by either hemorrhage, sepsis, or toxemia.

CONCLUSION AND SUMMARY

After a review of Simmonds' disease, and a brief consideration of obstetrical shock, and the work of Sheehan and Murdoch, upon post-partum necrosis of the anterior pituitary, the following conclusions can be considered as being of some significance:

1. Simmonds' disease is a definite clinical entity that occurs more frequently than formerly has been supposed.

2. Rarity of the syndrome in the past has, in part, been due to the difficulty in diagnosis, only the far advanced case being easily recognized and the great variation of symptoms that in incompletely developed cases simulate cachexia due to malignancy, tuberculosis, psychoses, etc.

3. That the essential lesion is one of the anterior lobe of the pituitary is shown by the demonstration of an experimental counterpart, and the records of recoveries with the employment of replacement therapy.

4. Tuberculosis, syphilis, sepsis, etc., may be considered as etiological factors, but are not the commonest causative agents producing the condition.

5. As far as can be ascertained, the mechanism for production of the lesion in the anterior lobe of the pituitary, (excluding tuberculosis, lues, etc.) is one of thrombosis rather than embolism, as was formerly upheld by Simmonds' the original investigator of the disease.

6. Obstetrical shock, or to use a better and more inclusive term, obstetrical accident, (and including all conditions increasing the risk and endangering the life of the patient at delivery, hemorrhage, shock, sepsis, toxemia, etc.) is an infrequent condition attending childbirth. The comparative rarity of obstetrical accident is of importance in determining or estimating the frequency of occurrence of Simmonds' disease or post-partum necrosis of the anterior pituitary--assuming at this time that obstetrical accident is of etiological significance.

7. Sheehan and Murdoch, investigating women dying in the puerperium of hemorrhage collapse, have been able to demonstrate a distinct lesion apparently appearing about the time of delivery; a lesion that is very characteristic as to its age, appearing 14 hours old after delivery, and correspondingly, one day, two days, etc.

By follow-up examination of patients exhibiting hemorrhage collapse at delivery, an appreciable number were found to present a syndrome of symptoms that had dated in many cases from the complicated delivery.

Working in the reverse direction, by questioning women presenting a comparable group of symptoms associated with the above group, histories of deliveries with hemorrhage collapse were derived from a relatively large percentage of patients.

8. From a standpoint of prophylaxis, the part played by obstetrical accident in the production of post-partum necrosis of the anterior pituitary, or Simmonds' disease is apparently of some importance.

Nothing absolutely definite nor conclusive can be said, but from the evidence reviewed in this paper the following points might be considered from an obstetrical and gynecological standpoint, as well as general medical:

a. The demonstration of Sheehan and Murdoch of typical necropsy findings on post-partum examination of the anterior pituitary gland, and its similarity to lesions observed in patients dying of Simmonds' disease is a significant point.

b. The significance of this point is further emphasized by the similarity of symptoms observed in Simmonds' syndrome and in patients supposedly receiving an anterior pituitary necrosis at the time of a complicated delivery.

c. Of outstanding importance also, is the relatively large number of patients suffering from Simmonds' disease that give a history of onset of symptoms that followed a delivery complicated by hemorrhage, shock, or sepsis, hemorrhage being the most frequent and important complication.

d. These points are all of significance in obstetrics from a standpoint of possible prophylaxis; and in gynecology and general medicine from a standpoint of diagnosis.

In obstetrics, carefully attended deliveries, with early diagnosis and immediate care of obstetrical complications would be instrumental in the prevention of any such post-partum sequelae as Simmonds' disease, or post-partum necrosis of the anterior pituitary.

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APPENDIX

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