ACUTE DEGENERATIVE CHANGES IN ADENOMAS OF THE PITUITARY BODY—WITH SPECIAL REFERENCE TO PITUITARY APOPLEXY

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DEGENERATIVE changes in pituitary adenomas and their attendant clinical manifestations occur not infrequently yet they have been mentioned in only a few of the more complete descriptions of these tumors. These changes usually consist of small hemorrhages and areas of necrosis with "cyst" formation, reparative fibrosis and sometimes calcification. Some writers relate such lesions to the apparent arrest of acromegaly or to the rapid development of dyspituitarism. However, in most instances these degenerative changes are regarded as unimportant findings without precise relationship to symptoms and without significant effect on the growth of the adenoma.

In the routine examination of the brains of individuals who have died unexpectedly we have several times discovered tumors of the pituitary gland in which widespread necrosis and/or extensive hemorrhage had occurred. Clinically, these changes were associated with a sudden onset of neurological symptoms such as ophthalmoplegia, blindness, stupor or coma and they have resulted in death within a few hours to days. Extensive lesions of this type have seldom been described. In fact, a review of the literature disclosed only 5 cases showing similar symptomatology and pathological findings. The following cases are presented, therefore, in order to call attention to these severe retrogressive pituitary lesions.

REPORT OF CASES

Case 1. (B.C.H. 115140, A 44–421) This patient, a 65-year-old negro, was hospitalized because of epigastric pains of 7 weeks’ duration. Investigation revealed nothing of importance except a low blood pressure (100/70) and a slight reduction of blood chlorides. A diagnosis of adrenal insufficiency was made and treatment with sodium chloride and desoxycorticosterone was instituted.

On the night of the 16th hospital-day the patient complained of severe frontal headache, and the next morning he was found semicomatose. Temperature was 105°F. and the neck was very stiff. The right pupil measured 6 mm., the left 4 mm. and neither reacted to light or on convergence; there was a complete right ophthalmoplegia. No other abnormal signs were elicited. CSF was xanthochromic and under a pressure of 180 mm.; it contained 155 RBC, 55 neutrophilic leucocytes and 295 lymphocytes/c.mm.; total protein 182 mg., and sugar 55 mg./100 cc.

On the 21st hospital-day there was definite improvement in that the patient was able to respond to simple questions. However, he remained confused and the
right ophthalmoplegia persisted. A second lumbar puncture, 1 week after the first, revealed xanthochromic fluid under a pressure of 105 mm. of water with 20 RBC and no WBC/c.mm.

Examination. Two weeks after the onset of headache the patient was still confused and disoriented. There was ptosis of the right eyelid and only very slight movement of the right eye. Movements of the left eye were probably normal though poor cooperation interfered with accurate testing. The right pupil was dilated and fixed to light (both directly and consensually) and on convergence; the left pupil now reacted normally. Vision was greatly reduced in the right eye and slightly impaired in the left but no accurate records of visual functions were obtained. Other cranial nerves were normal and there was no weakness, reflex change or sensory deficit of the limbs.

Course. The patient's condition remained poor and he died during the night of the 29th hospital-day.

Pathological Findings. A rounded mass of dark red tissue protruded from the sella turcica (Fig. 1). On cut surface it was dark red, very soft and without recognizable structure. The pituitary gland could not be identified as such. The mass had enlarged the sella to about thrice normal size and had elevated all of the clinoid processes. Lateral expansions of the mass had compressed both cavernous sinuses. The diaphragm of the sella had been destroyed and the tumor extended above the sella for a distance of 2.0 cm. Upon removal the mass was found to be spherical with a diameter of 4.0 cm.

The optic chiasm and hypothalamus had been displaced superiorly. The chiasm and right optic nerve were flattened and the latter was grooved by the overlying anterior cerebral artery. The optic tracts were not reduced in size. There were no other gross abnormalities of the brain.

Microscopic sections showed that the intrasellar tumor had undergone almost complete necrosis. In phloxine-methylene blue preparations only the faint outlines of some tumor-cells, stained a pale pink, could be seen (Fig. 2). The majority of these cells had disintegrated and most of the tissue had a homogeneous structureless appearance. Just inside the fibrous capsule of the mass, small compressed islands of recognizable pituitary cells remained; some of these cells were necrotic. The capsule and peripheral parts of the necrotic mass were impregnated with fibrin and infiltrated by neutrophilic leucocytes. In the capsule there were large numbers of proliferating fibroblasts, neutrophilic leucocytes, lymphocytes, plasma cells and macro-
phages. The capillaries and veins were unusually prominent owing to proliferation of adventitial and endothelial cells.

In the leptomeninges around the optic nerves and chiasm there were large numbers of lymphocytes, histiocytes, a few plasma cells and neutrophilic leucocytes. Similar cells were found in some of the perivascular spaces within the chiasm. Axis cylinders of nerve fibers within the chiasm and right optic nerve were reduced in number; of the remaining fibers, some were fragmented and others ended in bulbous enlargements. Within the chiasm and right optic nerve there were many hypertrophied astrocytes and scattered microglial cells of pleomorphic forms containing small droplets of fat. Many of the nerve cells of the tuberal nuclei and mammillary bodies had disappeared and numerous microglial phagocytes and plump astrocytes were present. The nerve cells of the right oculomotor nucleus were swollen, chromatolytic and had eccentric nuclei but the cells of other cranial nerve nuclei were normal. Throughout the cerebral cortex there was a very slight increase in the number and size of astrocytes.

Other important pathological findings were: a well differentiated adenocarcinoma of the colon which had not metastasized; congenital absence of the right adrenal and hypertrophy of the left one; pericholangitis with focal necrosis of the liver; and focal healed pyelonephritis. The thyroid and parathyroid glands and the testes were not examined.

Final Diagnoses: (1) Adenoma of pituitary body (? chromophobe) which had undergone recent infarct necrosis; compression of optic chiasm, right II, III, IV,
and VI cranial nerves and hypothalamus. (2) Adenocarcinoma of colon (without metastases).

Comment. There was no explanation of the infarction of the pituitary gland other than that it had outgrown its blood supply. There was not enough tumor-tissue left to permit identification by special stains. The cellular reaction in the capsule of the gland and in the adjacent leptomeninges, and the pleocytosis in the CSF were probably reactions to necrosis of tissue. The compression of the optic chiasm and the right optic nerve was a result of acute swelling of the tumor. The right optic nerve had been pushed against the overlying anterior cerebral artery. The ophthalmoplegia was due to compression of oculomotor nerves in the cavernous sinus. The stupor and coma may have been related to acute compression of the hypothalamus but alternative explanations include an impaired cerebral circulation, and some metabolic disorder associated with severe Addison's disease. The significance of the diffuse changes in the cerebral cortex is not known but they may be structural manifestations of a metabolic disturbance of brain function. The changes in the right oculomotor nucleus were secondary to damage of the allied nerve, that is to say, an axonal reaction.

Case 2. (NP 45–38) This patient, a 46-year-old man, died on the way to the hospital. The only available history was that for several days he had felt sick and had complained of severe headaches, and that a few hours before death he had become lethargic, stuporous and then comatose. The referring physician had detected no abnormality other than drowsiness.

Pathological Findings. Examination was limited to cranial structures. When the frontal lobes were elevated a considerable quantity of blood was found. It seemed to arise from the sella which was filled with dark hemorrhagic material, and it covered the floor of the 3rd ventricle, the optic nerves, chiasm and tracts, and the olfactory bulbs. A small amount of blood had also extended along the Sylvian fissures to the lateral surfaces of the cerebral hemispheres. The blood was largely confined to the subarachnoid spaces; it was of dark purplish-red color and had clotted. Just above and slightly to the right of the sella there was a soft, round, purplish-red mass of tissue about 1.5 cm. in diameter. This was connected by a thin stalk to the remains of the diaphragm of the sella. The cerebral and carotid arteries were intact and no source of the subarachnoid hemorrhage could be demonstrated.

A block of tissue including the sella turcica, cavernous sinuses and adjacent parts of the sphenoid bone was decalcified and sectioned in the coronal plane. The sella was found to be filled with necrotic cells none of which could be identified with certainty. In most places these cells were separated by red corpuscles and did not have the usual arrangement of normal cells of the pituitary gland. In a few places they were closely packed together forming broad sheets. There were a few islands of more normally arranged though necrotic pituitary cells just inside the capsule of the gland. The extrasellar mass had about the same composition as the intrasellar tissue. Structures within the cavernous sinuses appeared to be normal. In the subarachnoid spaces around the optic chiasm and floor of the 3rd ventricle there was relatively little reaction to the hemorrhage. Neutrophilic leucocytes and lymphocytes were found in numbers out of proportion to the number of red corpuscles, and a few macrophages containing red corpuscles were present. There were no significant
changes in the optic chiasm, orbital parts of the frontal lobes or hypothalamus.

**Final Diagnoses:** Neoplasm of pituitary body (? adenoma); extensive necrosis of tumor; intrasellar and subarachnoid hemorrhages.

**Comment.** At first it was thought that the subarachnoid hemorrhage was due to the rupture of a saccular aneurysm, but none was found. Moreover, the combination of intrasellar hemorrhage, extensive necrosis of the pituitary body and an attached extrasellar mass rendered this possibility untenable. Although the histology was poor owing to necrosis of tissue and to a loss of cellular detail incident to decalcification, it was quite apparent that both the intra- and suprasellar masses were neoplastic tissue. The sella was about 2.0 cm. in greatest diameter and the intrasellar portion of the tumor was only slightly larger than the extrasellar portion. Large parts of the tumor were necrotic and the hemorrhage seemed to have arisen from necrotic vessels within the neoplasm.

**Case 3.** (NP 46–27) This patient, a 64-year-old man, was brought to the hospital in a stuporous state after suddenly collapsing at home. He was said to have had episodic headache and mental confusion and a steadily increasing memory defect during the previous 3 years. No further history was available.

**Examination.** Temperature 100°F.; pulse 75; respirations 18, B.P. 100/76. The patient was stuporous and possibly aphasic. Both pupils were small and fixed to light. There was a right hemiparesis affecting the face, arm and leg. Tendon reflexes were active and about equal in the arms but they were unobtainable in the legs. Sensory functions could not be evaluated.

**Laboratory Data.** WBC 11,700 with a slight increase in proportion of neutrophilic leucocytes. CSF was under a pressure of 90 mm. of water and was blood-tinged with xanthochromia of the supernatant fluid.

**Course.** The mental state improved over a period of 2 weeks and although a considerable degree of confusion persisted, a partial aphasia, both motor and sensory, could be demonstrated. After 3 weeks' observation the patient was committed to a psychiatric hospital where, during succeeding months, there was little change in his condition; he remained apathetic, disoriented, hemiparetic and aphasic.

Five months later, while descending a stairway, he fell to the floor striking his head in the right parietal region. He was immediately comatose. The pupils were unequal and did not react to light. There was rigidity of the arms and legs, left more than right. Ankle clonus was obtained bilaterally; the right plantar reflex was extensor and the left was flexor. CSF was grossly bloody. Respiration became stertorous and irregular; temperature rose to 102°F.; signs of circulatory collapse supervened and the patient died 48 hours later without regaining consciousness.

**Pathological Findings.** There was hemorrhage beneath the skin and galea overlying a linear fracture in the right parietal and temporal bones. Small fresh epidural and subdural hemorrhages, not more than a few cc. in total volume, were found on the right side.

A mass of reddish, soft tissue protruded from a markedly enlarged sella turcica to compress the floor of the 3rd ventricle and extend into the left temporal lobe and lenticular nucleus (Fig. 3). At all points this mass was well demarcated, displacing but not invading brain, and it was surrounded by a thin capsule of connective tissue. The extrasellar part of the mass was of irregular shape, measuring 6.5 cm.
in greatest diameter. The tumor was soft and gray, and parts of it were hemorrhagic. The optic chiasm was displaced to the right and the left optic nerve and tract were almost completely destroyed. The left lateral ventricle was narrow but the right was about 3 times normal size. The 3rd and right lateral ventricles were displaced to the right.

Superficial contusions and small amounts of circumjacent subarachnoid and subpial hemorrhage were found on the inferior surface of the left temporal lobe.

The tumor was composed of small, closely packed cells which showed a slight tendency toward alveolar arrangement. These cells, 12 to 14μ in diameter, had round hyperchromatic nuclei and relatively little cytoplasm. There were no definite mitotic figures though some of the nuclei which were very dark may have been in a phase of mitosis. In some places the cells tended to be in groups demarcated by thin strands of connective tissue; elsewhere they were arranged in broad sheets. The stroma was scanty and there were only a few, thin-walled blood vessels. Large portions of the mass were necrotic; the cells though still visible were poorly stained, eosinophilic, and had shrunken nuclei (Fig. 4). In the hemorrhagic parts there were many well preserved red corpuscles and neutrophilic leucocytes. Numerous macrophages containing hemosiderin were found in one part of the mass. Mallory’s trichrome stain showed no granules in the cells. Because of the general morphology of the tissue and its apparent origin from within the sella it was assumed to be a pituitary adenoma probably of chromophobe type.

In sections of the contused temporal lobe there were areas of tissue necrosis with fresh hemorrhages, migration of neutrophilic leucocytes and shrunken pyknotic nerve and glial cells.

The only other postmortem findings of note were pulmonary congestion and oedema, and a lobular consolidation of the lower lobes of the lungs. Complete examination of the endocrine glands was not performed.

Final Diagnoses: (1) Tumor of pituitary body (? chromophobe adenoma) with extension to floor of the 3rd ventricle and left temporal lobe; hemorrhages, old and recent, and necrosis of tumor. (2) Fracture of temporal and parietal bones; epidural and subdural hemorrhages; cerebral contusions. (3) Pulmonary congestion and oedema; bronchopneumonia.

Comment. The dementia was probably related to the extension of the extrasellar tumor into the base of the brain. The abrupt occurrence of stupor,
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aphasia and right hemiparesis about 6 months before death may have been due to necrosis of parts of the tumor and to hemorrhage, both within the tumor and into the subarachnoid spaces. The fresh hemorrhage in the tumor may have been caused by the head-injury.

Case 4. (B.C.H. 1217174, NP 46-44) This patient, a 70-year-old man, entered the hospital for the first time in September, 1944, because of severe intermittent headaches of about 8 months' duration. He had also noted some loss of hearing and tinnitus in the left ear and had suffered one acute attack of vertigo. The only abnor-

Fig. 4. Case 3. Hematoxylin and eosin preparation (X 56) of a part of the mass in the temporal lobe showing islands of viable cells in the center and right upper corner, and extensive necrosis elsewhere.

mal signs noted at this time were inequality of the pupils (right larger than left), ptosis of right eyelid and diminution of hearing in left ear (nerve deafness). CSF pressure was 135 mm. of water; the fluid was acellular but its total protein was 78 mg./100 cc. X-rays of the skull showed marked thinning and elevation of the posterior clinoid processes and depression of the floor of the sella. The patient refused further investigation and left the hospital against the advice of his physician. His condition was said to have remained about the same until July, 1946 when, 2 days prior to re-entry, a sudden onset of severe headache was followed by nausea, vomiting and rapidly deepening stupor.

Examination. Temperature 107°F.; pulse 104; respirations 22 (Cheyne-Stokes); B.P. 80/50. The patient was silent and did not respond to spoken commands. If left undisturbed he lay motionless in bed unmindful of things going on about him. He would, however, withdraw his limbs from noxious stimuli. The neck was moder-
ately stiff. The eyes were turned toward the right; pupils were constricted and did not react to light. The limbs were limp and areflexic. Plantar responses were equivocal, probably extensor in type.

**Laboratory Data.** WBC 18,000/c.mm. with neutrophilic leucocytosis. CSF was under a pressure of 140 mm. of water; it contained 8,000 RBC and 93 WBC/c.mm.; total protein 83 mg./100 cc.

**Course.** The coma deepened. Temperature ranged between 106 and 107°F. despite vigorous treatment. Death occurred 6 hours after entry.

**Pathological Findings.** A mass of reddish-gray tissue about 2.8 cm. in diameter filled the sella turcica, extended up through the diaphragm and compressed the optic chiasm. A small amount of freshly clotted blood covered the posterior margin of the mass and occupied the adjacent subarachnoid spaces. There were small amounts of blood in the lateral and 3rd ventricles. Except for slight atherosclerosis of the large cerebral arteries, there was no other gross abnormality of the brain or of the other organs.

On microscopic examination large portions of the intrasellar tissue were seen to be necrotic and infiltrated with neutrophilic leucocytes. In the better preserved parts the cells were very close together and without special arrangement. Specific stains revealed no granules in the cytoplasm of the viable cells. The nuclei were round and quite darkly stained; there were no mitotic figures. Remnants of normal pituitary tissue were compressed into a narrow band just inside the gland's capsule. There was hemorrhage into some portions of the necrotic mass and into the adjacent meninges. The latter were infiltrated with neutrophilic leucocytes and lymphocytes.

**Final Diagnoses:** Adenoma of pituitary body (? chromophobe); compression of optic chiasm; necrosis of tumor; intrasellar and subarachnoid hemorrhages.

**Comment.** The factors leading to coma could not be reconstructed since the clinical data were limited and the autopsy was incomplete. Necrosis of and hemorrhage into the pituitary tumor were undoubtedly important. The visual fields were never examined and there was no mention of the optic discs at the time of the last examination.

**Case 5.** (NP 46–61) A 39-year-old housewife was first admitted to the hospital in September, 1946, with a chief complaint of headache. She was known to have had untreated diabetes during the previous 12 years. She had borne 7 children before the age of 26 years, at which time menstruation ceased and she became sterile. During the past 7 years there had been progressive coarsening of the features, deepening of the voice and steady increase in weight amounting to 20 pounds in the 6 months prior to entry. For 5 years she had been having moderately severe, intermittent headaches usually localized to the right supraorbital region. During the last year the fluid intake had increased to as much as 10 quarts daily. Three days before entry the headache became almost continuous, extremely severe and it was accompanied by diplopia. On the day of admission the patient swooned and was brought to the hospital.

**Examination.** The patient was an obese, lethargic, middle-aged woman with coarse features. The nose was broad and flat, the jaw prominent, the tongue large and the lips were thick. The fingers were short and stubby. There were no other abnormalities.
Laboratory Data. Fehling's test for sugar in the urine gave an olive-green color and acetone test was 4+. Fasting blood sugar was 410 mg. and blood-CO₂ combining-power was below 10 vol./100 cc. X-rays of the skull showed enlargement of the sella turcica.

Subsequent Course. The diabetic acidosis was treated with insulin and intravenous fluids. Within a few days the diabetes was controlled and the patient was discharged from the hospital on a regular dosage of insulin.

Three weeks later she was readmitted. Relatives said that she had been fairly well until a few hours before re-entry when she suddenly experienced a sharp pain in the right side of her face and then soon became disoriented and stuporous. Upon arrival at the hospital she was deeply comatose.

Temperature was 103°F.; pulse 80; B.P. 140/100. The right pupil measured 7 mm.; the left 3 mm.; neither reacted to light. The margins of both optic discs were blurred and there were small, round hemorrhages along the veins of both optic fundi. Plantar reflexes were extensor bilaterally. There was brick-red sugar reduction in the urine, fasting blood sugar of 345 mg. and blood-CO₂ combining-power of 39 vol./100 cc. Lumbar puncture yielded grossly bloody CSF which was xanthonochromic after centrifugation. Fluids and insulin were given but the patient died 3 hours after admission.

Pathological Findings. Examination was limited to cranial structures. A large mass of soft reddish tissue protruded from the sella turcica and was connected by thin pedicles to 2 large extrasellar masses of similar appearing tissue. One of the latter projected into the medial part of the right temporal lobe; the other, whose pedicle passed through the tentorial incisura, lay in the posterior fossa. The sella was much enlarged, its clinoid processes were thin and fragile, and its diaphragm was partially destroyed. The mass projecting into the temporal lobe was oval in shape and measured 5 cm. in greatest diameter. On cut surface it was dark red, soft, rather granular, and hemorrhagic in many places (Fig. 5). It covered the optic chiasm, elevating and displacing it to the left, and extended into the brain tissue between the tubercinerium and the medial part of the right temporal lobe. The right optic tract was severely compressed, being reduced to a thin ribbon of tissue. However, this mass was well demarcated from the brain by a thin investing capsule of connective tissue. In one place outside the capsule there was a hemorrhage which extended through the compressed brain into the temporal horn of the right lateral ventricle. The tumor in the posterior fossa was almost detached from the tumor above the tentorium. It was extremely soft, gray and measured 3 X 5 X 4.6 cm. It indented the
right anterolateral surface of the pons, the upper medulla and the middle cerebellar peduncle but it did not invade these structures. The midbrain was displaced to the left and there was a cerebellar pressure cone of moderate size.

The tumor was found to be composed of small cells about 12μ in diameter with relatively small amounts of clear cytoplasm and oval to round, rather heavily chromatinized nuclei. There was remarkable uniformity of cell type. No mitotic figures were seen. The stroma was scanty and relatively few blood vessels were found. Whereas large portions of the mass compressing the temporal lobe were necrotic, most of the mass in the posterior fossa was viable (Fig. 6). Extensive extravasation of red corpuscles was noted in many parts of the temporal lobe mass and in the circumjacent brain tissue, which was loose and fenestrated. In this region of the brain, nerve and glial cells were shrunken and pyknotic, and scattered neutrophilic leucocytes had migrated outside the blood vessels. The nerve cells in the mammillary bodies and those in the tuberal, ventromedial and supraoptic nuclei of the hypothalamus were compressed and darkly stained. There was no reaction to the blood in the subarachnoid spaces.

In Mallory trichrome preparations no granules could be seen but the histologic detail was poor in the parent, intrasellar portion of the tumor which had undergone extensive necrosis. Scattered cells of the anterior lobe were found just inside the capsule of the gland.

Final Diagnoses: Adenoma of pituitary body (? eosinophilic); extrasellar ex-
tensions compressing right temporal lobe, right optic tract, optic chiasm, pons and cerebellum; widespread necrosis of and hemorrhage into tumor; intraventricular hemorrhage; cerebellar pressure cone.

Comment. The diabetes mellitus, the premature menopause, the increase in weight, the deepening voice and the coarsening of features were parts of the acromegalic syndrome traceable to the adenoma of the pituitary body. The latter was presumably of eosinophilic type even though cytoplasmic granules could not be demonstrated in the viable (subtentorial) portion of the tumor. The terminal right-sided headache, coma and bloody CSF were results of hemorrhages into and necrosis of the tumor, hemorrhage into the ventricles, deformation of the midbrain, and cerebellar pressure cone.

DISCUSSION

A. Other Cases of Hemorrhage and Necrosis in Pituitary Adenomas

Extensive hemorrhage and necrosis in adenomas of the anterior lobe of the pituitary body are well documented pathological occurrences. There are, in all, 5 pathologically verified examples of such changes in the medical literature and at least 2 other cases in which the clinical facts are highly suggestive of the same lesions.

Bleibtreu4 in 1905 appears to have recorded the first example of these regressive changes. In the postmortem examination of a 21-year-old acromegalic patient he discovered that the pituitary gland had been replaced by a mass of orange-colored, amorphous material representing an old hemorrhage. Clinical data were not given.

A more interesting case is that presented by Kux10 in 1931. Here an eosinophilic adenoma had manifested itself by acromegaly and headache. While the patient was under observation there was a sudden onset of amblyopia, palsy of one of the internal rectus muscles and a drowsiness which quickly progressed to coma and, 2 days later, death. At autopsy a gross hemorrhage in a “fetal adenoma” of the pituitary gland was found. The hemorrhage had enlarged the tumor and had exerted pressure on structures in the cavernous sinuses and floor of the 3rd ventricle.

A similar case was reported by Dingley4 who in 1932 wrote of a patient with a chromophobe adenoma of the pituitary gland in which a large, fresh hemorrhage had evidently caused a sudden collapse with coma and death within a few hours.

In 1938, Voss13 described a 38-year-old man who had entered the hospital in a lethargic state with complete right ophthalmoplegia, a dilated, fixed left pupil, stiff neck and xanthochromic CSF. Autopsy disclosed a fresh hemorrhage into a chromophobe adenoma.

Coxon3 in 1943 reported a case in which there was a sudden onset of severe headache followed 24 hours later by diplopia and drowsiness. Death occurred 3 weeks later and a large hemorrhage was found in an eosinophilic adenoma. In this case the CSF was clear and acellular but the total protein was 170 mg./per 100 cc.
### TABLE 1

Reported cases of hemorrhagic necrosis of a pituitary adenoma

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age</th>
<th>Sex</th>
<th>Previous Symptoms</th>
<th>X-ray</th>
<th>Terminal Symptoms</th>
<th>CSF</th>
<th>Type of Adenoma</th>
<th>Other Pathologic Findings</th>
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<tr>
<td>4. Voss 1938</td>
<td>38</td>
<td>M</td>
<td>?</td>
<td>?</td>
<td>Semicoma; right ophthalmoplegia; dilated, fixed left pupil; stiff neck</td>
<td>Xanthochromic</td>
<td>Chromophobe</td>
<td>Fresh hemorrhage; compression right cavernous sinus &amp; hypothalamus</td>
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<tr>
<td>8. Brougham, Heusner &amp; Adams Case 1</td>
<td>65</td>
<td>M</td>
<td>Symptoms of adrenal insufficiency</td>
<td>?</td>
<td>Severe headache; semicoma; stiff neck; right ophthalmoplegia; impaired vision O.D.</td>
<td>Xanthochromia; 155 RBC; 350 WBC; T.P. 182</td>
<td>?</td>
<td>Necrosis of entire tumor; compression cavernous sinuses, 2nd nerve, chiasm &amp; hypothalamus</td>
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<tr>
<td>Case</td>
<td>Age</td>
<td>Sex</td>
<td>Diagnosis</td>
<td>Stigmata</td>
<td>Lab Tests</td>
<td>Histological Changes</td>
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<tr>
<td>10. Ibid. Case 3</td>
<td>64</td>
<td>M</td>
<td>Confusion; aphasia; headache; 1 episode of semicoma</td>
<td>Enlarged sella</td>
<td>Head-injury; comas; unequal pupils; left Babinski</td>
<td>Bloody</td>
<td>? chromophobe</td>
<td></td>
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<tr>
<td>11. Ibid. Case 4</td>
<td>70</td>
<td>M</td>
<td>Intermittent headaches, 5 months; unequal pupils; ptosis left lid; nerve deafness A.S.</td>
<td>Enlarged sella</td>
<td>Rapid development coma; stiff neck; constricted pupils; bilateral Babinski</td>
<td>8100 RBC; 93 WBC; T.P. 83</td>
<td>? chromophobe</td>
<td></td>
</tr>
<tr>
<td>12. Ibid. Case 5</td>
<td>39</td>
<td>F</td>
<td>Acromegaly; diabetes mellitus; headaches</td>
<td>?</td>
<td>Abrupt onset right facial pain; disoriented; stuporous; coma; unequal pupils</td>
<td>Very bloody; xanthochromic</td>
<td>? eosinophilic</td>
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<td>Hemorrhage &amp; necrosis in tumor; compression right temporal lobe, right optic tract &amp; chiasm; ventricular hemorrhage; cerebellar pressure cone</td>
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Other single cases almost surely of the same type, but without pathological verification, are those of Cairns and Jefferson. In each instance a patient believed to have an eosinophilic adenoma suffered the sudden onset of an ophthalmoplegia. Jefferson’s case was further marked by headache, drowsiness and sanguinous CSF. Spontaneous recovery was complete in both cases.

The cases of Van Wagenen, Dott, Bailey and Cushing and Sosman are more difficult to evaluate because extraneous factors complicate the picture. In Van Wagenen’s report of one of Cushing’s patients, a head-injury just prior to death may have caused or contributed to the formation of the hemorrhage in the pituitary tumor which was demonstrated at autopsy. In Dott, Bailey and Cushing’s case, 4 x-ray treatments had been given to an acromegalic woman immediately before the development of severe headache, temporal hemianopia in the left eye and stupor. Here the possibility of oedema and necrosis from roentgen therapy cannot be dismissed. Similarly, in Sosman’s case a single x-ray treatment was followed within a few hours by coma due apparently to a large fresh hemorrhage into a pituitary adenoma. It is of interest that in the latter 2 cases, operative removal of the hemorrhagic and necrotic tumor resulted in prompt recovery from the neurological symptoms.

There are still other references to operative and postmortem findings of liquefaction-necrosis and hemorrhage within pituitary adenomas, as for example in the writings of Kraus who regards such changes as not infrequent. In many of these cases the hemorrhages, which had the appearance of cysts filled with xanthochromic or brown fluid, were not of sufficient size to have produced neurological symptoms.

B. The Nature of the Pathological Process

A number of questions concerning these acute degenerative changes arise for discussion. (1) What is the essential nature of the lesions? What factors enter into their pathogenesis? (2) Are hemorrhage and necrosis separate pathological processes, or are both traceable to the same underlying circulatory disturbance, i.e., hemorrhagic infarction? (3) Do these changes occur more often in one type of tumor than another? Are they expressions of the degree of malignancy of the tumor?

From our pathological material it appears that both hemorrhage and necrosis are consequences of rapid growth of the tumor. Just as the glioblastomas and the brain metastases of some carcinomas, notably those of renal cell carcinoma and chorionepithelioma, often undergo hemorrhage and infarct necrosis, so with lesser frequency do these same changes occur in the larger and more rapidly growing pituitary adenomas. It seems probable that in most of our cases the tumor had merely outgrown its blood supply. However, in our Case 1 the necrosis was so complete that a swelling of the necrotic tissue within the confines of the sella may have led to compression of blood vessels and thus to further ischemia which involved all except the
subcapsular portion of the tumor. Thrombosed blood vessels were not demonstrated in our cases, but since the tumors were not sectioned serially this process may have been overlooked. Except in Case 3 there was no evidence suggesting that trauma or other extrinsic factors had been operative.

In some cases hemorrhage and necrosis coexisted but in others they occurred separately. It will be recalled that in our Case 1 there was necrosis of nearly all of the tumor but little or no hemorrhage. In our Case 2 a widespread necrosis of both intra- and extrasellar portions of the tumor was attended by extensive hemorrhage. In our Case 3 the recent brain injury made judgment of the original lesion uncertain. In our Case 4 necrosis and hemorrhage were both pronounced while in Case 5 hemorrhage was extensive whereas necrosis was relatively slight and limited to one of the extrasellar tumors. It is therefore our impression that these 2 processes are independent.

In our material and in the cases that have been collected from the literature, hemorrhage and necrosis occurred in both eosinophilic and chromophobe adenomas (Table 1). In view of the greater incidence of chromophobe adenomas it is perhaps noteworthy that these acute changes appear to have been found more frequently in eosinophilic tumors. There are no reports of these pathological changes having been found either in basophilic, or in verified fetal-cell or transitional-cell adenomas.

The relation of acute retrogressive changes to the possible malignant character of a hypophysial growth cannot be decided conclusively. The difficulty has been in the selection of satisfactory criteria of malignancy in pituitary adenomas, a topic that has been discussed at some length by Kraus. When judged as to degree of anaplasia of tumor-cells, infiltration of adjacent structures, and metastases to distant parts of the nervous system or to other viscera, it must be concluded that all the tumors here reported were probably benign. However, in 2 of the cases the necrosis of tissue was so extensive that it was impossible to estimate the degree of anaplasia.

C. Symptomatology

In all of our cases and in most of those reported by others, extensive hemorrhage and/or necrosis in a pituitary adenoma was attended by a fairly uniform symptomatology. Usually a patient who has had symptoms of a pituitary adenoma for months or years develops quite abruptly headache, amblyopia, diplopia, drowsiness, confusion or coma. The CSF is under normal or slightly increased pressure, is blood-tinged, xanthochromie or colorless, and contains an increased number of white blood cells and/or an elevated protein. With the development of coma the temperature usually rises and death often ensues within a few hours to days.

There are several variations of this syndrome that warrant further exposition. As regards mode of onset and speed of evolution, it should be pointed out that whereas the symptoms and signs are usually of sudden or acute development, within hours, in occasional cases additional changes appear after an interval of some days, as in Coxon's case where a unilateral
ophthalmoplegia occurred after a delay of several days. Also, the patient may either show clinical improvement as in our Case 1, or may recover as in the cases of Cairns and Jefferson.

An altered state of consciousness, occurring in all cases except that of Cairns, was the most frequent neurological abnormality. It consisted of drowsiness, mental confusion or stupor giving way to coma within hours to days. The explanation of these symptoms is not altogether clear. They develop much too quickly to be explicable by an endocrine disorder secondary to destruction of the pituitary gland. Subarachnoid and in some cases intraventricular hemorrhage are possible causes of coma but they were not operative in our Case 1, where there was little or no hemorrhage. In this case there was histologic evidence of compression of hypothalamic structures by the swollen tumor, and such compression may have been of importance in the production of stupor. Unfortunately, the hypothalamus was not systematically examined in our other cases.

Severe headache was another frequent symptom. Details concerning the location and character of the headaches were not provided by the clinical notes on our material. Headache may be due either to an acute swelling of the tumor, or to the meningeal irritation of subarachnoid hemorrhage. Stiff neck was usually present in cases marked by subarachnoid hemorrhage but in at least 1 of our patients this sign was found in the absence of such bleeding.

Diplopia and ophthalmoplegia were frequently observed. This varied from a complete ophthalmoplegia which was usually unilateral, to the palsy of a single muscle either unilaterally or bilaterally. The oculomotor nerve was involved more often than the abducens; data concerning the action of the trochlear nerves were not available. These cranial nerve palsies were caused not by tumor infiltration, but by compression of the nerves within the cavernous sinuses. The unilateral facial pain remarked in 1 of our cases was presumably due to irritation of the trigeminal nerve.

Dimness of vision was detected in only 2 of our cases. It was unilateral in both instances, and in 1 case it was traceable to upward displacement of the optic chiasm with compression of one optic nerve against the overlying anterior cerebral artery. The only other neurological abnormality of note was a right hemiparesis with aphasia which occurred in our case with tumorous compression of and hemorrhage into the left temporal lobe.

D. Diagnosis

Difficulties in diagnosis are to be expected particularly in cases that first come under observation after the supernation of coma. All of the frequent causes of coma must be considered and pituitary apoplexy will suggest itself only if there is a clear history of pre-existing symptoms of a pituitary adenoma, or if there are evident physical stigmata of endocrine disease, or if there is sellar deformity by x-ray examination. In those cases of known pituitary adenoma in which the patients become drowsy, stuporous or comatose,
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at least 3 other conditions incident to the growth of such tumors must be distinguished. They are: (1) An acute attack of adrenal insufficiency. (2) The development of a temporal lobe pressure cone caused by an extrasellar extension of tumor and/or hemorrhage into the compressed temporal lobe. (3) Convulsions.

It is well known that adrenal insufficiency may develop as a consequence of a pituitary adenoma. Not infrequently, as in our Case 1, the manifestations of Addison's disease are so indefinite as to escape notice or be misinterpreted. These patients often become drowsy, confused or comatose in the course of a few hours to days. The arterial hypotension and hypoglycemia which frequently accompany adrenal insufficiency may account for coma in some but not in all such cases. The syndrome of adrenal insufficiency can probably be distinguished from acute necrosis or hemorrhage in a pituitary adenoma by a more gradual onset of symptoms, by an absence of cranial nerve abnormalities, and by a normal CSF. The necessity of a careful assessment of the endocrine status prior to operation in those cases where pituitary apoplexy is quite certain requires no elaboration.

To differentiate between the syndrome caused by a massive extrasellar extension of a pituitary tumor with a secondary temporal lobe pressure cone, and that due to hemorrhage or necrosis in a pituitary adenoma may be difficult if not impossible. Coma, stiff neck and oculomotor palsy are common to both conditions. A temporal lobe pressure cone might be expected to occur only after embarrassment of the temporal lobe by the encroaching adenoma had announced itself by antecedent symptoms. Assuming, however, that evidence of a temporal lobe extension was at hand, it might be impossible to distinguish between these acute complications. Under such conditions lumbar puncture would be dangerous and perhaps indecisive. Prompt neurosurgical intervention would be justified in selected cases.

A convulsive state in cases in which there is an extension of the adenoma into a temporal lobe or the post-convulsive sequelae could conceivably be a source of difficulty in the differential diagnosis of the complications under discussion. A careful history of the illness, close observation of the patient and examination of the CSF should provide the necessary clues to the mechanism of symptom production.

E. Clinical Management and Prognosis

It is evident from cases here cited that in some instances the apoplectic insult will prove swiftly fatal. The outlook for patients surviving the initial impact of the illness will remain grave, and treatment at this critical juncture should be vigorously supportive. In addition to the application of conventional measures, special watch should be kept for the appearance of endocrine deficiencies for which replacement therapy is possible. Even under an adequate supportive regime some patients will fail to rally but others will reach a plateau of partial improvement from which some of them may be rescued.
The possibility of continued and eventually complete, spontaneous recovery must be given first consideration. That it may occasionally be realized is indicated by probable examples reported, one each, by Cairns and by Jefferson. It should, therefore, be stressed that as long as the clinical course moves in the direction of recovery, treatment should remain conservative. X-ray therapy should not be advised after pituitary apoplexy because radiation would be too apt to provoke additional acute degenerative changes. If the patient makes a full clinical recovery it is doubtful whether the risk of an operation undertaken to prevent recurrence of apoplectic attacks should be assumed.

Unfortunately, our pathological material suggests that few patients will make spontaneous improvement beyond a condition of partial and temporary betterment. An extensive though largely circumscribed extravasation of blood at the infundibular region, or a post-infarction swelling of the extrasellar portion of the adenoma would doubtless give rise, in most cases, either to paralytic effects upon adjacent parts of the brain, or to blockage of CSF pathways and progressive internal hydrocephalus. Operation would then become necessary not in any prophylactic sense, but for relief of chronic headache, hemiparesis, impending stupor, papilloedema or threatened optic atrophy. The principal objective would be that of evacuating necrotic and hemorrhagic material so as to remove the pressure from neural elements and/or the obstruction to the free flow of CSF. Admittedly, surgical attack upon an adenoma that has escaped from the confines of the sella is a formidable undertaking, but if due respect is paid both to the hypothalamus, and to the remnants of the hypophysis, the results of intervention may well be gratifying. Indeed, of 3 operations thus far reported as having been done for relief of apoplectic syndromes (Dott, Bailey and Cushing,\(^6\) Voss,\(^9\) Sosman\(^11\)), 2 were highly successful.

It is important to emphasize that if the acute symptoms here described overtake a patient who shows either the stigmata of acromegaly or those of pituitary insufficiency, the diagnosis of adenomatous apoplexy is tenable but only presumptive. In either instance the acute features of the illness might with equal plausibility be ascribed to the occurrence of a meningo-cerebral hemorrhage stemming, for example, from the rupture of a berry-aneurysm. Therefore, for the certainty of diagnosis which is requisite for operative treatment, intracranial vascular malformations should be excluded by angiography. This study might also provide valuable data regarding the suspected extrasellar extension of the pituitary lesion; it would not, however, obviate the need for pre-operative ventriculography. Use of the latter procedure has been urged by writers (Jefferson\(^6\), White\(^14\)) who have concerned themselves with the surgical treatment of the extrasellar adenomas that have not undergone acute degenerative changes. Similar indications for its use would obtain in planning operative exposures for the lesions under discussion.
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SUMMARY

The clinical and pathological findings in 5 cases of adenoma of the pituitary body are presented. The unique feature of these cases is that hemorrhage into and/or extensive necrosis of the adenoma was responsible for the sudden onset of a fairly uniform syndrome consisting of drowsiness, stupor or coma, headache and stiff neck, oculocutaneous and sometimes ambotropia or hemiparesis. Some abnormality of the CSF, usually blood or xanthochromia, though sometimes only slight pleocytosis or an elevated protein, was invariably present. These acute retrogressive changes are believed to be related to an excessively rapid growth of some pituitary adenomas. The necessity of correct diagnosis is emphasized. Several conditions that might prove troublesome in the differential diagnosis are discussed. These include crises of adrenal insufficiency, a temporal lobe pressure cone, and convulsive states. A program for the clinical management of cases of pituitary apoplexy is submitted.

REFERENCES