Primary Hypothyroidism and Hypopituitarism in a Young Woman

Stenographic reports of weekly clinicopathologic conferences held in Barnes and Wohl Hospitals are published in each issue of the Journal. Members of the Departments of Internal Medicine, Radiology, and Pathology of the Washington University School of Medicine participate jointly in these conferences. Kenneth M. Ludmerer, M.D., and John M. Kissane, M.D., are the editors of this feature.

A 33-year-old woman was admitted to the St. Louis Jewish Hospital on September 27, 1982, with altered mental status, nausea, and vomiting.

The patient was married in 1970 and took oral contraceptive pills for four years. In 1974, she became pregnant but had a spontaneous abortion at four months. Afterwards, she had oligomenorrhea and could not conceive. For that reason, she and her husband were evaluated for infertility. Her husband was treated empirically with testosterone, but pregnancy was not achieved.

In 1979, the patient underwent dilatation and curettage. Subsequently, persistent amenorrhea developed and never resolved. Further evaluation at that time included normal levels of prolactin, thyroxine, luteinizing hormone, and follicle-stimulating hormone. One month prior to admission, she had an episode of orthostatic dizziness. Her thyroxine level was found to be 2.4 μg/dl (normal 4.5 to 11.5) and her thyrotropin level was 32 mIU/liter (normal 4). Therapy was begun with levothyroxine, and her symptoms improved. She remained well until three days prior to admission, when abdominal pain, headache, nausea, and anorexia developed. The symptoms progressed, and on the day of admission, she became extremely lethargic and barely arousable. She was brought to the Jewish Hospital emergency room, where she was treated with intravenous glucose and naloxone with some improvement. She was admitted to the medical intensive care unit.

Physical examination revealed a lethargic ill-appearing woman in obvious discomfort. The blood pressure was 100/70 mm Hg, the respiratory rate 22 per minute, the heart rate 110 per minute, and the temperature normal. The thyroid was not palpable, and no focal deficits were identifiable on neurologic testing. The remainder of the examination was unremarkable.

Laboratory results included a serum sodium level of 130 meq/liter, potassium 4.3 meq/liter, chloride 89 meq/liter, and bicarbonate 22 meq/liter. The serum chemical results and complete blood count were normal, as were results of chest radiography, abdominal obstructive series, and electrocardiography. A urine drug screen gave negative results. Electroencephalography revealed diffuse slowing. The cerebrospinal fluid was unremarkable except for a protein level of 53.
Treatment with prednisone and fludrocortisone was begun. The serum sodium level gradually rose to 150 meq/liter, and the fludrocortisone was stopped. The luteinizing hormone level returned to 12 mIU/liter, the follicle-stimulating hormone level at 2.9 mIU/liter, the estradiol level at 17 pg/ml, and the prolactin level at 8 ng/ml. A three-day intravenous ACTH stimulation test was performed with an increase in the plasma cortisol level from 2.4 to 64.9 μg/dl. The visual fields were normal. However, repeated computed tomographic scanning of the head with contrast visualized a 1.3 cm mass within the sella turcica. Steroid replacement therapy was continued, and she was readmitted to Barnes Hospital for a procedure.

**CLINICAL DISCUSSION**

Dr. Marc Hammerman: In summary, this patient presented to Jewish Hospital with a three-day history of abdominal pain, headache, nausea, vomiting, and anorexia. At the time of admission, she was described as lethargic and barely arousable. Following treatment to stabilize her medical condition, she was evaluated for hypothalamic-pituitary-endocrine dysfunction. Computed axial tomography of the region of the sella turcica was performed and was said to show an intrasellar mass. I have been told that additional studies were performed at Barnes Hospital prior to a diagnostic procedure. At this time, I will ask Dr. Hodges to review the radiographic findings.

Dr. Fred J. Hodges, III: Conventional complex tomograms of the skull were taken through the mid-sagittal and mid-coronal cuts of the sella (Figure 1). The sella turcica was of normal size and configuration, but the tuberculum was composed of dense, thick bone, which suggests hyperostosis. The underlying sphenoid sinus was normal. The first computed tomographic scan we have is the coronal examination after intravenous contrast injection, performed at the St. Louis Jewish Hospital (Figure 2). It demonstrates an intra- and suprasellar enhancing mass with a lucent and poorly enhancing intrasellar component. These computed tomographic features are quite typical of pituitary adenoma. One month later, transverse computed tomographic scanning was performed at the Mallinckrodt Institute (Figure 3). It demonstrates an intra- and suprasellar mass before injection that undergoes enhancement after contrast injection. Apparently, there was no change in the one-month interval. Intra-arterial digital subtraction angiography was carried out, and although rather coarse, it did show that the carotid arteries were normal in position and that there were grossly abnormal vascular structures.

The radiologic diagnosis at the time was pituitary adenoma. However, there were several radiologic features atypical of adenoma. Pituitary adenoma classically...
sically begins within the sella and usually extends above the sella only after the sella has become enlarged. Thus, the normal-sized sella in this case should lead to consideration of other entities, including metastasis, although there was no known primary, and inflammatory lesions, such as tuberculosis or fungal infections, although there was no cerebrospinal fluid support. Other supra- and perhaps intrasellar entities to be considered are lymphoma, dysergminoma, and craniohypophynglioma. Other, even more rare, lesions could produce this radiographic picture also. The hyperostosis should raise the question of meningioma and perhaps epidermoid tumor and sarcoid granuloma.

Radiologically, then, the most likely diagnosis was pituitary adenoma with suprasellar extension but without solid evidence of hemorrhage. Minor deviations from the classic appearance make it necessary to consider a variety of other pathologic processes.

Dr. Hammerman: I think it is reasonable to conclude that there was an abnormality in the area of the sella turcica and/or in the suprasellar region. It also seems likely that this woman underwent a surgical procedure in order to delineate the nature of this abnormality. I believe that it is possible to explain most of this patient's problems on the basis of a single pathologic entity. My discussion will conclude with a single diagnosis and an explanation as to why I think that diagnosis is consistent with most of the medical problems. First, however, I will discuss the diagnostic possibilities in the light of the patient's history, findings on physical examination, and hospital course.

This patient showed evidence of multiple endocrine gland failure either prior to admission, at the time of admission, or during hospitalization. She had been oligomenorrheic since a miscarriage in 1974 and had been unable to achieve a second pregnancy. She had experienced amenorrhea since 1979. Her plasma estradiol level measured during her hospitalization was low, as were her levels of plasma luteinizing hormone and follicle-stimulating hormone. Thus, this patient had clinical and laboratory findings consistent with hypogonadal hypogonadism.

Primary hypothyroidism had been diagnosed one month prior to hospitalization. At that time, the patient had elevated plasma thyrotropin. Thyroid hormone replacement was begun, and at the time of admission, the patient's plasma thyroxine was within the normal range and thyrotropin was appropriately suppressed.

This patient's medical condition was deemed sufficiently unstable at the time of hospitalization to prompt admission to a medical intensive care unit. Abnormalities of plasma osmolality and plasma electrolyte concentrations subsequently developed. Despite the findings at the time of hospitalization and despite her hospital course, the 8 A.M. plasma cortisol level measured on the third hospital day was only 2.5 μg/dl. The presence of such a low plasma cortisol level despite significant stress provided good evidence for adrenal
insufficiency [1]. Also suggestive of adrenal insufficiency were her presenting symptoms of nausea, vomiting, anorexia, and lethargy and the finding of orthostatic hypotension. The patient underwent testing to determine whether adrenal insufficiency might be primary or secondary. The response to a single injection of synthetic ACTH was subnormal, but barely so [2]. Subsequent ACTH infusion resulted in a good response to this trophic hormone [1,3]. On the basis of these two tests, we may conclude that her adrenal insufficiency was secondary to pituitary dysfunction [1–3]. Furthermore, the responses to synthetic ACTH and ACTH infusion suggested that the deficiency of endogenous ACTH had been of sufficiently short duration that the ability of this patient’s adrenal glands to respond to trophic stimuli was nearly normal. Axelrod [4] reviewed the results of several clinical studies designed to define the time course of development of hypothalamic-pituitary-adrenal suppression following initiation of glucocorticoid therapy in dosages large enough to suppress endogenous ACTH. He concluded that significant adrenocortical atrophy and depressed responsiveness to exogenous ACTH administration generally occurred within one to two weeks. Thus, the laboratory data are consistent with an etiologic event resulting in secondary adrenal insufficiency that was sudden and that might have occurred within a week or two of hospitalization (4).

Impaired renal clearance of free water was diagnosed in this patient on the basis of hyposmolality of plasma in the presence of urine that was less than maximally dilute. It is well recognized that hypothalamic-pituitary-adrenocortical insufficiency in humans is associated with water retention. Agus and Goldberg [6] have demonstrated inability to excrete a free water load in patients with anterior hypopituitarism. This abnormality was correctable with oral glucocorticoid therapy. The pathophysiologic mechanism of the inability to excrete free water in states of glucocorticoid insufficiency is not known. Possible mechanisms include: (1) an associated extracellular fluid-volume depletion resulting in elevated levels of antidiuretic hormone in plasma; (2) an associated fall in the glomerular filtration rate resulting in increased reabsorption of free water by the proximal tubule and decreased water delivery to the distal renal tubule; (3) increased water permeability of the distal nephron under conditions of glucocorticoid insufficiency; and/or (4) enhanced sensitivity of hypothalamic osmoreceptors in states of glucocorticoid insufficiency [6]. Green et al. [7] showed that inability to excrete free water in adrenalectomized Brattleboro rats could be corrected by glucocorticoid plus mineralocorticoid administration. This observation in the Brattleboro rat, an animal that cannot produce antidiuretic hormone, suggests that the inability to excrete free water in adrenal insufficiency and subsequent correction with replacement therapy are not dependent upon the presence of antidiuretic hormone.

In the patient under discussion, glucocorticoid and mineralocorticoid replacement therapy resulted in normalization of plasma osmolality and plasma electrolyte concentrations.

To summarize at this point, I believe that the patient we are discussing showed evidence of hypogonadotropic hypogonadism, secondary adrenal insufficiency, and primary hypothyroidism. The diagnosis of anterior hypopituitarism is suggested by the first two problems. One cause of hypopituitarism that should be considered is Sheehan’s syndrome [8].

Enlargement of the pituitary gland occurs during pregnancy secondary to hyperplasia of lactotroph cells stimulated to proliferation by estrogen. The enlarged gestational pituitary is unduly susceptible to injury. The cause of Sheehan’s syndrome, or postpartum pituitary necrosis, is unknown. Possible causes include spasm of the hypothalamic pituitary arterioles that give rise to the hypothalamic-pituitary portal veins, or thrombosis of the portal blood vessels secondary to excessive blood loss at the time of delivery [8,9]. This would result in interruption of blood flow to the anterior pituitary and infarction of pituitary tissue. It must be remembered that most of the blood supply to the anterior pituitary is through the hypothalamic-pituitary portal vessels [10], whereas the posterior pituitary has an arterial source of blood. Thus, the posterior pituitary is usually, although not always, spared in Sheehan’s syndrome [9].

Clinical manifestations of Sheehan’s syndrome may become apparent over a 15- to 20-year period of time after the etiologic event and may culminate in total or partial pituitary insufficiency. Initially, patients fail to lactate after giving birth, fail to resume normal menstrual flow, and begin to lose body hair. Later, pallor, lethargy, stupor, and/or hypoglycemia may develop if the anterior hypopituitarism remains untreated. Although Sheehan’s syndrome may occur in the absence of hemorrhage, it usually results from peripartum or postpartum hemorrhage. Thus, the incidence of Sheehan’s syndrome is inversely related to adequacy of obstetric care.

I have asked Dr. Strickler from the Department of Obstetrics and Gynecology to discuss this patient’s obstetric history in relation to her present problems. Initially, however, I would like Dr. Strickler to address two specific questions. First, did this woman have pituitary insufficiency at the time of her pregnancy and could this have explained her miscarriage and subsequent events? Second, did this patient have Sheehan’s syndrome and did her apparent anterior pituitary insufficiency date from her miscarriage?

Dr. Ronald Strickler: Did this woman have hypop-
Hypothalamic-pituitary dysfunction that caused her abortion? No. Hypothalamic-pituitary dysfunction is not a cause for abortion in the middle trimester. Unlike laboratory rats and some mammals that depend on the continuing stimulation of the ovarian corpus luteum for pregnancy maintenance, human pregnancy rapidly becomes independent of the hypothalamic-pituitary-ovarian axis. Csapo, from this institution 10 years ago, showed that corpus luteum progesterone was critical through the eighth week of pregnancy dated from the last normal menstrual flow. Therefore, the placenta, an apparently autonomous organ, maintains the necessary steroid hormone milieu.

There have been reports of pregnant women with acute pituitary insufficiency due to central nervous system trauma, as well as reports of conception in women with long-standing hypothalamic-pituitary dysfunction. Such observations attest that the "master gland" is not necessary for pregnancy maintenance, labor, or vaginal delivery at term, assuming thyroid and adrenal replacement is adequate.

Did this woman have Sheehan's syndrome from a pituitary infarction following her miscarriage? No. We have no information that this woman, at the time of her abortion, had hemorrhage and hypotension, the classic clinical correlates for postpartum pituitary necrosis. Not every woman shows apoplectic, and the onset of symptoms can be gradual. However, these women customarily lose lactotropin function; five years after the abortion, our patient had a normal serum prolactin level. Usually, women with pituitary infarction are amenorrheic and hypogonadal due to absent gonadotropin function. This woman continued to have menstrual periods, albeit with less flow. Moreover, five years after the pregnancy loss, several follicle-stimulating hormone and luteinizing hormone levels were normal. Finally, this woman's hypothyroidism is primary and not secondary to progressive pituitary insufficiency, again suggesting normal pituitary function following the miscarriage.

What then, is the relationship of the second-trimester abortion to this patient's total problem?

To put this abortion into perspective, consider the normal reproductive performance of 100 healthy ova exposed to sperm (Table I). A single mid-trimester spontaneous abortion is not unusual; it occurs in 1 to 3 percent of all gestations.

The causes of most abortions, whether in the first or second trimester, are usually not detected, but studies from women with habitual abortion give us some insight (Table II).

Structural chromosomal abnormalities are seen in tissue from at least 50 percent of first-trimester abortions and in 10 to 20 percent of tissue from second-trimester abortions. For comparison, 5 percent of stillborn and 0.5 percent of liveborn infants have chromosome abnormalities. In 20 percent of couples who experience repeated first- and second-trimester abortions, one partner is a balanced translocation carrier.

Mullerian fusion defects, such as uterine septum, occur in one of 1,000 women. These anatomic variations account for 25 percent of second-trimester abortions. Cervical incompetence has an estimated prevalence of one in 125 to one in 2,000 gestations. Painless cervical dilation permits prolapse of the bag of waters into the vagina, rupture of the membranes, and delivery with minimal or no labor. The cause of cervical incompetence is unknown, but there is often a history of cervical trauma from childbirth or surgery. Leiomyomas, if they are sufficiently large and compromise the volume of the uterine cavity, may rarely explain abortion. Intrauterine adhesions (Asherman's syndrome), the result of vigorous curettage, endometritis, or uterine surgery, contribute to infertility, but their role in spontaneous abortion is unknown.

Any maternal illness that causes high fever (e.g., pyelonephritis) can cause pregnancy wastage. Diseases and microorganisms specifically associated with abortion include syphilis, malaria, Toxoplasma, cytomegalovirus, smallpox virus, Chlamydia, Ureaplasma, and Candida.

Luteal-phase defects and progesterone deficiency cause only early first-trimester abortion. As explained,

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<tr>
<th>Number</th>
<th>Outcome</th>
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<tr>
<td>16</td>
<td>Nonfertilization</td>
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<td>33</td>
<td>Premature or chemical abortion</td>
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<td>16</td>
<td>First-trimester abortion</td>
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<td>3</td>
<td>Second-trimester abortion</td>
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<td>30</td>
<td>Liveborn</td>
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TABLE II Causes of Habitual Abortion

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<td>Chromosome structure anomalies</td>
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<td>Mullerian fusion</td>
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<td>Cervical incompetence</td>
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<td>Leiomyomas</td>
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<td>Intrauterine adhesions</td>
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<td>Endocrinologic causes</td>
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<td>Luteal phase defect</td>
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<td>Diabetes mellitus</td>
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<td>Thyroid dysfunction</td>
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<td>Maternal illness</td>
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<td>Drugs, pollutants, irradiation, trauma</td>
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<td>Immunologic causes</td>
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<td>Placental Fluor Infarction</td>
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the placenta makes human pregnancy endocrinologically autonomous beyond the eighth week of gestation. Diabetes mellitus increases the risk of antepartum fetal death, usually in the last trimester. In women with well-controlled diabetes, there is no increased pregnancy wastage. Nonetheless, glucose tolerance testing in each trimester is appropriate for women who have had repeated abortions. Thyroid dysfunction, especially hypothyroidism, is often cited to cause abortion, but much of the support comes from old data based on basal metabolic rate studies. Both hyper- and hypothyroidism are real, but uncommon, causes of infertility and very, very rare causes of abortion.

Certainly, any serious maternal medical illness may contribute to abortion, but this is rare. The exception is hypertension. High blood pressure compromises uteroplacental blood flow leading to growth retardation, abortion, and pregnancy wastage. Very few environmental insults are clear causes of abortion. Anticancer drugs, acute radiation doses in excess of 30 rads, and penetrating wounds would be clear examples. Although we avoid medications for pregnant women, counsel abstinence from smoking and alcohol, contraindicate radiography, and offer advice against using solvents, cleaners, and house paints, there are no data to support most prohibitions.

Finally, there is much current interest in the role of immunologic causes of both infertility and pregnancy loss. Increased sharing of major histocompatibility antigens on human leukocytes from husband and wife has been identified in some reports. Absence of maternal blocking antibodies to the recognition of paternal antigens is a second proposal to explain abortion. There are two interesting associations with habitual abortion. Maternal florid infarction is an uncommon, unexplained disease wherein fibrin deposition within the decidua basalis, the floor of the placental lake, encases the placental villi, which became atrophic and necrotic. Fetal growth retardation, fetal death, and recurrent abortion correlate with this condition. Second, the "lupus anticoagulant" immunoglobulin interferes with the prothrombin activator complex. These patients do not have a bleeding disorder; rather, they are prone to thrombotic accidents. The presumed cause is interference with the production or release of vascular intimal prostacyclin. "Lupus anticoagulant" correlates with mid-trimester abortion.

We have no information to favor any cause besides chance in this patient, but let me speculate that this woman has an immune deficiency. I speculate that this was the cause of her second-trimester abortion. I presume that she underwent post-abortion curettage, and I suspect that intrauterine adhesions secondary to curettage contributed to her subsequent reduced menstrual flow and infertility. Because of the focus on a male infertility problem, the Asherman's syndrome was not noted, and dilatation and curettage in 1979 aggravated the adhesions, causing amenorrhea. In other words, I think an end-organ cause of her amenorrhea is more likely than an ovarian or pituitary cause. Moreover, the gonadotropin levels were normal, and the amenorrhea dated from the time of the surgical procedure, further arguing against an endocrinologic cause of the amenorrhea. A relationship between the immune deficiency I am hypothesizing and the development of uterine adhesions, if there were any, is not known. The second declaration of her proposed autoimmune syndrome was the development of hypothyroidism due to thyroid gland failure. Finally, I would submit that this woman's Addisonian presentation resulting from pituitary insufficiency was a third sign of an immune polyendocrinopathy.

Dr. Hammerman: The diagnosis of autoimmune polyendocrinopathy is an interesting one and may certainly be relevant to this patient. Before discussing this condition, however, I would like to consider the specific presenting problems in this patient within the context of a diagnosis of acute pituitary insufficiency or pituitary apoplexy.

The syndrome of pituitary apoplexy is usually introduced by a severe headache and is commonly associated with diplopia, fever, altered consciousness, nausea and vomiting, and occasionally visual loss, stiff neck, photophobia, hypotension, and hypothermia. Patients may experience seizures, hemiparesis, cerebellar signs, or cranial nerve palsies. Findings in the cerebrospinal fluid may resemble those of subarachnoid hemorrhage and include the presence of red blood cells and/or polymorphonuclear leukocytes in the fluid and elevated protein [11]. This patient had most of the neurologic symptoms commonly associated with pituitary apoplexy [11] and also had evidence suggestive of an intrasellar or suprasellar mass. In addition, there is good reason to believe that her secondary adrenal insufficiency was of recent onset. Thus, I must speculate that the event prompting her hospitalization may well have been acute pituitary insufficiency. Hemorrhagic infarction of a pituitary adenoma has been described as a cause of pituitary apoplexy [11,12]. Such infarction has been postulated to result from interference with the blood supply to the anterior pituitary and/or pituitary adenoma secondary to tumor mass obstructing blood flow through the hypothalamic-pituitary portal vessels [12].

Whether or not anterior pituitary insufficiency in this patient was of sudden onset is subject to debate. However, I believe there is no doubt that the patient had anterior hypopituitarism. Considerable variability exists in the clinical presentation of this condition in adults. Evidence of growth hormone deficiency is most common within a population, followed in frequency by in-
sufficiency of gonadotropins, thyrotropin, and ACTH [13]. Thus, the fact that this patient’s pituitary was able to respond to primary thyroid insufficiency by increasing thyrotropin secretion one month prior to hospitalization does not rule out the diagnosis of hypopituitarism. In addition, it would not be inconsistent that ACTH secretory function was preserved until one to two weeks prior to hospitalization.

Pituitary adenomas represent the most commonly defined cause of hypopituitarism. Using Mallory’s trichrome staining method, it is possible to divide pituitary cells (and pituitary adenomas) into three types: (1) chromophobes, which stain grey; (2) acidophils, which stain red; and (3) basophils, which stain blue. It is probably more useful to divide cells functionally. Separation of pituitary cell types on the basis of cellular function can be accomplished through the use of various staining and microscopic techniques [14]. Such methods permit characterization of pituitary cells as: somatotrophs, which secrete growth hormones; mammotrophs, which secrete prolactin; corticotrophs, which secrete ACTH; thyrotrophs, which secrete thyrotropin; and gonadotrophs, which secrete gonadotropins. In addition to these, adenomas may arise from mixed somatotrophs and lactotrophs or from undifferentiated cells. The latter group comprises approximately 20 percent of pituitary adenomas.

An intriguing possibility in this patient is that hyperplasia of thyrotropin-secreting cells within the pituitary, secondary to primary thyroid dysfunction, resulted in pituitary dysfunction. Such a series of events would link primary hypothyroidism with secondary hypoadrenocorticism and hypogonadotrophic hypogonadism. Yamada et al. [15] have shown that enlargement of the sella turcica occurs routinely in adults with primary hypothyroidism. It is well recognized that hyperplasia of thyrotropin-secreting cells may accompany the primary hypothyroid state in experimental animals [15]. However, hypopituitarism is not routinely associated with primary hypothyroidism in humans [15]. Autonomous production of thyrotropin in this patient, such as would occur in a thyrotroph cell adenoma, can be excluded by the finding of a normally suppressed plasma thyrotropin value at the time of hospitalization. Thus, I think that it is unlikely that her presentation resulted from pituitary insufficiency secondary to hyperplasia of thyrotrophic pituitary cells.

Putting aside the question of linkage between primary hypothyroidism and anterior hypopituitarism for a moment, I would like to consider that the patient may have had a nonpituitary tumor of the third ventricular region as a cause of hypopituitarism. The most common of these is the craniopharyngioma, which arises from epithelial cells rests carried with Rathke’s pouch into the pituitary fossa. It should be remembered that the anterior pituitary gland arises embryologically as an out-pouching of ectoderm from the roof of the oral cavity (Rathke’s pouch) and becomes associated with the posterior pituitary, which arises as an out-pouching of ectoderm from the floor of the primitive diencephalon.

Craniopharyngiomas are most commonly suprasellar, but in 75 percent, there is evidence of radiologic abnormality within the sella turcica [16]. Craniopharyngiomas are primarily found during the first two decades of life, but symptoms may emerge as late as the seventh or eighth decade. Involvement of visual fields is common because of the suprasellar location, and intracranial calcification is usually seen. The absence of these two findings makes craniopharyngioma unlikely in the patient under discussion. Other nonpituitary tumors of the third ventricular region include germ cell tumors such as pinealoma, glioblastomas such as astrocytoma or pilocyticoma, choroid plexus papilloma, or angioma [16].

Conditions other than pituitary or nonpituitary tumors may be associated with hypopituitarism. These include granulomatous diseases such as sarcoidosis and tuberculosis or histiocytosis X. In addition, syphilis or hemochromatosis may involve the pituitary [9]. There is no evidence to suggest that the patient we are discussing had any of these conditions. However, I would like to spend a few minutes discussing sarcoidosis because the endocrinologic manifestations of this condition have been well reviewed. Mayock et al. [17] summarized findings in 145 patients with sarcoidosis and in patients in nine clinical series selected from the medical literature through 1983. They determined that clinically apparent pituitary involvement with sarcoidosis was seen in about 1 percent of cases. Clinical thyroid involvement was also described in about 1 percent of cases. Winnacker et al. [18] reviewed endocrinologic findings in sarcoidosis. They emphasized the importance of vascular and perivascular granulomas in the pathogenesis of hypothalamic-pituitary abnormalities associated with this condition. In addition, they noted that proliferating granulomas may destroy pituitary tissue. Diabetes insipidus was reported to be particularly common in hypothalamic-pituitary sarcoidosis. Anterior hypopituitarism was also reported to be part of the clinical spectrum. Radiologic evidence of an enlarged pituitary fossa was unusual in these cases of sarcoidosis, as was calcification in or above the pituitary. Hypothyroidism in association with sarcoidosis was rare. Because of the absence of more common manifestations of sarcoidosis in the patient we are discussing, I will exclude this condition from further consideration.

The final portion of my discussion will concern the possibility that this patient had an autoimmune polyendocrinopathy. In 1926, Schmidt [19] described an
association between nontuberculous Addison’s disease and chronic lymphocytic thyroiditis. The coexistence of primary thyroid and nontuberculous adrenal insufficiency has come to be designated Schmidt’s syndrome. In 1964, Carpenter et al [20] suggested that Schmidt’s syndrome may be a polyendocrinopathy, the basis of which was immunologic. These investigators reviewed previously reported cases of Schmidt’s syndrome, 24 autopsied cases of Addison’s disease, and 15 new cases of Addison’s disease. Of the 15 patients with new cases, 13 had circulating antibodies against thyroid tissue, and nine had antibodies against adrenal tissue. In addition, Carpenter et al [20] described three persons with evidence of anterior hypophysis. These patients had accumulations of mononuclear cells within the pituitary with foci of necrosis. The lesions were said to resemble those in the adrenals.

It has since become evident that endocrine glands other than the thyroid and adrenal can be involved in the syndrome of autoimune polyendocrinopathy [21]. These include islets of Langerhans, parathyroid glands, gonads, and the anterior pituitary [20,21]. Volpe [21] has listed other nonendocrine conditions that may be part of this pathologic process including pernicious anemia, vitiligo, rheumatoid arthritis, idiopathic thrombocytopenic purpura, myasthenia gravis, Sjogren’s syndrome, and chronic active hepatitis. Bottazo et al [22] have reported antibodies directed against prolactin-secreting pituitary cells in 19 patients with a variety of endocrine deficiency diseases. This finding provides strong support for the existence of autoimmune anterior hypophysis in association with polyendocrinopathy.

Doniach [10] reviewed four cases of autoimmune or lymphocytic hypophysitis. In each instance, the finding of lymphocytic infiltration of anterior pituitary tissue was made at postmortem examination. Clinical hypopituitarism was diagnosed either during life or in retrospect in each patient. Two of the four patients had concurrent autoimmune thyroiditis with lymphocytic infiltration of thyroid tissue [23,24], one had atrophic gastritis with pernicious anemia [24], and another had lymphocytic infiltration of adrenal and parathyroid glands [25]. Asa et al [26] have subsequently reported two cases of lymphocytic hypophysitis associated with pregnancy. The condition presented as a mass lesion within the sella turcica in one pregnant patient. The other presented with amenorrhea and postpartum failure to lactate. These investigators reviewed eight additional cases of lymphocytic hypophysitis from the medical literature and from their own experience. All of the patients were women. In five of the 10, the disease was detected in the postpartum period, and in two others, during pregnancy. Thus, an association between lymphocytic hypophysitis and pregnancy was postulated. Portocarrero et al [27] have recently reported an additional case of lymphocytic hypophysitis, with presentation in the postpartum period.

I believe that the patient we are discussing is similar to patients described in case reports and reviews of lymphocytic hypophysitis. It is probable that both her anterior hypopituitarism and her primary hypothyroidism can be explained on the basis of an autoimmune polyendocrinopathy. In view of the findings of Asa et al [26], it is probably not coincidental that her clinical problems began after a miscarriage. I predict that the patient underwent trans-sphenoidal hypophysectomy and that a diagnosis of autoimmune or lymphocytic hypophysitis was made on the basis of the tissue removed.

PATHOLOGIC DISCUSSION

Dr. Daniel McKeel: The diagnosis made was not infarction or typical lymphoid adenohypophysitis, but those considerations serve as a nice lead-in to the pathologic discussion. The patient had a preoperative diagnosis of pituitary microadenoma, based primarily on the neuroradiologic studies that have been described. At surgery, which was a trans-sphenoidal operation on the pituitary gland, the surgeon was surprised to note sclerosis of the sella, a finding that contrasted with the usual pituitary adenoma, in which the sella is thinned or even ruptured. The patient’s gland was fibrotic, a second finding that contrasted with the softened or liquefied consistency of many pituitary adenomatous tumors. Rather than a discrete adenoma, the surgeon saw a hypophysis that was described as yellow, shrunken, and fibrotic. Two gland portions were sampled for frozen section examination. The first was 0.3 by 0.1 by 0.1 cm and the second measured 0.5 by 0.4 by 0.3 cm. I examined the biopsy specimens, as did the neuropathologist. The first frozen section showed fibrous tissue that may have been dura. The second piece was more interesting and showed islands of preserved glandular epithelium, representing adenohypophysial secretory cells. One focus appeared to be an area of necrosis with polymorphonuclear leukocytes in the center and several probable giant cells around the periphery. Compression artifact made the tissue somewhat more difficult to interpret.

Interpretation of the permanent sections centered around the differential diagnosis of a destructive process that caused progressive hypopituitarism and that was characterized by necrotizing granulomas with neutrophils and a diffuse lymphoplasmacytotic inflammatory infiltrate. Dr. Hammerman has illustrated the large number of entities that occur in and around the pituitary gland and the sella turcica. From the more
specific set of criteria defined by the frozen sections, a smaller list of diagnostic possibilities must be considered. These entities are listed in Table III.

The histopathologic findings definitely merit consideration of syphilis and tuberculosis as etiologic possibilities. However, silver stains for spirochetes and gram stains and acid-fast stains for mycoplasma in the biopsy specimens gave negative results. Sarcoidosis was a possibility that could not be ruled out with certainty, although the absence of clinical evidence of pulmonary or other systemic involvement and a normal level of angiotensin-converting enzyme argued against it. Sarcoid granulomas may exhibit central necrosis [28,29]. None of the suggestive cytologic features of sarcoid granulomas described in the same articles were identified in our material. Pertschuk et al [29] have described a purportedly reliable tissue test for sarcoidosis, in which angiotensin-converting enzyme is localized within sarcoid granulomas using the immunoperoxidase method in conjunction with an antibody raised against purified angiotensin-converting enzyme. The test is stated to have excellent specificity for sarcoid granulomas versus all other types. Unfortunately, this test is not yet available at our center.

Next, we now know from the clinical discussion that bland coagulation necrosis or hemorrhagic infarction were shown by Sheehan and co-workers [30,31] to be the predominant pathologic lesions in acute postpartum pituitary necrosis. Our patient's illness had its probable onset during or following a pregnancy years prior to her pituitary surgical procedure. In that setting, we might expect to find an atrophic, fibrotic gland, especially if more than 50 percent of the adenohypophysis were infarcted originally. The operative findings were consonant with these findings. However, the microscopic findings were decidedly different from the typical chronic stage of Sheehan's postpartum necrosis.

Simmonds [32] reported in 1917 another subset of patients who had pituitary insufficiency. I would like to quote what he said:

In rare cases, the pituitary gland of elderly women may show characteristic granulomas not only with lymphocytic infiltration and epithelioid cells but also with true giant cells. Independently of the granulomas, giant cells are present also in intact glandular tissue. The granulomas are reminiscent partly of military tubercles but are entirely unrelated to tuberculosis or syphilis.

Sheehan and Summers [30], in an extensive report on postpartum and other types of pituitary insufficiency in 1949, recognized 14 patients who had granulomatous adenohypophysitis in addition to the four patients described previously by Simmonds. These authors, but particularly Sheehan and Summers, stressed the importance of concomitant lymphocytic infiltration. Thus, the entity of granulomatous adenohypophysitis with giant cells and lymphocytic infiltrates has indeed been recognized for many years.

What I want to suggest about the case we are discussing is the possibility that there may be a spectrum of disease, with purely lymphocytic adenohypophysitis being the predominant early lesion, and the granulomatous component being the later component of the same disease process. Of the cases of pure lymphocytic adenohypophysitis currently reported in the medical literature, all have occurred in women and over half have been associated with pregnancy or lactation at the time of initial clinical presentation. Several recent cases [26,33,34] have presented in pregnant women as an intrasellar mass lesion that led to trans-sphenoidal decompressive surgery. A computed tomographic scan from one such case reported in 1982 by Wilson's group

**TABLE III** Differential Diagnosis Based on Histopathologic Evidence of Necrotizing Granulomas and Lymphocytic Infiltration of Adenohypophysis

<table>
<thead>
<tr>
<th>Entity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Postpartum lesion</td>
</tr>
<tr>
<td></td>
<td>Acute, infarction; chronic, fibrosis with atrophy (Sheehan's syndrome)</td>
</tr>
<tr>
<td>Lymphocytic adenohypophysitis</td>
<td>Granulomatous adenohypophysitis</td>
</tr>
<tr>
<td>Miscellaneous infectious and other granulomatous processes</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 4. Photomicrograph of lymphoid adenohypophysitis lesion to illustrate parenchymal tissue with lymphoid nodule that has a suggestion of a central germinal center. No giant cells are present (hematoxylin and eosin stain; original magnification X 200, reduced by 40 percent).](image)
from San Francisco [34, Figure 1] showed the suprasellar extension of a mass that mimicked a pituitary adenoma, but the patient actually had lymphocytic adenohypophysitis. Microscopically, in lymphocytic adenohypophysitis, the pituitary is characteristically replaced by extensive sheets of lymphocytes with some tendency to form nodules [35] (Figure 4). Some of the lymphocytic foci exhibit epithelial cell formation in the center that may be interpreted as germinal center structures. In a typical case of lymphocytic adenohypophysitis, sheets of lymphocytes are seen surrounding residual islands of parenchymal cells. Aas et al [26] have presented ultrastructural evidence that the lymphocytes are cytotoxic and form intimate contacts with pituitary secretory cells prior to or while destroying them. I will draw parallels between their findings and ours in the present case. The extensive loss of anterior pituitary parenchyma with some replacement fibrosis is usually of sufficient magnitude to explain the observed degree of clinical hypopituitarism.

Recognition of the entity I believe our patient had, granulomatous adenohypophysitis with extensive lymphocytic infiltration, preceded the description of purely lymphocytic hypophysitis in the literature but may be related to it. An article by Kleaer and Norgaard [36] best describes this process under the title: "Granulomatous hypophysitis and thyroiditis with lymphocytic adenitis." Our patient also had suggestive clinical evidence of thyroid and adrenal failure, and autoimmunity cannot be excluded as an etiologic explanation for their occurrence with the evidence presented in the clinical protocol. Permanent sections of anterior pituitary biopsy tissue from our patient showed a marked loss of secretory cells. Low-magnification examinations of routine hematoxylin and eosin preparations revealed pink areas of fibrous tissue, as well as extensive infiltration with inflammatory cells. One focus, which was also present in the frozen sections, displayed geographic necrosis as shown in Figure 5. At higher magnification, the focus contained an area of central necrosis in the center of which were polymorphonuclear leukocytes. Around the edge of the necrotic focus were seen both inflammatory cells and several pale, ill-defined cells that could have been either residual secretory cells or giant cells. Some very discrete giant cells surrounded by inflammatory cells and epithelioid-like cells were present in several areas in the specimen. In other areas, there were islands of parenchymal tissue with inflammatory cells in close apposition to the secretory cells and loss of the parenchymal cells in the surrounding tissue. In aggregate, in both pieces of tissue submitted for permanent sections, I estimate there was a 70 to 80 percent loss of parenchyma and replacement by inflammatory infiltrate.

The histologic concomitant of the fibrosis noted by the neurosurgeon was shown by a reticulin silver stain (Figure 6). Islands of residual parenchymal cells were seen within a dense accumulation of reticulin-rich interstitial connective tissue. Thus, although there was some increase of connective tissue, there was no dense collagenous fibrosis characteristic of chronic Sheehan syndrome observed many years after its onset. Diffuse entinal histologic stains demonstrated islands of preserved secretory cells with some orange growth hor
TABLE IV  Ultrasstructural Similarities between Granulomatous and Lymphoid [26] Adenohypophysitis

- Degranulated, inactive secretory cells
- Focal oncocytic change in secretory cells
- Sheets of small to medium-sized lymphocytes
- Activated cytotoxic lymphocytes interdigitating with secretory cells
- Inflammatory cells within perivesical basement membranes
- Giant fused secretory granules in ACTH cells
- Proliferated basement membranes around blood vessels and secretory cell acini

...mone cells and some adjacent ACTH cells. Definite thyrotrophs and gonadotrophs were sparse and difficult to identify. Immunoperoxidase staining demonstrated very few residual prolactin cells. Thus, we gathered definite histologic evidence that some pituitary secretory cells were preserved, but that there was an overall marked decrease of all types of functional hormonal cells.

Ultrastructural analysis was performed for two reasons. Extensive staining procedures had apparently ruled out the presence of bacteria, fungi, syphilis, and tuberculosis; all special stains for microorganisms had shown none. Nevertheless, special stains for spirochetes, especially, are notoriously capricious, so we used electron microscopy to help exclude any infectious process. I think we effectively did that. We also wanted to determine the exact nature of the cellular infiltrate in the gland, and whether the residual parenchymal cells looked like viable pituitary secretory cells.

If only the granulomatous and the giant cell components already described had been present, we would have lumped the case with those reported by Simmonds, Sheehan, and Klaer and Norgaard and called it simply granulomatous hypophysitis. The specific ultrastructural features that link the present case with more recently described cases of lymphoid adenohypophysitis as described by Asa et al [26] are summarized in Table IV. The predominant lymphocytic infiltrate was seen especially well in a 1μ plastic section of glutaraldehyde osmium-fixed material (Figure 7). Other areas of the biopsy specimen showed foci of densely granulated cells, some of which were growth hormone and ACTH cells by electron microscopic criteria. Additional unique features of this case included the presence of numerous neutrophilic leukocytes and mature plasma cells, the giant cells, and a focus of cellular necrosis.

In summary, we diagnosed necrotizing granulomatous hypophysitis with extensive lymphocytic infiltration...

Figure 7. Photomicrograph of 1μ plastic section of biopsy specimen embedded for electron microscopy after fixation in glutaraldehyde and osmium. This represents an enlarged view of the central cellular infiltrate surrounding a necrotizing granulomatous lesion. Like the lesion shown in Figure 4 of lymphoid adenohypophysitis, the cells are predominately small and medium-sized lymphocytes with some larger cells that require electron microscopic examination for identification (toluidine blue stain, 1μ plastic section; original magnification × 800, reduced by 40 percent).

...or, granulomatous-lymphoid adenohypophysitis. I believe the demonstrated extent of gland destruction adequately explained most of the clinical findings. An aspect of the past clinical history that remains unexplained was the episode of optic neuritis that required steroid treatment. Could this have been a clue to an occult immunologic disease process? Not mentioned in the protocol was the fact that the patient's sister had insulin-dependent diabetes mellitus and that her mother had the adult-onset form of diabetes. With a strong family history of diabetes, it seems possible that she had a diabetic hyperglycemic tendency that was masked by an absence of glucocorticoids and perhaps growth hormone at the tissue level with a resultant relative lack of insulin antagonism.

Dr. William Glatter: Did the biopsy material show any evidence of hemorrhage?

Dr. McKeel: No, there was no evidence of pituitary hemorrhage seen by either the neurosurgeon or by the pathologists to suggest that pituitary apoplexy caused the symptoms that led to surgical exploration.

Dr. Hammerman: I would like to add that, as Dr. McKeel implied, the syndrome of polyendocrine dysfunction is familial.

Final histologic diagnosis: Granulomatous adenohypophysitis with extensive lymphocytic infiltration.
REFERENCES


