THE CASE FOR BRANCHIOGENIC CANCER (MALIGNANT BRANCHIOMA)*

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"If there is one pit-fall in science more dangerous than another it is that of regarding hypotheses as proven facts."—William H. Welch.

THE THEORETICAL CLINICO-PATHOLOGIC ENTITY known as malignant branchioma is somewhat unique in the field of oncology for the reason that in the final analysis its chief distinguishing characteristics are negative rather than positive. The main basis for the belief in the existence of such an entity rests solely on the fact that offhand there is no other more reasonable explanation for the histogenesis of certain cervical tumors. In this report the evidence both for and against the existence of such a specific tumor as branchiogenic cancer will be presented and analyzed.

In 1940, when we began the review of the clinical material in preparation for this study, we held the commonly accepted view that such an entity existed, although we realized, as many others, that the diagnosis of branchiogenic cancer is too often and too loosely made. This paper has been re-written a number of times as the clinical material and the general subject has been more critically reviewed, and the longer we consider the proposition the less confidence we have in the existence of an entity which warrants the specific name "branchiogenic cancer." In any event, it is our opinion that the case for branchiogenic cancer is far from being conclusively established. As will be discussed in more detail later, the only absolute proof of the existence of a specific tumor such as branchiogenic cancer would be the histologic demonstration of cancer arising in the wall of a branchiogenic cyst; so far as is known, no well-documented case of this kind has ever been recorded.

REVIEW OF THE LITERATURE

Von Volkmann, in 1882, was the first to suggest that some cervical cancerous tumors might arise in the vestigia of branchial clefts.[24] He postulated such an origin after observing three patients with carcinomatous masses in the upper neck in whom he could discover no other primary lesion after direct visual and digital examination of the oral cavity and pharynx. At that time the laryngeal mirror, developed by Czermak in 1858, had not come into common

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use. Von Volkmann's discussion, based upon three short term case observations, was entirely theoretical; it is hardly correct, therefore, to credit him, as has been done, with having *shown* that certain cervical carcinomas are of branchiogenic origin.

In the progressive development of medical science there is a natural, though often erroneous, tendency to assume that a given disease originates at the site where symptoms first appear. Such a fallacious concept, as regards malignant tumors of the neck, is exemplified in John C. Warren's *Surgical Observations of Tumors* published in 1837. In this monograph[25] several operative cases are reported which are classified as "malignant scirrhous of the lymph glands of the neck" and "fungoides of the neck." Warren plainly implies that these tumors arose in the "glands" but in the light of present-day knowledge, their actual character can be suspected from the fact that in some of the cases he reported the growths eventually were found to extend to the "parietes of the pharynx." Such "extensions" of the tumor to the pharynx were undoubtedly the sites of the primary growths. Fifty-three years later (in 1935) Crile & Kearns[5] arrived, by the same illogical reasoning, at the same dubious conclusions when they reported 28 cases of alleged branchiogenic cancer, none of which survived five years, and when they mentioned a case of their own which was first diagnosed as cancer of the larynx but "proved" at autopsy to be of branchiogenic origin, "invading the pyriform sinus."

Following Von Volkmann's original report the subject of branchiogenic cancer was not often mentioned in the medical literature but the tumor appears to have been generally accepted as being specific. In 1900 Nicholas Senn,[20] who wrote rather extensively on neoplastic diseases in general, apparently considered branchiogenic cancer of little significance, since he mentions no other growth except "chondroma branchiogenes" as arising in vestigial branchial clefts or branchial cysts. James Ewing,[6] in 1919, although admitting that there was no specific histologic pattern characteristic of branchiogenic cancer, nevertheless appeared to accept Von Volkmann's theories. Curiously enough, however, Ewing, in his discussion of the subject, mentions difficulty in swallowing as one of the early symptoms, which suggests to us that in the cases he had discussed there were probably undetected pharyngeal primaries.

Almost from the beginning there have been some skeptics who questioned the existence of such an entity. In 1893, John Bland Sutton[21] commented:

"One of the facts connected with epithelioma of the mucous membrane of the mouth —and it matters little whether the disease begins on the tongue, cheek, hard or soft palate, or gums—is the extraordinary size which the infected lymph glands in the neck sometimes attain, whilst the ulcer scarcely exceeds 1 cm. in diameter. This is worth bearing in mind, because an enlargement of the cervical lymph glands in individuals past middle age should always induce the surgeon to examine the various recesses of the mouth and fauces for small, inconspicuous epitheliomatous ulcers, and with every care they sometimes escape detection during life. It is necessary to emphasize this, because a good deal has been written about "branchiogenous cancer," or, as it is sometimes called, "malignant cyst" of the neck. The tumor is most commonly observed after the age of 50, and is

deeply seated in the neck, usually near the fork of the carotid; it grows with great rapidity, and in many cases softens in the center and gives rise to fluctuation. The overlying skin becomes brawny and red, and the resemblance to an abscess is so striking that, in several cases, I have known a knife to be used under this impression. Gradually the implicated skin sloughs, and then an epitheliomatous chasm forms in the neck. Microscopically the tissue of these tumors is characteristic of epithelioma. Some writers are of opinion that these are primary epitheliomata, arising in remnants of branchial clefts. My belief is that, in most of the cases, these gland masses are secondary to epitheliomata originating in recesses of the pharynx or naso-pharynx, and the theory that they arise in remnants of branchial clefts is pure fiction."

Willis,[27] in 1934, is distinctly skeptical when he states that branchiogenic cancer should be "tolerated neither as a clinical diagnosis nor as a histologic finding on surgical material." Many authors in discussing branchiogenic cancer call attention to the possibility of silent primary lesions in the mouth and pharynx and emphasize the necessity for careful examination in these areas. A few mention the desirability of a five-year follow-up but, nevertheless, accept Von Volkmann's theory of branchiogenic origin of some cervical cancers and in their own cases appear willing to make such a diagnosis on minimal evidence.[3, 4, 8, 13, 15-17, 19, 22]

In a survey of the medical literature on malignant branchioma we have found between 225 and 250 cases reported by 34 authors. The indefiniteness of this total is due to the vagueness and uncertainty of the authors in some of the reports. Of this total number of alleged cases it is not possible to accept more than three as presenting reasonable evidence of branchiogenic origin, as judged by the diagnostic criteria employed in the Head and Neck Clinic at the Memorial Hospital. These three cases (all five-year survivals after surgical excision of cervical carcinomas) are contained in a report of 80 alleged cases by Oliver.[16] In the remaining 77 cases of Oliver's series the only evidence of branchioma was the failure to find a primary lesion during a short period of observation, before the patient was lost to follow-up or up to the time of death. No author except Oliver reports five-year survivals in alleged cases of branchioma, and it is certainly significant that in 96 per cent (77 cases) in Oliver's series there were no five-year survivals. In Oliver's report most of the cases are from the Laboratory of Surgical Pathology at the Johns Hopkins University and the patients were not personally observed. Many of them were reported as having died within two to three months after radical excision (neck dissection). The cause of death was not stated and even the question of recurrences was not discussed. It seems likely that many of these cases did die of undetected primary lesions elsewhere.

DEFINITION

The term, *branchiogenic cancer* refers to those malignant tumors which are believed to arise in vestigial remnants of branchial pouches (Lat. *branchia;* Gr. *Branchio* = gills). Most of the growths considered under this heading are epithelial in character, and therefore the designation *branchiogenic carcinoma* is frequently used as an all-inclusive term. Theoretically, connective tissue

growths could also arise in vestigial branchial remnants, so that the term *malignant branchioma* would be more specific.

In order to consider even the tentative diagnosis of branchiogenic cancer in a given case it is necessary to assume that the cervical tumor arose primarily in the neck. As will later be discussed in more detail, there are no histologic criteria which would serve to differentiate metastatic cancer from that arising in branchiogenic vestigia. Any clinical opinion that a given tumor originates primarily in the neck or in a branchial remnant must rest entirely upon the assumption that there is no other primary lesion elsewhere. Experience on the Head and Neck Service at the Memorial Hospital has shown that frequently cervical metastasis is the first, and for a long time the only symptom of silent or cryptic cancer in the upper respiratory and upper alimentary tracts. We have, therefore, established the following criteria to fulfill the requirements for even a tentative clinical diagnosis of branchiogenic cancer.

MEMORIAL HOSPITAL CRITERIA FOR THE TENTATIVE DIAGNOSIS OF BRANCHIOGENIC CANCER

1. The cervical tumor must have occurred somewhere along a line extending from a point just anterior to the tragus of the ear, downward along the anterior border of the sternomastoid muscle to the clavicle.

2. The histologic appearance of the growth must be consistent with an origin from tissue known to be present in branchial vestigia.

3. The patient must have survived and have been followed by periodic examinations for at least five years without the development of any other lesion which could possibly have been the primary tumor.

4. The best criterion of all would be the histologic demonstration of a cancer developing in the wall of an epithelial-lined cyst situated in the lateral aspect of the neck.

We have searched diligently over a period of several years to find a case in which cancer could be demonstrated to arise in the wall of an epithelial-lined cyst in the neck. A few years ago one of us studied 63 cases of branchiogenic cyst observed on the Head and Neck Service at the Memorial Hospital. The cysts had all been excised and examined histologically. In this group there were found three cases in which the question of malignant transformation arose at first, but more careful study of the tissue sections failed to disclose the necessary evidence in a single instance. Recently, there have come to our attention two other cases of cervical cysts in which the first histologic examination of the surgical specimen appeared to reveal both cancer and a benign cyst wall. After more careful study, however, it was the final opinion of the pathologist that such histologic evidence of cancer arising in a benign cyst wall was not present.

If cancer can arise in vestigial branchial remnants, then logically it could arise also in vestigia of thyroglossal ducts. Thyroglossal cysts are fairly common and are always found in the midline of the neck at about the level of the hyoid bone. Nevertheless, we have never observed cancer of epithelial origin arising at this site. In our opinion this observation in itself throws at least some

doubt upon the validity of the theory of branchiogenic cancer. In this connection, it might be mentioned that cases of thyroid carcinoma arising from the thyroid tissue in thyroglossal cysts and tracts have been reported (but not epidermoid carcinoma).

The experience on the Head and Neck Service at the Memorial Hospital as regards the clinical course and morbid anatomy of head and neck cancer in general has impelled the application of the rigid standards itemized above before even the tentative diagnosis of branchiogenic cancer can be considered. *We have followed too many cases in which cancer appeared first and apparently only in the neck, and in which a silent cryptic primary lesion elsewhere in the body became evident only after an extended interval up to four years, to permit us to accept the diagnosis of branchiogenic cancer under any other standards.* If these criteria are accepted, then there follows apparently the paradox that a patient cannot die of branchiogenic cancer within a five-year period. It is plain, however, that should such an entity exist, many patients would die of the disease within five years unless the growth were controlled.

Examples of typical cases in which a diagnosis of branchiogenic cancer might be made erroneously or on scant evidence are given below.

CASE REPORT

M. T., a physician, age 30, was seen first in September, 1945. He stated that 11 months previously (October, 1944) he had noted an enlarged "gland" in his left neck. At the time, he was interning in a large metropolitan hospital and for the succeeding period of 11 months consulted several members of the attending staff, receiving a variety of opinions; no biopsy was made, however, and no treatment was advised.

Physical Examination. At the first examination (September, 1945) a smooth, ovoid, moderately firm, non-tender, movable mass about 5 cm. in diameter was found lying under the anterior edge of the left sternomastoid muscle at about the level of the bifurcation of the carotid artery. Repeated examinations of the oral cavity, nasopharynx, hypopharynx and larynx and a general physical examination revealed no evidence of a primary lesion. Roentgenograms of the chest were negative. An aspiration biopsy of the cervical mass was made and the pathologic diagnosis was "metastatic epidermoid carcinoma." The pathologist suggested the nasopharynx as the most likely site of the primary lesion and the lung as the second most likely site.

After repeated examinations of the nasopharynx, a specimen was removed from a slightly raised area on the posterior nasopharyngeal wall which originally had been considered to be a normal anatomic variant. The histologic report of the biopsy was "normal pharyngeal tonsillar tissue." The findings in the nasopharynx were considered to be so indefinite that no further biopsy was attempted. In the face of negative findings for a primary lesion, treatment by radiation therapy was instituted to the cervical mass while the search for the primary lesion was continued. Over a period of 3 weeks the tumor received a total of 7000 r in divided doses with the following factors: 250 kv, 1½ mm. cu. filter, 50 cm. TSD, a single 6 cm. circular port; a total of 25 mc. of gold radon seeds were implanted through the skin into the tumor in 3 divided doses. The cervical mass regressed over a period of 6 weeks and has not recurred locally.

During the next 2 years a search for the primary lesion was continued and at each monthly follow-up visit the oral cavity, nasopharynx, and hypopharynx were examined thoroughly for a primary lesion. A total of 22 such negative examinations are recorded on the patient's clinical record. After a period of 2 years of apparent freedom from disease, the patient failed to keep his appointments and in response to inquiries replied by

letter that he had entered the practice of medicine and was too busy to take time out for further follow-up examination.

After an absence of about 1 year (4 years following the onset of symptoms and 3 years following treatment of the cervical mass) the patient re-appeared, stating that the main reason for failure to return for follow-up was that it depressed him to be examined regularly for what he knew had been cancer. About 6 weeks previously, in October, 1948, he had noted an enlargement of the lymph nodes in the right neck, impaired hearing in the right ear (4 weeks' duration) and some obstruction in the left side of the nose with recurrent nosebleeds (2 weeks' duration). Re-examination revealed the left nasal cavity to be blocked by a large necrotic mass, and on mirror examination a bulky tumor was found in the left nasopharynx, occluding the choana. A mass 2½ cm. in diameter was found under the anterior edge of the sternomastoid muscle in the upper right neck. A biopsy of the nasopharyngeal tumor was made and a report returned of "epidermoid carcinoma."

The site of the original tumor in the left neck was free of palpable disease. Treatment was again instituted by radiation therapy and there was prompt regression of both the nasopharyngeal and cervical tumors. About one year later the patient developed generalized metastases.

Comment. This clinical report illustrates several important features to be kept in mind when considering a diagnosis of branchiogenic carcinoma. This case would have been accepted for a period of four years by many as one of branchiogenic cancer on the following basis: (1) a proved carcinomatous cervical tumor appearing in 1944 without evidence of any other primary lesion after 22 thorough examinations of the mouth and pharynx; (2) the patient remaining well without recurrence of cancer elsewhere for about four years following treatment of the cervical tumor. Then, as a final denouement, there appeared four years later a previously undetected growth in the nasopharynx. Only three of the reported cases of so-called branchiogenic carcinoma in the literature have presented such presumptive evidence for a period as long as four years.[16] Nevertheless, the case reported above finally proved to be one of the common varieties of pharyngeal cancer in which cervical metastasis characteristically appears as the first symptom and in which the primary lesion remains silent (cervical metastasis appears as the first symptom in over 50 per cent of cases of cancer of the nasopharynx). It is particularly significant that the nasopharynx was suspected all along as the site of the primary lesion despite the fact that 22 examinations at monthly intervals for a period of two years failed to reveal it. This case report also illustrates the lack of justification for accepting the opinion of any examiner on a single or even multiple examinations as reliable proof of the absence of a primary lesion.*

* Typical but by no means unique examples of unwarranted case reports of branchiogenic carcinoma are the following:

Lillie, Cox, and Teufel[10] report the case of a man, aged 55, with an "indurated ulcer of the lower lip" and a "hard, tender gland" in the left submaxillary region. Both lesions were excised and examined histologically. The ulcer of the lip was diagnosed as "epithelioma, grade I," and the submaxillary tumor as "malignant cyst, grade III." A few months later a second "malignant cyst" was removed from the right submaxillary region. Two and one half years later, a third "cyst" was removed from the submental region; the latter was also found to be a "malignant cyst." The authors disregard the fact that the clinical history was typical of cancer of the lip with cervical metastases. Attaching great

THE EMBRYONAL BRANCHIAL APPARATUS: DEVELOPMENTAL ANATOMY

The theory that lateral cervical cysts and fistulas may be related to some abnormality in the development of the branchial arches and pouches during embryologic life was first advanced by Acherson[2] in 1832. Since then, this basic hypothesis has received wide acceptance, although there have been some differences of opinion as to the precise details of the mechanism by which such abnormalities occur.

It is generally agreed by authorities in this specialized field of anatomy that there are four branchial pouches, separated by five branchial arches which develop through a combined interplay of ectoderm and entoderm. On the other hand, Wenglowski,[26] a Russian embryologist of considerable competence, believes that there are actually five and that the fifth groove in the arch gives rise to the thymus gland. From the entodermal primitive pharynx, four outpouchings develop and advance toward four corresponding invaginations of the ectodermal precursor to the skin of the neck. This advance may progress until confluency of the two pouches occurs, but it usually stops short of this stage and regression sets in without continuity ever being established. The lining of all of these pouches consists of squamous epithelium. As the pharyngeal component advances, it may carry with it aggregates of lymphoid tissue (of the tonsillar type and lacking the peripheral sinuses of lymph nodes), mucous-secreting glands, and bits of smooth muscle. This series of events is usually first recognizable embryologically during the latter part of the first month of intrauterine life and regression is well under way by the middle of the second month. In human beings, then, the process is of short duration and is usually complete within a month of its recognizable onset.

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significance to the difference in grading of the tumors of the lip and neck, respectively, as reported by the pathologist, the authors conclude that the cervical tumors were "multiple branchiogenic carcinomas" arising in the second branchial and the "mesobranchial" (*sic*) clefts, respectively, in a patient with cancer of the lip.

A second example of an unwarranted diagnosis of branchiogenic carcinoma with an even more ingenious explanation is that of Vokoun.[23] He reports the case of a woman, age 44, who sought medical advice because of dysphagia of four months' duration. He states that a diagnosis of "tuberculosis of the larynx" had previously been made for the reason that "the larynx had a peculiar pallor of the roof—a condition many nose and throat men consider tuberculous." The author states that "under the right mandible, deep in the neck, was a tender, firm, fixed mass the size of an olive, directly beneath the angle of the jaw." A roentgenographic examination was made with the patient swallowing a barium mixture and "with considerable difficulty, she managed to force some of the mixture past the esophagus, which showed a constriction opposite the area of the tumor in the neck." After a preliminary gastrostomy, the cervical mass (the size of an olive) was surgically exposed and a specimen was removed for biopsy. The histologic examination revealed "sections of tumor tissue, embryonal in form, highly malignant in character."

Although the history and clinical setting were typical of cancer of the hypopharynx and upper end of the esophagus with cervical metastasis, and despite the fact that a cervical tumor "the size of an olive" could hardly by itself have caused dysphagia of four months' duration, nevertheless the author concludes that this was a "carcinoma arising from an epithelial rest in an obliterated (*sic*) branchial cleft."

Arey[1] considers the first branchial pouch as the precursor of the external auditory and auricular concha and the second pouch as the antecedent of the tonsillar fossa; the third and fourth grooves contribute to the development of the thymus and parathyroid glands. Wenglowski agrees as far as the development of the first and second clefts are concerned; however, he distinguishes an anlage—which he calls the pharyngo-thymic duct—derived from the third and fourth pouches. This anlage is supposed to contribute to the development of the thymus and parathyroid glands and the lateral lobes of the thyroid gland. The fate of the fifth groove (ultimo-branchial body) remains controversial and attempts definitely to assign each individual case of branchiogenic cyst to an origin from a specific embryonic pouch are also likely to be challenged. In summary, an analysis of the accumulated evidence indicates that the second branchial groove is probably the origin of most branchial lesions that present in the neck.

In any case, branchiogenic cysts and branchiogenic cancer can theoretically arise anywhere between the level of the zygoma and the clavicle. The most common site of branchial cysts is at the level of the hyoid bone (third and fourth clefts).*

PATHOLOGY

Most experienced pathologists agree that there are no gross or microscopic features which could possibly differentiate cancer of metastatic and of branchiogenic origin, respectively. For this reason, a diagnosis of malignant branchioma is never even suggested by the Department of Pathology in Memorial Hospital.

In the present series, surgical specimens were available in five cases, and in these the tumors varied in size from 3.5 to 6 cm. in diameter. All were solitary tumors of smooth contour and firm consistency. In brief, no one specimen could be differentiated grossly from metastatic cervical cancer.

Histology. The diagnosis of cancer was proved in the 15 cases herein reported by means of aspiration biopsy in three cases, by incisional biopsy in

* It is curious that although the branchial apparatus in the embryo is situated along a line from the zygoma to the clavicle, nevertheless branchiogenic cysts are almost always found at the level of the carotid bifurcation. Any cyst in the lateral aspect of the neck above or below this level should be viewed with suspicion as regards its branchiogenic origin. In two cases recently observed by us there were cysts just above the middle of the clavicle, both proved by aspiration to contain clear straw-colored fluid. Both were diagnosed clinically as of branchiogenic origin and at operation from the standpoint of surgical anatomy were thought to be branchiogenic cysts. Nevertheless, histologic examination of the excised specimens showed small areas of papillary adenocarcinoma, thyroid type. With this discovery the diagnosis was changed to thyroid cancer (cryptic primary) with cervical metastasis. Hemithyroidectomy and neck dissection were performed on the homolateral sides and the surgical specimens in both cases showed primary carcinoma in the corresponding thyroid lobe, with metastases to several lymph nodes. These experiences raise some doubt in our minds as to the validity of a diagnosis of branchiogenic cyst for lesions situated in the lateral aspects of the neck either above or below the level of the hyoid bone. It must be admitted, however, that these observations by themselves could not be used as evidence against branchiogenic cancer, since in most of the alleged cases the tumor is also reported to be located near the level of the hyoid bone.

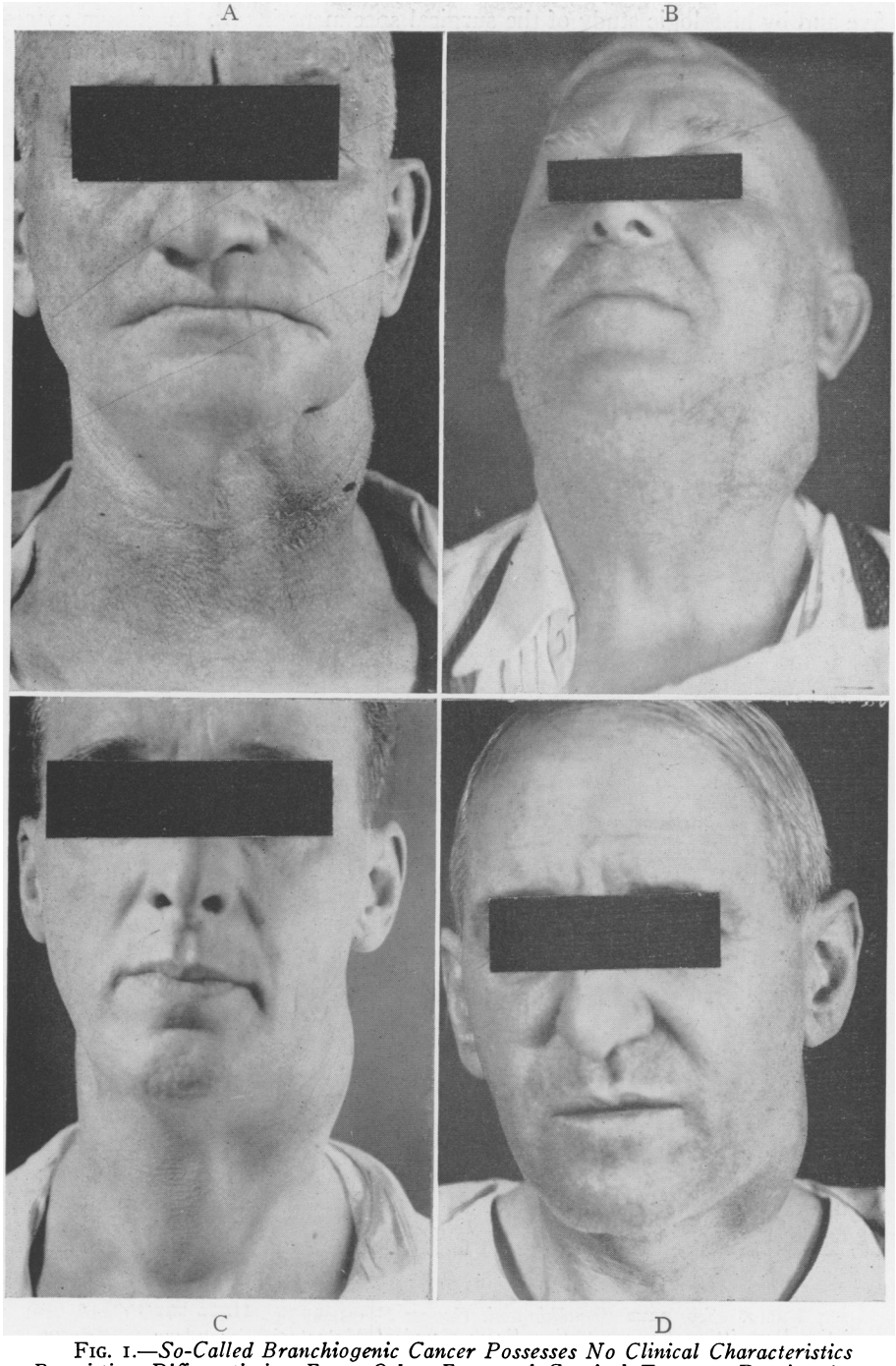

FIG. 1.—*So-Called Branchiogenic Cancer Possesses No Clinical Characteristics Permitting Differentiation From Other Forms of Cervical Tumors.* Despite the fact that all of the above four patients present an identical picture on clinical examination, a different etiology for the cervical mass exists for each case: (a) primary undetermined (b) floor of mouth primary (c) nasopharynx primary (d) tongue primary.

five and by histologic study of the surgical specimens in six. In nine instances the diagnosis was established from submitted microscopic slides (incisional biopsy made before the patient came to the Memorial Hospital). In the present series the histologic diagnoses were: epidermoid carcinoma (seven cases), squamous carcinoma (six cases), adenocarcinoma (one case), and anaplastic carcinoma (one case). Oliver[16] and others infer that there are characteristic histologic patterns in branchiogenic cancer. In none of our cases was the

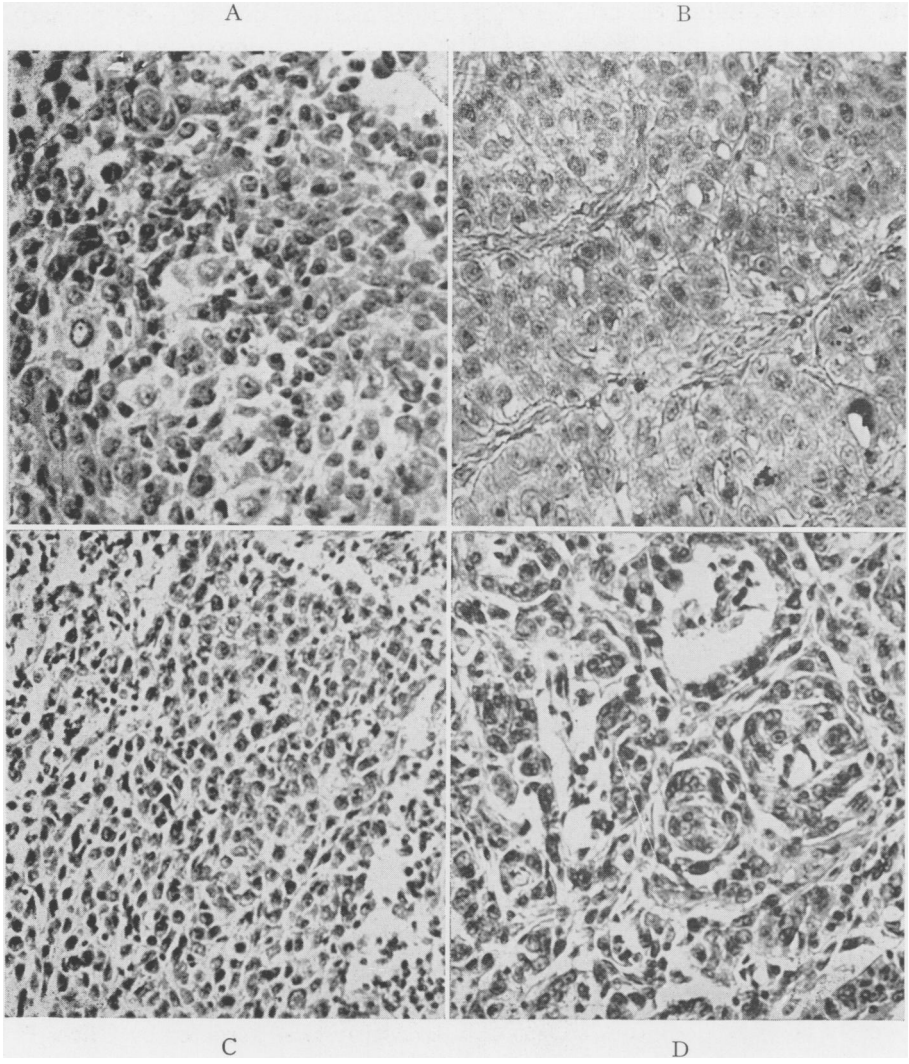

FIG. 2.—*So-Called Branchiogenic Cancer Possesses No Microscopic Characteristics Permitting Differentiation From Cervical Metastasis Secondary to Primary Tumors Occurring in the Mouth and Pharnyx.* A, B, C, and D are representative microphotographs from neck masses present in the patients shown in Figure 1. The pathologists report was squamous or epidermoid carcinoma in all four specimens and it can be seen that so-called branchiogenic carcinoma possesses no characteristics, clinical or histologic, permitting recognition as a specific entity.

histologic appearance different from the ordinary run of cervical metastatic carcinoma secondary to primary lesions in the upper respiratory or upper gastro-intestinal tracts (Figs. 1 and 2).

ETIOLOGY, SYMPTOMATOLOGY AND CLINICAL COURSE IN 15 CASES OF CERVICAL CARCINOMA WITHOUT ANY OTHER DEMONSTRABLE PRIMARY TUMOR SURVIVING FIVE YEARS FOLLOWING TREATMENT

An analysis of the cases herein presented reveals no clinical features differing from metastatic cervical cancer except for the fact that no other primary lesion was found in any of the cases. There was only one prominent symptom, namely, the presence of a cervical tumor which proved to be epidermoid carcinoma or adenocarcinoma on histologic examination. The clinical course up to the time of admission was slow and uncomplicated in all instances.

Incidence. The observation of a patient for five years following treatment of a solitary carcinomatous mass in the neck without the discovery of any other primary lesion is rarely encountered at the Memorial Hospital. During the eight-year period, 1933–1940, inclusive, over 5000 new cases of primary malignant tumors above the level of the clavicle were observed on the Head and Neck Service and only 15 cases (0.3 per cent) were encountered which might be tentatively classified as branchiogenic cancer. For purposes of comparison it may be significant to mention that during the eight-year period when these cases were observed, there were 450 cases of cancer of the lip, 470 cases of cancer of the tongue, and about 470 cases of cancer of the larynx.

Age and Sex. In the 15 cases considered in this report, 12 of the patients (80 per cent) were more than 50 years old; in about half of the patients the tumor appeared after the age of 60. This age incidence is identical with that of cancer of the mouth and pharynx. The youngest patient was ten and the oldest 72 years of age. Parkinson[17] has reported an alleged case of branchiogenic cancer in a seven-year-old male followed for 2½ years after surgical removal of a cervical tumor which proved to be epidermoid carcinoma. The follow-up period is too short for the acceptance of this tumor as one of branchiogenic origin.

In the present series there were 13 males and two females; this sex incidence approximates that of mouth and pharyngeal cancer in general. McWhorter[13] reports a ratio of three males to one female, and Oliver[16] a ratio of nine to one, in their respective series. Hertzler[7] makes the surprising statement that branchiogenic carcinomas "occur most frequently in aged females."

Duration of Symptoms. In this series the average duration of symptoms, that is, the presence of a "lump in the neck," was two months, and the range from one week to two years. Cases such as one of those reported by Oliver,[16] where a mass had been present since birth in a 54-year-old woman, and those reported by others in which a tumor had been present for 16, 19, and 34 years, respectively, have never been observed at the Memorial Hospital. If such cases were of true branchiogenic origin, the growth could have developed in preexisting branchiogenic cysts.

Location of the Tumor. As previously stated, branchiogenic cysts can occur anywhere along a line beginning just in front of the tragus of the ear and running downward along the anterior border of the sternomastoid muscle to the clavicle. It is significant, however, that in all of our cases the tumors appeared at about the level of the hyoid bone, the site of the highest nodes in the internal jugular chain and in which cervical metastases are most likely to appear from a primary lesion in the oral cavity or pharynx. There was an equal predilection for the right and left sides of the neck.

Size. In the present series the range in the size of the cervical tumors when the patient first reported to the Memorial Hospital was between 3.5 to 8 cm. in diameter, with a median size of about 5.5 cm.

Pain. None of our patients complained of pain and in our opinion there is no factual basis for such assertions as that of Crile[5] who says of branchiogenic carcinoma, "the occurrence of pain is fairly frequent." Hertzler's[7] statement that in malignant branchioma pain is often referred to the ear seems to us to be of little significance, since bulky infiltrating metastatic masses in the upper neck frequently produce pain in the ear (reflex through the vagus and/or cervical nerves).

Clinical Characteristics. In our cases there were no anatomic or clinical characteristics differing from those found in metastatic cervical cancer. In brief, the cervical tumors were ovoid, firm, non-tender, movable masses, all located somewhere along the course of the internal jugular vein, in the same location where metastatic cervical cancer is most frequently found.

Methods of Treatment Employed. The clinicians on the Head and Neck Service at the Memorial Hospital have always been surgeons who have themselves employed surgery or radiation therapy, or a combination of the two, as indicated in the individual case. Although the members of the staff have always been reluctant to operate on patients with cervical carcinomatous tumors without demonstrable primary lesions, nevertheless, over the period of the last 25 years there were many cases in which the patients have been operated upon as well as irradiated. It is significant that in 14 out of 15 patients with cervical carcinomatous tumors but without a demonstrable primary lesion who have survived five years or more, the treatment has been by radiation therapy. In only one case (a 12-year-old girl with adenocarcinoma) was surgery alone employed. The fact that in our series there is only one five-year survival following surgery and 14 following radiation therapy suggests not only the possibility but even the probability that in many, if not all, of these irradiated cases there was a primary lesion in the pharynx which fell within the beam of cancer-lethal radiation and that in these cases such a primary lesion was controlled without ever being discovered.* From the standpoint of the morbid

* Several cases have been observed at Memorial Hospital with residual cancer in the neck following radiation therapy given elsewhere, in which on the basis of histologic examination of the cervical tumor and symptoms associated with the beginning of the illness the former presence of a primary lesion in the nasopharynx seemed likely; in these cases, however, a physical examination at the time of admission to Memorial Hos-

anatomy of a primary lesion in the pharynx and metastasis in the neck, the two might readily lie within 1 to 3 cm. of each other, and from the physical standpoint the distribution of the tissue dose of radiation would be such as to make it entirely possible for the undiscovered small primary to be sterilized at the same time as the cervical mass.

The methods of radiation therapy employed were fractionated roentgen radiation alone in two cases, the dosage varying from 3600 r × 2 to 4000 r × 2 (200—250 kv, 1.5 mm. copper filter; 50 cm. TSD 3.5—7 cm. circular ports); in five cases of fractionated irradiation, in dosages about as previously mentioned, there was supplementary implantation of gold radon seeds in doses of 20-30 mcs; in six cases interstitial radiation alone, in doses varying from 30-56 mcs., was used; in five cases surgery was employed (local excision or radical neck dissection) either preceding or following radiation therapy. From this résumé of the treatment factors it can be seen that the radiation dosage was in the cancer-lethal range, and that it was often found to be successful in mouth or pharyngeal cancer.

In a single case of the present series, surgical excision alone was employed for a solitary tumor situated in the upper neck in a girl ten years of age. Neither by the findings at operation nor by the histologic examination of the surgical specimen can it be definitely stated that the tumor might not have arisen in the tail of the parotid salivary gland. The case is included here as a concrete example of the negative character of all recorded evidence for the branchiogenic origin of any cervical tumor; in brief, although we have recorded in this report 18 cases (including Oliver's three cases), nevertheless we must conclude that the evidence for such an origin of cervical cancer remains unproved.

DIAGNOSIS

The relative importance of the subject of branchiogenic cancer should not be judged solely on the basis of its doubtful identity or at least its rare incidence, for in doing so one would be inclined to relegate this hypothetical tumor to a status no more significant than that of a medical curiosity. The importance of the subject lies rather in the frequency with which the diagnosis of branchioma is unjustifiably made in cases where the patient complains only of a cervical mass and in which no other focus of growth is discovered immediately or even by repeated examinations. When a final diagnosis of malignant branchioma is made on such tenuous and scant evidence, it naturally follows that treatment will be given only to the cervical mass and that no further search for a primary lesion will be made. Since it is axiomatic that the cure of cancer is not possible without aggressive treatment directed to the primary growth

pital failed to reveal any such growth. In some, the therapist had given radiation directed to the center of the head (through the face, top of the head, occiput and the sides) for the sole reason that some consultant had suggested the possibility of that vague entity sometimes referred to as a "Schminke tumor" (a loosely-used term referring to anaplastic carcinoma located somewhere in the pharynx), but had never established the presence of such a lesion by clinical examination, biopsy, and histologic confirmation.

itself as well as to the metastasis, all patients in whom an erroneous diagnosis of branchiogenic cancer is made and persisted in are doomed to die of cancer, unless by accident the primary lesion should happen to lie within the beam of radiation. *In these facts lie the main importance of the subject of malignant branchioma.* Von Volkmann's[24] belief that the cervical tumors in his three cases arose primarily in branchiogenic remnants was based solely on the fact that he did not discover a primary lesion in the mouth or pharynx by inspecting the mouth and exploring the pharynx with a palpating finger. After almost 70 years, the uncritical and haphazard acceptance of the diagnosis continues and cases of alleged branchiogenic cancer are still reported, even though they are poorly documented and supported by only flimsy evidence.

The naïve confidence that a single and often casual examination of the oral cavity and pharynx permanently and unequivocally rules out the possibility of a primary lesion in these regions is widely held at the present time despite the fact that about 60 years ago at least one observer knew enough about the clinical behavior of oral and pharyngeal cancer to utter plain words of caution in this regard. Sutton[21] merely called attention to the possibility of an obvious primary which could be discovered if a competent search were made. With our present-day knowledge, however, we know that not only may a silent primary often be discovered by a thorough examination when the patient first comes for treatment, but that a cryptic primary in the mouth or pharynx may first become apparent after repeated examinations as long as four years after the initial appearance of a cervical metastasis.

Reports in the literature regarding the greater frequency of branchiogenic cancer are unacceptable after critical review. For instance, Pizetti[18] reviews a series of 100 cases of lateral cervical carcinomatous tumors in which he designates 11 as branchioma; in none of these are the rigid criteria previously listed in the present study met. In one of Pizetti's patients the growth "invades the pharynx," and it is rather obvious that in this case he was dealing with pharyngeal cancer metastatic to the cervical lymph nodes. In general, this series of supposed branchiogenic cancers are so poorly documented that such a diagnosis could hardly be considered even from a speculative standpoint. In the current medical literature[5, 8, 19] branchiogenic cancer is often discussed with unwarranted confidence, supplemented with published photographs of patients but without any suggestion that the diagnosis of the tumor is difficult and uncertain. Such a bland attitude serves only to perpetuate the confusion as regards this theoretical entity. In our opinion the subject of branchiogenic cancer should not be discussed in the literature unless the reader is cautioned as to the rarity of the tumor (if it does exist) and the uncertainty and complexities of the diagnosis.

In a recent publication[14] we have called attention to the frequency with which cervical metastasis occurs as the first symptom of cancer of the mouth and pharynx. Cervical metastasis with a silent primary lesion occurs in about 8 per cent of all cases of cancer of the mouth, pharynx and thyroid gland. Differently stated, in a consecutive series of about 3900 cases of cancer of the

head and neck, cervical metastasis was the first symptom in 218 (about 5 per cent) while in specific areas, such as the mouth, pharynx, or thyroid gland, cervical metastasis with no complaint referable to a primary lesion is present in 8 per cent. In cancer of the nasopharynx, cervical metastasis is the first and for a time the only symptom in about one-third of the cases, and in only 70 per cent is the primary lesion discovered within a period of six months.

The basic truths clearly stated by Sutton more than one-half a century ago are largely disregarded by many observers, who appear willing to make definite diagnoses of branchiogenic cancer after a single negative examination for a primary lesion, or in other cases make such a diagnosis without waiting for the longer period, during which time a cryptic primary may be discovered. While most authors agree with these precepts in theory, they almost invariably disregard them in practice and in reporting their own cases. Others apparently place undue emphasis on postmortem findings when the necropsy examination reveals no evidence of a primary lesion. The clinician who has repeatedly searched for and finally found small silent primaries in the nasopharynx, tonsil or base of the tongue, will have little confidence in the ability of the pathologist to explore sufficiently all of these relatively remote areas to rule out with assurance the presence of a primary lesion by postmortem examination.

It is fallacious and even misleading to suggest that there are significant differences in contour, consistency, mobility and tenderness in the differential diagnosis of such lesions as branchiogenic cancer, metastatic cancer, melanoma, Hodgkin's disease, lymphosarcoma, etc. It was formerly considered a mark of clinical erudition and diagnostic acumen to memorize lists of differential criteria to distinguish clinically such diseases as tuberculosis, syphilis, and the sub-varieties of cancer, but in recent years with the development of dependable laboratory tests much of this purely inductive method of diagnosis has proved to be unreliable and impractical.*

In brief, the diagnosis of branchiogenic cancer is too frequently and too loosely made, and it is fair to state that the over-all competence as regards the knowledge of cancer can be fairly well judged, either in the individual surgeon or in a tumor clinic, as being inversely proportional to the frequency and confidence with which the diagnosis of branchiogenic cancer is made.

After several months were spent in collecting and analyzing the evidence and in preparing the preliminary drafts of this paper, we began to have serious doubts as to whether there was any dependable evidence either in the literature or in our own material to prove the existence of such an entity as branchiogenic cancer.

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* One of us (H. M.) can remember back 25 years when a distinguished surgeon of that day confidently stated that he could differentiate such diseases as melanoma, Hodgkin's disease and metastatic cancer by palpation alone. He steadfastly maintained this view-point, although he was repeatedly proved wrong by subsequent biopsy. We have observed many cases in which there was a maximum range of variation in the consistency of tumor masses, supposedly characteristic of growths such as lymphosarcoma, melanoma, Hodgkin's disease and metastatic cancer.

THE CASE FOR AND AGAINST BRANCHIOGENIC CANCER

Up to this point in the present report it has been repeatedly implied that we have considerable doubt as to the actual existence of such a clinical and pathologic entity as branchiogenic cancer, but we have also stated that we know of no better explanation for the histogenesis of certain cervical cancerous tumors. Throughout the present discussion attention has been called to the frequency with which a diagnosis of branchiogenic carcinoma is made on inadequate evidence. Accordingly, the evidence both for and against the existence of a tumor of such origin will be examined, and the various possibilities considered.

When a patient with a cervical carcinomatous tumor and no other demonstrable primary lesion survives for a period of five years following treatment to the cervical mass only, can one state that the cervical tumor was the only focus of the growth, and in addition, that it was of branchiogenic origin? Such a conclusion must necessarily be based upon circumstantial evidence, for as previously mentioned, there are no histologic criteria to prove the branchiogenic origin of a cervical malignant epithelial tumor. So far no case has been reported in which cancer has been found arising in a branchial cyst or in any recognizable remnant of the embryonal branchial apparatus. If a carcinomatous tumor of the neck does not arise in a vestigial remnant, is there any other reasonable explanation for the histogenesis of the cervical cancer? Several of these possibilities will now be discussed.

Evaluation of the Evidence for Branchiogenic Origin in 15 Reported Cases of Cervical Cancer. The 15 cases herein reported fulfill the criteria for malignant branchioma previously referred to, that is, cervical carcinomatous tumors occurring in the lateral aspects of the neck, histologically proved, without any other demonstrable primary lesion, treatment given to the cervical tumor alone, and the patient followed systematically without recurrence for a period of at least five years. As we have previously mentioned, only three reported cases in the literature so far have fulfilled these criteria. Nevertheless, radiation therapy was used in 14 of our 15 cases and although four of these had surgery, the surgery itself cannot be given complete credit for the cure. In all cases the radiation dosage was within the cancer-lethal range. It is entirely possible that a primary undetected lesion existed, that it was situated within the beam of cancer-lethal radiation and that it never became clinically evident (base of tongue, tonsil, pharyngeal wall, extrinsic larynx).

Metastatic Carcinoma with Spontaneous Regression of the Primary Lesion. A number of cases are on record (6, 11, 12) in which histologically proved cancer, both primary and metastatic, have been observed to disappear without any treatment whatever. In any alleged case of branchiogenic cancer, therefore, it is theoretically possible that the primary lesion in the mouth or pharynx did regress spontaneously while the metastasis persisted. Although this explanation will probably not be acceptable, to many, nevertheless, it has actually more factual evidence to support it than does the theory of branchiogenic

origin, for while spontaneous regression of malignant tumors has been observed, the origin of cancer in the wall of a branchiogenic cyst has not.

In the Head and Neck Clinic at the Memorial Hospital several cases, not included in this report, have been encountered in which there were numerous cervical tumors, apparently multiple metastatic nodes, in which, following treatment by radiation and/or surgery, the patients remained well for more than five years without the discovery of any primary lesion. In these cases the simultaneous appearance of multiple enlarged nodes, occasionally bilateral, was such as to make the diagnosis of cancer of branchiogenic origin extremely remote, so that we have not even included them in the 15 cases considered in this report. In clinics where large numbers of cancer patients are observed, cases will occasionally be seen in which the clinical behaviour is so bizarre and unusual that it is impossible to classify them either clinically or anatomically. In many of these the evidence strongly suggests that the primary lesion may have regressed spontaneously.

Cancer in Epithelial Rests in Lymph Nodes. One of the theories in support of the primary origin of certain cancers in the neck is that they arise from epithelial rests in lymph nodes. Some years ago James Ewing, in a personal communication, stated to one of us that he had observed remnants of glandular acini in cervical lymph nodes which he interpreted as embryonal rests, but conceded at that time that he had never seen any remnants of squamous epithelium in lymph nodes which could possibly be of branchial cleft origin. In a personal communication, Fred Stewart stated that he has never observed any structural components in normal cervical lymph nodes which he could interpret as being of epithelial origin. In brief, the theory that cervical carcinoma can arise in epithelial rests in lymph nodes is even less tenable than that they arise in branchial remnants.

The Significance of the Absence of Even a Single Case Report with Cancer in the Wall of a Branchiogenic Cyst. Branchiogenic cysts occur with relative frequency and constitute one of the most readily identifiable varieties of cysts which originate from the embryonal branchial apparatus. If cancer can arise in vestigial branchial remnants, it would seem almost inevitable that in an appreciable number of cases observed over a long period of years cancer would be found in the wall of a branchiogenic cyst or lateral cervical fistula. So far as we know, no such case has ever been reported; in a series of 63 cases of branchiogenic cysts studied by one of us, there were one or two in which the question of malignant transformation was first considered but subsequent examination revealed no evidence that such a diagnosis was warranted. In our opinion, acceptable proof that such a tumor as branchiogenic cancer does exist must await the demonstration of cancer arising in such a cyst. The demonstration of such a phenomenon would represent the evidence *prima facie* in the case for branchiogenic cancer. All efforts to prove such a case have already been discussed in this paper.

THE CLINICAL MANAGEMENT IN CASES OF CERVICAL CARCINOMA WITHOUT ANY OTHER DEMONSTRABLE PRIMARY LESION

Since in any given case of cervical tumor a diagnosis of branchiogenic cancer must remain uncertain and highly improbable for many months or even years, it is hardly logical to propose a specific plan of treatment for this particular growth. It seems rather more reasonable to discuss the immediate management of *those malignant cervical tumors which might be branchioma but which nevertheless are probably not on the basis of chance alone.*

Consider then the case of the patient who presents only a cervical mass and in whom there can be demonstrated at first no other focus of growth as a possible primary lesion. What sequence of procedures should be followed in such a case to establish a diagnosis and give the patient the greatest possible chance of permanent cure? Among the alternatives are (1) aspiration biopsy (2) incisional biopsy (3) radiation therapy (4) local excision of the mass and (5) unilateral neck dissection. Whatever is done, *the search for a primary lesion should never be relaxed.*

Aspiration Biopsy. One of the clearest indications for aspiration biopsy is a cervical tumor of an undetermined nature, since the procedure is both rapid and safe and, in addition, does not alter the clinical setting. Should the sectioned plug of tissue show epidermoid carcinoma, the probabilities are that there is a cryptic primary lesion somewhere in the oral or pharyngeal mucous membranes. Search should be continued indefinitely for such a primary lesion. Should the sectioned plug of tissue reveal adenocarcinoma, particular attention should then be given to the thyroid and major salivary glands, lung, pancreas, gastro-intestinal and urologic tracts as possible sources of the primary growth. If the aspirated specimen shows lymphoid tissue only, further help should be sought from the pathologist to determine the possibility of lymphomatous disease or whether the cells are non-neoplastic, in which case a further aspiration biopsy may be indicated. Only if the report is "epidermoid carcinoma" need any serious thought be given even to the remote possibility of branchiogenic carcinoma and if repeated examinations over a period of several days fail to disclose any primary lesion, consideration must then be given to the management of the known cancerous cervical mass.

Incisional Biopsy. The partial surgical removal of a mass for diagnostic purposes* is always objectionable and should be avoided if there is any alternative procedure. Incisional biopsy will seldom be indicated if aspiration biopsy is performed competently. When repeated aspiration biopsy has failed to provide a positive histologic diagnosis, due consideration should be given to complete (rather than partial) excision of the mass. In our series, incisional biopsy had been carried out before referral to us in six (almost half) of the cases. The resultant scarring and local extension of the growth in the operative

* *Incisional biopsy* may be defined as cutting into a tumor mass and removing a fragment for biopsy, while *excisional biopsy* may be referred to as the removal of all of the local tumor or enlarged lymph node. The first procedure is objectionable and should be avoided if the entire mass can be excised.

area from such a procedure is a serious handicap to subsequent successful treatment by any method.

Local Excision. If a cervical tumor has been proved to be carcinoma by aspiration biopsy (or other means), a simple local excision without any supplementary treatment is, in our opinion, inadequate. In most cases wider surgical excision, that is, block neck dissection is clearly indicated. In the present series simple local excision had been carried out elsewhere in four cases and the patients were subsequently referred to Memorial Hospital because of local recurrences.

In any case, to perform a local excision of a cervical mass immediately on admission seems to us a rather haphazard and irresponsible procedure. Such local excisions are frequently carried out by surgeons as the initial diagnostic procedure and after the pathologist's report of a malignant tumor has been made the patient is either discharged with no provision for follow-up or sometimes urgently referred to a tumor clinic, the surgeon being obviously relieved to wash his hands of the whole affair. Such a routine is to be unequivocally condemned. The surgeon should either withhold any operative procedure or should assume complete and permanent responsibility for his initial surgery.

Radiation Therapy. The conscientious surgeon experienced in the clinical management of cancer will be somewhat loathe to propose immediate surgery in proved cases of cancerous cervical tumors. He will dread the possibility that within a few days, weeks or months after excision of the mass, a primary lesion in the mouth or pharynx (or elsewhere) will become evident. Furthermore, he will realize that his surgery has not only been useless, but even meddlesome, in that the protective screen of lymphatics which stands between the primary lesion and the systemic lymph channels has been removed.

For these reasons, after a positive report of cancer from aspiration biopsy has been obtained, it is more prudent to defer surgery and apply radiation therapy to the cervical mass while continuing the search for a primary lesion. In most cases a combination of fractionated roentgen radiation and gold radon seeds will permanently sterilize the local tumor while preserving intact what remains of the protective screen of lymphatics. Under such a plan, should a primary lesion appear later (which it usually does), treatment can be instituted to the primary growth and to any metastasis with the assurance that previous radiation therapy has not seriously affected the clinical setting.

Neck Dissection. When the cervical tumor is larger than 3 to 4 cm. in diameter, consideration should be given to the serious sequelae incident to the necessary large cancer-lethal dose of radiation. In these bulky tumors radical neck dissection of the affected side may often be preferable to radiation therapy. The term "radical neck dissection," as used in our clinic means the removal of the sternomastoid muscle, internal jugular vein, submaxillary salivary gland and all lymphatics of the affected side of the neck from the inferior border of the mandible above to the clavicle below and from the midline of the neck to the anterior edge of the trapezius posteriorly.

Neck dissection is referred to at this point mainly as an alternative to

radiation therapy in large cancerous cervical tumors, although it was not employed in any of the 15 cases included in this report. Frequently, when we resort to neck dissection in cases of bulky cervical cancers of doubtful origin, a small primary growth in the thyroid gland previously obscured by the large metastasis is found in the surgical specimen by the pathologist. With thorough and planned clinical investigation of cervical tumors, radical neck dissection will seldom be indicated except for proved metastatic cancer and a definitely established primary lesion.

In brief, then, we advise a cautious approach to the problem of the management of cancerous cervical tumors without any other obvious primary lesion. If the mass appears clinically and histologically to be amenable to radiation therapy, we recommend that procedure while the search for a primary tumor continues. Should the cervical tumor appear to be too bulky or radioresistant, it is best to perform radical neck dissection of the affected side rather than mere local excision. Incisional biopsy is to be condemned as the initial diagnostic procedure.

SUMMATION AND EVALUATION OF THE EVIDENCE

When a theory has been passively accepted for more than 70 years and become ingrained in medical thought, it is obviously difficult to uproot it on presumptive evidence alone, despite the fact that the original theory itself was based on presumptive evidence. The hypothesis that cancer can and does arise in branchial remnants is attractive and admittedly a ready explanation for the histogenesis of certain cervical tumors. What then should be the current attiture toward this problem?

When the analysis of the clinical data preparatory to making this report was begun, we assumed that the existence of branchiogenic cancer was proved and proposed mainly to call attention to the fact that the diagnosis should be made guardedly, and to point out that in most cases the diagnosis was too loosely and too confidently made. In attempting to reduce the mass of presumptive evidence to concrete, indisputable facts we finally were forced to the conclusion that there is at the present writing no proof available to support belief in the existence of such a tumor. On the other hand, there is no better explanation as to the nature of certain cervical tumors, and it therefore must be admitted that the problem is unproved either for or against the existence of branchiogenic cancer.

SUMMARY AND CONCLUSIONS

1. The actual existence of a clinical entity deserving the specific term *branchiogenic cancer,* is entirely hypothetical.

2. There may be no other more reasonable explanation for the origin of certain rare cervical tumors.

3. A definite diagnosis of branchiogenic cancer cannot be made on a histologic basis.

4. The diagnosis of branchiogenic cancer in a given case of cervical tumor should always remain tentative and should never even be considered unless the

patient has survived for a period of at least five years without the discovery of any other primary lesion.

5. A systematic plan for the management of these selected cases of cervical carcinomatous tumors is presented.

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