Histologic Changes in the Central Vegetative Centers of the Hypothalamus in Carcinoma as an Indication of Vegetative Functional Disturbances

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Alone and in collaboration with others I have made a histological study of the hypothalamus in approximately 200 human brains, from patients exhibiting a wide variety of clinical conditions.

A review of the pathologic changes occurring in chronic and acute psychoses, epilepsy, and mental deficiency, with a discussion of the possible meaning of these changes, was published in a recent paper (7); the changes of the hypothalamus in diabetes mellitus (8) and heat stroke (9) also have been recorded.

Our present knowledge—still far from complete—of the fiber connections and functions of the hypothalamus have been reviewed by Fulton (3), Masserman (6), Ingram (4), Ranson and Magoun (10), and others. Some of the functions that have been found to be influenced by the hypothalamus are temperature control; sleep; carbohydrate, fat, water, protein, and oxygen metabolism; and those of many viscera such as the cardiovascular, urinary, and digestive systems. There is much evidence to support the view that the nuclei of the hypothalamus influence the autonomic nervous system and the endocrine glands. Beattie, Brow, and Long (2), Fulton (3), and others have advanced the view that the anterior hypothalamus exerts its influence upon the parasympathetic, while Bard (1), Riech and Brenner (11), and others conclude that the posterior hypothalamus is concerned with the excitation and integration of sympathetic reactions.

The evidences available indicates that the cell groups of the hypothalamus cannot be considered as separate centers, each having a single specific function comparable to the lower centers distributed throughout the brain stem and spinal cord. In the hypothalamus many vegetative functions are brought under a central mechanism, coordinated and controlled for a broader purpose and in the interests of the total body economy.

The anterior and posterior hypothalamus each give rise to a fiber tract that descends to the mid-brain, medulla, and spinal cord. The supraoptic nucleus sends most of its fibers to the hypophysis, which receives some fibers from the posterior hypothalamus and from the paraventricular nucleus of the anterior hypothalamus also. The anterior hypothalamus exerts its influence chiefly upon the parasympathetic nervous system and the islands of Langerhans, the posterior hypothalamus chiefly through the sympathetic nervous system and the thyroid and suprarenal glands, while the hypophysis is under the influence of both regions. It is apparent, then, that the hypothalamus utilizes to a large extent the autonomic and endocrine systems in achieving its broad purpose of coordinating vegetative functions in the interest of the total organism.

Thus it seems likely that the nuclei of the hypothalamus—and, perhaps, other closely associated centers outside the anatomical limits of the hypothalamus—are normally in a state of physiological balance. If this be true then disease, injury, or dysfunction involving one or more of the nuclei would probably tend to throw the entire mechanism out of balance, so that the effects would be more far reaching than might be expected were the nucleus concerned with a single specific function.

It is obvious that hypothalamic dysfunction will exist whenever disease or injury attacks the region directly. It is also possible that disease, injury, or dysfunction in any part of the body, that tends to throw vegetative functions out of balance or to threaten the welfare of the total organism, may eventually involve the hypothalamus because the central mechanism will be called upon to attempt a restoration of normal function.

Because of these possibilities the striking histological abnormalities that occur in the hypothalamus of the cancer patient may be of considerable significance.

HISTOLOGY

According to Malone (5), who classifies the nuclei of the hypothalamus on the basis of cell type rather than topography, there are 5 distinct cell groups.
The nucleus tubero-mamillaris.—This is composed of large cells, slightly smaller than those of the supraopticus, which they somewhat resemble. They begin at the optic chiasm and extend past the oral half of the mammillary body, tending to group themselves around the medial, ventral, and lateral sides of the fornix. The cells increase in number toward the posterior end of the nucleus, and are most numerous at the oral end of the mammillary body (Fig. 1, A). The nucleus tuberis lateralis.—The cells of this nucleus are considerably smaller than those of the other third ventricle, extends through the entire length of the hypothalamus (Fig. 1, A), and is broadest posterior to the optic chiasm, where the cells spread laterally into the tuber cinereum and ventrally into the infundibulum.

The nucleus supraopticus.—This is composed of large, polygonal cells with very coarse processes. The Nissl substance is collected in large masses that are concentrated at the periphery of the cell, leaving a clearer area surrounding the nucleus.

This nucleus surrounds the beginning of the optic nuclei, with the exception of the substantia grisea. They have a relatively small nucleus with a large amount of cytoplasm, in which are seen minute, lightly staining Nissl bodies.

This nucleus consists of several groups of cells, more or less closely associated, embedded in the lateral or basilar portion of the tuber cinereum (Fig. 1, A). The more expanded part of the nucleus lies in the area ventromedial to the cerebral peduncle. These groups are so definitely circumscribed and so characteristic in appearance in the human brain that they are readily identified.

The substantia grisea.—The cells of this nucleus are smaller than those of any other cell group. There is considerable variation in their size, the smaller cells predominating close to the wall of the third ventricle. The cells possess relatively large nuclei, with a small amount of cytoplasm containing fairly large Nissl bodies.

This cell mass lies immediately adjacent to the tract (Fig. 1, B). A larger cell mass lying anterolateral, and a smaller mass lying posteromedial to the tract, are usually connected by a thin layer of cells.

The nucleus paraventricularis.—The cells of this nucleus are similar in appearance to those of the supraopticus, but vary considerably in size.

The cells are arranged in an elongated column with its long axis perpendicular to the base of the brain, and its lower end situated just in front of the supraopticus nucleus (Fig. 1, B).

MATERIAL AND METHODS

This study is based upon 19 brains of cancer patients who came to autopsy from the Cincinnati General and the Hamilton County Chronic Disease Hospitals. After fixation in formalin the diencephalon was embedded in celloidin, sectioned 35 microns in thickness, and stained by the modified iron-hematoxylin method described in previous reports.
Cell loss in the hypothalamic nuclei was evaluated by counting the cells in at least two microscopic fields within each nucleus, and comparing the number with that obtained in corresponding areas of 10 control brains that were apparently normal. The percentage of normal and chromatolytic cells was recorded in each instance.

**Abstracts of Clinical Cases**

**Case 1.**—W. M., colored, male, aged 52, with a strongly positive Wassermann. Postmortem examination disclosed a carcinoma of the lung with metastases to the right fronto-parietal lobe of the brain, liver, suprarenals, ribs, and epicardium. There was cystic degeneration of the pituitary.

**Case 2.**—J. R., white, male, aged 67. On postmortem examination there were noted multiple pulmonary abscesses and adenocarcinoma (suggestive of prostatic origin); adenomatous hyperplasia of the prostate; cerebral neoplasm (glioblastoma multiforme) surrounding an area of softening in the right frontal and parietal lobes.

**Case 3.**—F. S., colored, female, aged 62. Postmortem examination revealed a carcinoma at the junction of the pharynx and esophagus.

**Case 4.**—M. S., white, female, aged 38. Postmortem examination revealed a hypernephroma on the right side with extension to the suprarenal, and with metastases to the hilar lymph nodes, lungs, and liver.

**Case 5.**—W. B., colored, male, aged 65. Postmortem examination revealed a lymphosarcoma with metastases to the kidneys and extensive invasion of the left ureter and the left common iliac vein.

**Case 6.**—J. R., white, male, aged 78. Postmortem examination disclosed an adenocarcinoma of the stomach with necrosis; adenoma of the pituitary with degeneration; leiomyoma of the colon; lymphangioma of the intestine; extensive encephalomalacia.

**Case 7.**—S. E., white, male, aged 64. Postmortem examination showed adenocarcinoma of the pancreas with metastases to the pleura, lungs, and liver; an old area of softening in the right cuneate nucleus; generalized arteriosclerosis; and adenomatous hyperplasia of the prostate.

**Case 8.**—F. C., white, male, aged 48. Postmortem examination disclosed adenocarcinoma of the peritoneum, mesentery, and appendix, with acute fibrous peritonitis; recent active apical and hilar node tuberculosis; and low grade hepatic cholangitis with degeneration of the bile ducts.

**Case 9.**—A. W., white, male, aged 59. Postmortem examination showed an advanced adenocarcinoma of the stomach with metastases to the regional lymph nodes and the subcutaneous tissue near the umbilicus.

**Case 10.**—W. S., white, male, aged 57. At postmortem examination there were found an extensive gastric carcinoma with perforation and peritonitis; metastases to regional nodes, retroperitoneal nodes, pancreas, spleen, and lungs; and a meningioma involving the dorsolateral surface of the precentral, superior, and middle frontal convolutions of the right side.

**Case 11.**—E. B., white, female, aged 69. Postmortem examination revealed a carcinoma of the stomach and adenomatous hyperplasia of the thyroid.

**Case 12.**—M. Q., white, female, aged 74. Postmortem examination showed an epidermal carcinoma in the vagina and cervix with infiltration of the parametrium and a paraaortic abscess.

**Case 13.**—R. C., white, female, aged 61. Postmortem examination disclosed metastatic adenocarcinoma in the brain (scattered throughout the cortex and striatum), lungs, liver, spleen, suprarenals, and iliac lymph nodes—probably primary in the fundus of the uterus; papillary adenoma of the uterus; syphilitic aortitis; tertiary syphilitic cutaneous ulcerations of the leg; syphilitic cirrhosis of the liver.

**Case 14.**—E. K., white, female, aged 58. At the postmortem examination there were found a malignant tumor of the anterior mediastinum involving all the anterior mediastinal structures, with partial occlusion of the superior vena cava; undifferentiated carcinoma of the thyroid.

**Case 15.**—W. J., colored, male, aged 48. The postmortem examination revealed a scirrhous adenocarcinoma of the stomach with metastases to the mesenteric, pancreatic, perigastric, periaortic, superior mediastinal, and suprachlavicular lymph nodes.

**Case 16.**—M. C., white, female, aged 83. Postmortem examination showed a highly malignant anaplastic adenocarcinoma involving the pancreas, stomach, transverse colon, small intestine, kidneys, adrenals, ovary, mesentery, lung, and periaortic and peripancreatic lymph nodes.

**Case 17.**—F. M., colored, male, aged 45. Postmortem examination disclosed a carcinoma of the pancreas, with metastases to the liver and the mesenteric and prevertebral lymph nodes.

**Case 18.**—L. M., white, male, aged 63. The postmortem examination showed a scirrhous carcinoma of the right side of the pharynx, with metastases to the surrounding lymph nodes, right pleura, right lung, and liver.

**Case 19.**—S. W., colored, male, aged 59. Postmortem examination revealed an adenocarcinoma of the prostate; mural thrombosis and myocardial degeneration; left hydrothorax; massive pulmonary and cerebral edema; diffuse cortical atrophy; focal cerebral softening and cortical degeneration.
DISCUSSION OF FINDINGS

The study represents a miscellaneous collection of carcinomas of varied origin; some with extensive metastases, others with few or none.

In cases 1 and 13 there was metastasis to the brain, and in case 2 there was a glioblastoma. The involvement of the brain may have contributed to the cell changes in the hypothalamus. Case 5 was included because of a previous history of carcinoma of the prostate, although the terminal neoplasm was a lymphosarcoma.

The histologic alterations in the hypothalamus are illustrated in Fig. 2, where the cases are arbitrarily arranged in order according to the cell count in the nucleus tubero-mamillaris. This was done in order to show graphically to what extent, if any, the cell loss and chromatolysis in the various nuclei conformed to a uniform pattern. One hundred per cent represents average cell count found in the group of control brains.

The graph shows a striking variability of both the chromatolysis and cell count as we compare the degree of involvement of the five nuclei concerned. There is a slight tendency for the curve representing the cell count to ascend for the supraoptic and paraventricular nuclei as it does for the tubero-mamillaris. However, the exceptions to this rule are more numerous than the cases that conform. We can conclude only that the pattern of involvement of the nuclei of the hypothalamus in carcinoma is rather variable.

There is a striking number of instances in which the cell count is considerably above normal. This is true particularly of the nucleus tubero-mamillaris, and to a lesser degree of the nuclei supraopticus, tuberis lateralis, and paraventricularis. In 12 cases the cell count for the nucleus tubero-mamillaris ranged from

![Graph showing cell count and percentage of chromatolytic cells in hypothalamic nuclei in 19 cases of carcinoma. 100 per cent represents average cell count in a series of 10 control brains.](attachment:graph.png)
8 to 74 per cent above normal. The average cell count for this group was 29.4 per cent above normal. To check the significance of this deviation a second group of 15 brains, showing no obvious abnormalities in the hypothalamus, was studied. This second group showed an average cell count of 103 per cent, as compared with the original 10 control cases.

The only condition noted in the hypothalamus of cancer patients that would suggest a congenital anomaly was this tendency toward overdevelopment in some of the nuclei. Considering the widespread cell destruction that occurs in carcinoma this overdevelopment was probably more pronounced originally than was apparent at the time of death.

A study of the hypothalamus in approximately 200 cases suggests that a considerable amount of chromatolyis in the hypothalamic nuclei indicates the presence of a disease in which these nuclei are involved. In cases free from such disorders we find an average of not more than 6 to 8 per cent of chromatolytic cells in the nuclei tubero-mamillaris, substantia grisea, supraopticus, and paraventricularis. In various combinations of control groups 15 per cent of chromatolytic cells are commonly found in the nucleus tuberis lateralis.

In the patients suffering from carcinoma the average proportion of chromatolytic cells was 62.6 per cent for the nucleus tubero-mamillaris; 57 per cent for the nucleus tuberis lateralis; 36.7 per cent for the substantia grisea; 56.5 per cent for the nucleus supraopticus; and 55.8 per cent for the nucleus paraventricularis. This indicates that in carcinoma there is extensive involvement of all the nuclei of the hypothalamus.

In the material studied there was also evidence of widespread cell destruction in the hypothalamus. The tendency for some of the cases to have more than the normal number of cells in 4 of the nuclei made it difficult to estimate accurately the amount of cell destruction that had occurred. This factor, however, makes it probable that the amount of cell loss was greater than is shown by the cell count.

There was no apparent relationship between the origin or site of the tumor and the degree or pattern of hypothalamic involvement. The case histories in most instances did not permit a reliable estimate of the duration or the speed of growth and metastasis of the neoplasm. It is of interest to note, however, that in 5 of the cases, 4, 7, 13, 16, and 18, showing the most extensive metastasis the cell count for 4 of the hypothalamic nuclei was considerably higher than the average for the remainder of the group. The average count for the group with extensive metastasis was 122 per cent for the tubero-mamillaris; 85 per cent for the tuberis lateralis; 105.8 per cent for the supraopticus; and 85.2 per cent for the paraventricularis. For the remaining cases the average cell counts for the corresponding nuclei were 109.3, 75.8, 78.6, and 63 per cent.

It seems possible that the high count associated with pronounced chromatolysis may represent a state of hyperexcitability, and hence perhaps of hyperfunction, in these nuclei. We cannot exclude the possibility, however, that the greater amount of cell loss associated with the less malignant carcinomas may be due to the longer period of time during which the disease was active.

A striking feature of this study is that in carcinoma all 5 of the cell groups were found to be involved. As these are commonly thought to compose a central control and integrating mechanism for many, if not all, vegetative functions the involvement of all in carcinoma might well influence virtually every vegetative function, including the autonomic, endocrine, and metabolic.

The extensive studies carried out by many investigators on a wide variety of vegetative functions in both experimental cancer and in cancer patients have been reviewed by Stern and Willheim (12). On the whole they suggest abnormalities in oxygen metabolism; respiratory quotient; potassium:calcium ratio; and carbohydrate, protein, fat, and water metabolism. Virtually all the endocrine glands have been suspected by various investigators of playing a role in neoplastic growth and several, but not all, regard these functional deviations as systemic in character rather than confined to the tumor proper.

A survey of these functional studies seems to justify these general conclusions. (a) Widespread deviations in vegetative function occur in experimental animals and in patients afflicted with cancer. (b) These abnormalities are usually not of sufficient magnitude to make it certain that the deviation of any one function is of primary importance. (c) The deviations are subject to wide variation; they do not conform to a uniform pattern.

These conclusions are supported by the fact that in carcinoma there is an extensive but variable involvement of the central mechanism in the brain for the control and integration of vegetative functions. The present study does not enable us to say whether these cell changes in the hypothalamus are primary or secondary in nature.

The present study suggests the need for further research along certain lines. Most functional studies have been concerned with a single function in a large series of animals or patients, a type of study that is of fundamental importance and that has produced much valuable knowledge. However, it should be supplemented by an attempt to evaluate as far as possible the total complex of vegetative functions in the same indi-
individual or group, since such an approach should help to evaluate the reaction of the total organism to cancer.

If a postmortem study of the hypothalamus could be repeated on a group of patients in which a more complete series of functional tests had been made it might lead to a better understanding of the relationship of the hypothalamus to the functional disorders occurring in cancer.

It would be of interest to make a comparative study of the hypothalamus in high tumor and low tumor strains of animals. This should indicate whether there is any congenital anomaly or histological alteration in the high tumor strain that might be considered as predisposing toward malignant growth. If the hypothalamus is involved in tumor-bearing animals, a study of the cell changes through the successive stages of tumor development might indicate whether these changes are primary or secondary.

**SUMMARY**

A histologic study was made of 5 nuclei of the hypothalamus in 19 patients with proved carcinoma.

Extensive chromatolysis and cell destruction indicated that all these cell groups are involved in carcinoma. The pattern of these changes showed a wide range of variation.

A congenital overdevelopment of some of the nuclei was indicated, but the cell destruction that occurs in carcinoma made it impossible to evaluate this factor properly.

The 5 nuclei studied are regarded as constituting a central mechanism for the control and integration of vegetative functions. This control is mediated largely through the autonomic and endocrine systems and influences most, if not all, metabolic functions.

The cell changes in the hypothalamus suggest a widespread but variable instability or irregularity of vegetative functions in the patient with carcinoma. This is in keeping with the findings of numerous investigators who have made functional studies in animals or human patients with cancer.

**REFERENCES**

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