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METASTATIC TUMOURS IN THE THYREOID GLAND *

RUPERT A. WILLIS, M.D., B.S.

(From the Baker Research Institute, Alfred Hospital, Melbourne, Australia)

I. INTRODUCTION

Malignant neoplasms of many kinds are distributed embolically in the arterial blood stream, and establish secondary tumours in various tissues. One of the most neglected problems of oncology is that of the preferential tissue affinities of the different types of malignant cell. Certain tissues and organs, for example the liver, are very frequent sites of metastases from neoplasms of very diverse kinds; while other tissues and organs, such as the skeletal muscles or the intestinal tract, are rarely the seat of malignant metastasis. Moreover, various tumours display decided predilections in the distribution of their metastases, notorious examples of this being the frequency of secondary growths in bones in cases of renal or of thyreoid carcinomata. For the many vagaries of metastatic distribution observed in individual cases of malignant disease, no generally satisfactory explanations have been advanced. Various mechanical theories have been suggested, as for example that the movement of certain tissues inhibits the effective embolic lodgement of malignant elements; and the permeability of the capillaries of various tissues for minute solid particles has been much discussed. Other workers, however, have held that chemical rather than mechanical and circulatory factors play the principal rôle in determining the sites of development of metastatic growths. Thus Paget (1889)[1] speaks of certain tissues as being "congenial soil" for malignant growth, and views favourably the conception of Fuchs that

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certain organs may be "predisposed" for the growth of malignant emboli; and Mallory (1914)[2] in referring to this problem says "Conditions of a chemical nature probably play an important part." Ewing (1928)[3] expresses the opposite view in the statement that "there is as yet no evidence that any one parenchymatous organ is more adapted than others to the growth of embolic tumor-cells."

I have been struck by the relative immunity from malignant metastases displayed by certain richly arterialised organs. In cases of systemic haematogenous dissemination of malignant tumours, the embolic influx into the various tissues of the body must be proportional to their respective arterial blood supplies, yet such richly vascular organs as the intestine, the spleen and the thyreoid gland, are amongst the least frequent sites of development of secondary growths. Most noteworthy in this respect is the thyreoid gland, which, next to the adrenal gland, is the most richly arterialised tissue in the body. The adrenal gland receives approximately 650 cc. of arterial blood per 100 grams of tissue per minute, and thrice this amount during a rise of blood pressure produced by adrenalin (Neuman, 1912).[4] The corresponding figure for the thyreoid gland is only slightly less, namely 560 cc. per 100 grams per minute (Burton-Opitz, 1910).[5] With these high figures may be contrasted, for example, the relatively scanty arterial supply of the liver which receives only 26 cc. of arterial blood per 100 grams per minute (Burton-Opitz), or, according to Barcroft and Shore (1912),[6] 12 cc. for the resting liver and 23 cc. for the active liver subsequent to the digestion and absorption of food. Taking the total weights of the liver and thyreoid gland to be 1500 and 25 grams respectively, it will be seen that the thyreoid actually receives approximately one-half the volume of arterial blood received by the entire liver. Yet, while the liver is very frequently the seat of metastases from tumours of diverse kinds distributed in the systemic blood stream, metastatic growths in the thyreoid gland are unusual. The striking disparity between the arterial vascularity and the incidence of metastatic neoplasms in thyreoid tissue decided me to make a study of secondary tumours in this organ, with a view to determining, if possible, whether circulatory or chemical factors appeared to afford the better explanation of that disparity.

II. Review of the Literature

The following résumé of recorded cases which exhibited metastatic tumours in the thyreoid makes no claim to completeness. A reasonably careful search has been made of available pathological literature, but doubtless a number of isolated case reports in which thyreoid metastases are recorded have escaped discovery. However, the material reviewed is adequate for the purposes of this paper, and the writer hopes that no important references on the subject have been omitted. A description is given first of those cases in which metastatic growths in the thyreoid exhibited some noteworthy peculiarity, such as a special relationship to other pathological conditions of the gland. Then follows briefer reference to cases in which no details concerning the condition of the organ are recorded, or in which no striking peculiarity was observed.

Virchow in his book on tumours,[7] stated that malignant goitre might be either primary or secondary, that the latter might be either by direct extension from neighbouring growths or by metastasis from remote parts, and that cancerous or sarcomatous metastases might lodge in a thyreoid gland already goitrous. Virchow exemplified such metastatic growths by two cases. The first case was that of a goitrous cretin, aged 53 years, who had had a testicular tumour removed eight years previously. At autopsy the old nodular goitrous thyreoid contained a prominent tumour mass consisting of cells with large nuclei, and similar tumours were present in the lungs and sternum. Despite the long intervening period, Virchow regarded these several growths as metastases from the testicular tumour, and not as primary carcinoma of the thyreoid. Virchow's second case was a female, aged 65 years, with a primary growth of the posterior pharyngeal wall. The thyreoid gland, which exhibited diffuse colloid goitre, was the seat of two prominent metastatic tumours. Other secondary growths were present in the pancreas and kidney. In the same work, speaking of malignant melanotic tumours, Virchow also remarked of the less frequent sites of metastases that "the thyreoid gland appears to be involved more frequently than the spleen."

Kaufmann in his Lehrbuch (Reimann's translation 1929, p. 537)[8] remarks the infrequency of metastatic neoplasms in the thyreoid gland, and states his experience that melanotic growths are the most

frequently encountered, an opinion confirming that of Virchow to which reference has been made above. Kaufmann also mentions the case of a woman, aged 59 years, in whom an ovarian carcinoma produced minute metastases in an adenoma of the thyreoid and in no other part of the gland.

Naegeli (1912)[9] records the case of an elderly female in whom an adenocarcinoma of the rectum produced metastases in thyreoid adenomata. The thyreoid had been the seat of long-standing irregular enlargement, and the cancerous deposits were most prominent in the degenerated adenomatous areas. A small probable metastasis in one lung was not examined microscopically.

Kettle (1912)[10] mentions a case in which he observed in an adenoma of the thyreoid, a metastasis from a squamous carcinoma of the uterus.

Rost (1912)[11] describes the case of a man, aged 48 years, with "hypernephroma" metastases in the lungs, clavicle, thyreoid and many lymph glands. The thyreoid was much enlarged by long-standing goitrous changes, and contained also an area of secondary growth. The malignant elements were separated from the surrounding thyreoid tissue by a wide zone of connective tissue, and from Rost's description it is apparent that the metastasis had become established in a fibrosed area of the goitrous gland.

Müller (1912)[12] describes a male patient, aged 64 years, who died with haemangiomatous growths in the gums, pleura, lungs, bowel, bones and thyreoid gland. This organ was much enlarged: the right lobe was extensively calcified; the left lobe contained many adenomata, and in one of these, 2.5 cm. in diameter, there was an angiomatous nodule 8 mm. in diameter. While inclining to the view that the condition was a "system disease" involving the vessels of the various organs, Müller admits the possibility of metastasis from one of the tumours as a primary focus. Microscopically the growths presented the structure of cavernous angioma, with however, proliferation of the endothelial cells which in places were desquamating into the vascular spaces.

Most pathologists accept the neoplastic character of chloroma which therefore may be included legitimately in the present paper.

Sauer (1914)[13] describes a case of this disease in a male, aged 36 years, exhibiting in addition to other lesions, chloroma nodules in the thyreoid, spleen, kidneys and prostate. The thyreoid gland was

decidedly enlarged, and contained a number of well defined greenish nodules in both lobes. These proved to be thyreoid adenomata infiltrated by chloroma cells which extended thence into the adjacent, more normal thyreoid tissue. Sauer could discover only one other previously recorded case of chloromatous deposits in the thyreoid gland, described by *Pribram* (1909)[14] in a male, aged 22 years.

Herxheimer (1925)[15] describes diffuse myeloblastic infiltration of the thyreoid in a case of leukaemia.

Reinhart (1917)[16] records the case of a female patient, aged 38 years, who suffered from carcinoma of the left lung with metastases in the right lung, pleura, kidneys, adrenals, liver, thyreoid, lumbar spine, and thoracic and retroperitoneal lymph glands. In the right lung and in the bronchial glands, chronic tuberculosis coexisted with the malignant disease. The thyreoid, only slightly enlarged, contained several metastatic nodules of growth, and was also the seat of tuberculous disease with fibrosis, lymphocyte accumulation, and numbers of tubercles. Reinhart remarks on the unusual combination of cancerous metastasis and tuberculous disease of the thyreoid which is an infrequent site of either of these conditions, and suggests the possibility of a causal relationship of the *locus minoris resistentiae* kind.

Prym (1924)[17] records a case of chorionepithelioma in a woman, aged 44 years. Metastases were present in the lungs, brain, liver, bowel mucous membrane, both kidneys and thyreoid gland. This last organ was the seat of multiple adenomata, and the metastatic deposit was located within one of the adenomatous areas.

In the above cases the striking relationship of the metastatic growths in the thyreoid gland to other abnormalities necessitated special comment. In many other cases no such noteworthy associations are recorded, or, more often, no details whatever are available concerning the condition of the organ. It is not necessary, therefore, to describe these cases individually, and the abbreviated information given in the following list will suffice.

Foerster (1858).[18] Carcinoma of cervix uteri.
Rosenblatt (1867).[19] Carcinoma of liver.
Blau (1870).[20] Carcinoma of corpus uteri.
Beck (1884).[21] Carcinoma of lung. Male, 65 years.
Siegel (1887).[22] Carcinoma of lung. Female, 68 years.
Ehrich (1891).[23] Carcinoma of lung. Female, 52 years.
Kantorowicz (1893).[24] Carcinoma of breast. Female, 51 years.

Kaufmann (1902).[25]
(1) Malignant rhabdomyoma of prostate. Male, 26 years.
(2) Carcinoma of prostate. Male, 43 years.
Kaufmann (Lehrbuch, Reimann's translation, 1929).[8]
(1) Carcinoma of pharynx. Male, 62 years. (p. 824.)
(2) Adenocarcinoma of uterus. Female, 73 years. (p. 1681.)
Hirschfeld (1906).[26] Sarcoma of ala of ilium. Male, 36 years.
Grimm (1907).[27] Carcinoma of breast.
Offergeld (1909).[28] This author in a study of metastases from uterine cancer found records of seven cases with thyreoid metastases. The original account is not immediately available to the present writer.
Davidsohn (1911).[29] Malignant melanoma of adrenal. Male, 58 years.
Chalier and Bonnet (1912).[30] Malignant melanoma of rectum. Male, 48 years.
Kettle (1912).[10] Squamous carcinoma of breast. Female, 69 years.
Mori (1913).[31]
(1) Malignant melanoma of eye. Male, 43 years.
(2) Carcinoma of breast. Female, 42 years.
(3) Carcinoma of breast.
Schöppler (1917).[32] Carcinoma of lung. Adult male.
Handley (1922).[33] Malignant melanoma of skin. Female, 34 years.
Jeannée (1925).[34]
(1) Carcinoma of bronchus. Male, 39 years.
(2) Malignant melanoma of skin. Female, 42 years.
(3) Carcinoma of bronchus. Male, 54 years.
Chajutin (1926).[35] Carcinoma of liver. Male, 60 years.
Derischanoff (1926).[36] Carcinoma of breast. Female, 58 years.
di Biasi (1926).[37]
(1) Squamous carcinoma of breast. Female, 47 years.
(2) Carcinoma of breast. Female, 48 years.
(3) Naevus carcinoma of skin. Male, 52 years.
(4) Carcinoma of breast. Female, 69 years.
(5) Malignant melanoma of adrenal region. Male, 83 years.
(6) Carcinoma of breast. Female, 73 years.
(7) Carcinoma of breast. Female, 60 years.
(8) Carcinoma of lung. Male, 52 years.
In two other cases described by di Biasi, metastases recorded in the thyreoid were queried, these two cases therefore are excluded.
White and Brunton (1927).[38] Brief reference is made to two cases in which it is stated that thyreoid metastases were present, but information given is inadequate to justify inclusion.
Brandt (1927).[39] Carcinoma of kidney. Female, 75 years.
Girdwood (1929).[40] Malignant melanoma of skin. Female, 42 years.

If we regard Hodgkin's "granuloma" as neoplastic in nature, involvement of the thyreoid in that disease also falls in the scope of this paper. Osler (1885)[41] mentions two cases of thyreoid enlargement due to deposits of "Hodgkin's tissue," but gives no details. Beitzke (1909)[42] described a case of Hodgkin's disease in a woman, aged 65 years, in which the lymph glands of the upper parts of the

body were involved, and tumour-like masses were present in the bone marrow, skull periosteum, liver and thyreoid gland.

Finally, mention must be made of three cases referred to by Ewing (1928, p. 961),[3] namely Pick's and Ehrhardt's cases of osteosarcoma and Fraenkel's case of melanosarcoma. As the original reports are not immediately accessible, and as there appears to be doubt as to whether the tumours in the thyreoid were primary or secondary, I have excluded these cases from further consideration in this paper.

III. Personal Observations

The following examples of metastatic tumours in the thyreoid gland have been observed by the writer in personally conducted autopsies. The descriptions are abbreviated, but all essential details are included.

Case I. *Clinical History:* Male, 47. In 1923, left eyeball excised for pigmented intra-ocular tumour. Good health thereafter for over four years. July 1927, recurrence of tumour in orbital cavity, and clinical enlargement of liver. Death in February 1928.

Autopsy Findings: Recurrent melanotic tumour of orbit. Numerous partly pigmented, partly colourless metastases in the myocardium, endocardium, right lung, liver (280 ounces), kidneys, both adrenals, retroperitoneal tissues and thyreoid gland. The latter, otherwise normal, contained a solitary pigmented metastasis 1.5 cm. in diameter in the left lobe.

Histological Findings: Tumour cells, both polyhedral and fusiform, arranged both diffusely and in discrete clumps in relatively scanty stroma. Pigment formation varies in degree in different areas, in places absent, in places massive, both intra- and extracellular in situation.

Case II. *Clinical History:* Female, 54. January 1927, "indigestion" appeared. June 1927, radical excision of rectum after preliminary colostomy. Good health thereafter for nearly two years. April 1929, pain in right leg and some difficulty with micturition; vaginal examination revealed large hard mass occupying right side of pelvic cavity. Death in September 1929.

Autopsy Findings: Large firm cancerous mass in pelvic cavity, adherent to sacrum and right pelvic wall, and infiltrating perineum and lower part of uterus. A moderate number of small scattered

metastases in the liver, spleen, kidneys, adrenals, pancreas, dura mater, several ribs and thyreoid gland. The last named organ was small and of normal external appearance, but on section a metastasis 1 cm. in diameter was found in the upper pole of the right lobe (Fig. 1), and two smaller separate nodules 3 mm. in diameter near the isthmus. The thyreoid tissue throughout was pale and tough and exhibited irregular strands of fibrous tissue. Subsequent microscopic study revealed extensive fibrosis, parenchymatous atrophy, and plentiful accumulations of lymphocytes.

Histological Findings: Anaplastic polyhedral and signet-celled carcinoma, in parts exhibiting loose alveolar formation, in parts diffuse; scanty suggestions of adenomatous grouping; mitoses plentiful; stroma scanty; much degenerative change (Fig. 2).

CASE III. *Clinical History:* Female, 61. January 1929, patient noticed a small lump in left breast. June 1929, paresis of left limbs appeared, with spasticity and extensor plantar reflex on left side. Thereafter, rapid emaciation and asthenia, mild convulsive spasms of left arm, and aphasia. Death in August 1929.

Autopsy Findings: Non-ulcerating mass 5 cm. in diameter in left breast, adherent to skin and invading pectoral muscles; tissue partly dense and hard, partly soft and mucoid. Apical axillary and supraclavicular glands involved with extension to upper two ribs and intercostal spaces. Numerous small nodules of growth beneath visceral and parietal pleura on both sides; a few metastases in lung substance. Metastases also present in liver, left kidney, both adrenals, dura mater, cerebrum and the thyreoid gland. This organ was somewhat enlarged and exhibited irregular colloid retention and many small adenomata and cysts. It contained a solitary metastasis 1 cm. in diameter in the right lobe near the isthmus (Fig. 3).

Histological Findings: Primary tumour an adenocarcinoma with extensive areas of mucoid change. Metastases similar, but less prominently adenomatous and more often carcinoma simplex in type (Figs. 4 and 5).

CASE IV. *Clinical History:* Female, 70. A firm mass the size of a walnut in left breast for 30 years. Early in 1928 this began to enlarge. December 1929, rapid growth of mass with cough and dyspnoea. By January 1930, mass was a firm hemispherical tumour 10 cm. in diameter projecting anteriorly, adherent to skin but not to muscles or chest wall. Death in February 1930.

Autopsy Findings: Mammary tumour restricted to fat and not involving pectoral muscles; axillary glands not enlarged. Numerous large metastases in both lungs and in parietal pleurae and mediastinal glands. A few small nodules in the liver. Thyreoid, of normal size, contained several adenomata up to 1 cm. in diameter; and the left lobe presented two tiny firm white nodules which proved microscopically to be metastases. These were not situated in adenomatous tissue.

Histological Findings: Anaplastic spindle and polyhedral-celled carcinoma, largely diffuse but partly alveolar in arrangement; numerous mitoses; scanty stroma.

CASE V. Female, 58. (Reported in detail elsewhere.)[43] Anaplastic carcinoma of breast; thyreoid almost totally replaced by metastatic growth; clinical symptoms of myxoedema.

CASE VI. Female, 41. (Reported in detail elsewhere.)[44] Malignant sacral chordoma with widespread metastases. The thyreoid gland was enlarged to double its normal size and was the seat of prominent fibrosis and many adenomata. Several chordoma metastases were present, the largest 8 mm. in diameter (Fig. 6). Several of these lay within adenomatous areas. Microscopically the thyreoid tissue exhibited extensive fibrosis, parenchymatous atrophy and lymphocytic infiltration (Fig. 7).

CASE VII. *Clinical History:* Female, 53. September 1929, postprandial epigastric pain and loss of weight. December, laparotomy revealed inoperable gastric cancer. Death in March 1930.

Autopsy Findings: Extensive gizzard carcinoma of the stomach with metastases in the coeliac and upper lumbar lymph nodes, the liver, peritoneum, ribs, sternum, skull and thyreoid. Microscopic tumour emboli were found also in the lungs. The thyreoid gland was small, pale and tough, and contained a single metastatic nodule 6 mm. in diameter.

Histological Findings: A disorderly adenocarcinoma. The metastasis in the thyreoid (Fig. 8) consisted of irregular acini of columnar-celled carcinoma set in an abundant, partly hyalinised fibrous stroma, which extended into the adjacent thyreoid tissue where cystic and calcareous changes were also present.

CASE VIII. *Clinical History:* Male, 73. Intermittent haematuria began in 1925. Pain in right loin and sacro-iliac region began in 1927. A swelling appeared in the latter situation in 1928. This

steadily enlarged. Haematuria continued; fibrinuria also present, the urine sometimes being very viscid and almost gelatinous. Skiagrams revealed erosion of the right ilium. Died July 1930.

Autopsy Findings: Large tumour of left kidney (28 ounces) with gross invasion of renal vein and projection of tumour into inferior vena cava. Metastases in lungs, liver, pancreas, thyreoid gland, ribs and ilium. The caudal pole of the right lobe of the thyreoid contained an irregular haemorrhagic metastasis 2 cm. in diameter with several neighbouring but connected satellite nodules (Fig. 9).

Histological Findings: Typical clear-celled papillary carcinoma of the kidney (Fig. 10). The thyreoid tissue exhibited some general fibrosis, vascular degeneration and pigmentation, but these changes were not excessive for the patient's age.

CASE IX. *Clinical History:* Female, 56. January 1929, pain and lump noticed in left breast; radical amputation in April; carcinoma simplex with axillary glands involved. September 1929, recurrence in right breast; amputation; carcinoma simplex; subsequent local recurrence and signs of intrathoracic extension. Died October 1930.

Autopsy Findings: Extensive nodular infiltration of both pectoral regions, with invasion of intercostal spaces and extensive involvement of pleurae and thoracic lymph glands. Metastases in liver, adrenals, peritoneum, abdominal and cervical lymph nodes, dura and thyreoid. The thyreoid was small, tough and poorly vesicular, and contained eight to ten metastatic nodules up to 5 mm. in diameter, as well as several diffuse areas of infiltration.

Histological Findings: Small spheroidal-celled carcinoma simplex. The thyreoid metastases occurred both as localised nodules and as diffuse infiltrations (Fig. 11). The thyreoid tissue itself was the seat of advanced fibrosis, parenchymatous atrophy and irregular adenoma formation with distorted irregular vesicles poor in colloid. Several of the metastatic nodules lay in the centres of adenomatous areas.

CASE X. *Clinical History:* Male, 54. April 1930, noticed small nodule in right ear near meatus. A month later mass appeared in neck just below ear. By June the ear nodule had become an ulcer 1.5 cm. in diameter on the inner aspect of the pinna, and there was a hard mass of glands in the upper cervical region. Diathermy of the ulcer given and radium needles buried in glands. Temporary improvement, but died in October 1930.

Autopsy Findings: Nodular recurrence in caudal wall of meatus, and large infiltrating mass in neck. Internal jugular vein obliterated and invaded and contained friable tumour thrombus. Massive metastases in lungs and thoracic lymph glands. A few small metastases in left kidney, right rectus abdominis muscle, mesentery, inguinal glands of both sides, and thyreoid. This last organ, otherwise substantially normal, contained two small white nodules each 4 mm. in diameter.

Histological Findings: Highly anaplastic non-cornifying epidermoid carcinoma with many mitoses, many giant tumour cells and frequent diffuse arrangement. The white nodules in the thyreoid proved to be small spherical adenomatous areas containing infiltrating metastatic tumour deposits (Fig. 12).

IV. Discussion and Deductions

The frequency of metastatic growths in the thyreoid gland

The numerical incidence of secondary tumours in any given organ is difficult to assess with accuracy, and this difficulty is greater in the case of certain organs which unfortunately are not always examined at autopsy with the same thoroughness as the major viscera. In many collected statistics which contain valuable figures concerning the incidence of metastatic growths in the lungs, liver, spleen and other principal organs, one feels less confident of the information relating to such viscera as the testis, the pituitary body or the thyreoid. Probably the German and other continental pathologists are the least fallible in this respect, and the following figures given by Müller (1892)[45] may be cited. In 521 autopsy cases of carcinoma, in which metastases were present in 47.2 per cent., the thyreoid gland was involved in 1.5 per cent. In 102 cases of sarcoma, 63.7 per cent. of which exhibited metastases, the thyreoid was involved in 3.1 per cent. Kitain (1922),[46] in a statistical study of 452 autopsies on cases of cancer, found the thyreoid gland the seat of metastases in 14 (*i. e.*, 3.1 per cent.), the sites of primary growth being breast 8, skin 1, larynx 1, pancreas 1, pharynx 1, thymus 1, lung 1.

My own experience suggests that the thyreoid is more frequently the seat of metastatic deposits than is generally recognised. Of my

ten cases, nine occurred in a series of 170 consecutive autopsies on unselected malignant cases of all kinds, the incidence of metastases in the thyreoid thus being 5.2 per cent. Admittedly no statistical deductions can be made from so small a series of cases; nevertheless I attribute this relatively high incidence of thyreoid deposits at least in part to the fact that the gland in each case was dissected out and thoroughly sectioned, a procedure not always adopted in routine autopsy work. Had this not been done, the metastases present in Cases II, IV, VII, IX and X could readily have eluded discovery. From personal experience, I am satisfied that mere bilateral section of the thyreoid in situ, a procedure frequently adopted, is an inadequate examination of the organ.

INFLUENCE OF TUMOUR-TYPE AND ORIGIN ON FREQUENCY OF THYREOID METASTASES

Little reliable information can be obtained from the literature regarding the relative incidences of thyreoid metastasis from various

	Cases
Carcinoma of breast	15
Malignant melanoma	9
Carcinoma of bronchi and lungs	8
Carcinoma of uterus	4
Carcinoma of kidney	3
Chloroma	2
Carcinoma of liver	2
Carcinoma of rectum	2
Carcinoma of pharynx	2
Carcinoma of stomach	1
Carcinoma of testis	1
Carcinoma of ovary	1
Carcinoma of prostate	1
Malignant rhabdomyoma of prostate	1
Carcinoma of skin of ear	1
Haemangio-endothelioma	1
Malignant sacral chordoma	1
Choriocarcinoma	1
Sarcoma of bone	1
Total	57

individual tumour groups. Kaufmann's impression that the incidence is relatively high in the case of melanotic growths receives statistical confirmation from the figures given by Eiselt (1861),[47] who, in 50 autopsies on such cases, found an incidence of 12 per

cent. This figure much exceeds the estimates cited above for malignant tumours in general.

Further information on the relationship between the type and origin of the primary neoplasm and the frequency of thyreoid metastases may be obtained by a tabulation of the origins of the 57 tumours reviewed in this paper.

The high place occupied by carcinoma of the breast is doubtless due to the great frequency of that disease. Yet it is noteworthy that an almost equally frequent neoplasm, gastric carcinoma, is poorly represented. Melanoma and lung carcinoma, both relatively uncommon tumours, take second and third places on the list. Lung cancer, which is recognised as possessing an unusual tendency to metastasise to the brain and adrenal glands (Dosquet, 1921),[48] evidently exhibits also a similar predilection for the thyreoid. The position occupied by melanoma in the table confirms the relatively high incidence of thyreoid metastases in this disease remarked by Kaufmann and by Eiselt.

THE RELATION OF METASTASES TO PREËXISTING ABNORMALITIES OF THE THYREOID

Frequently, records of secondary growths in the thyreoid give no detail regarding the condition of the thyreoid tissue. In a number of cases, however, in which structural details are recorded, the association of the metastatic deposits with areas of abnormal thyreoid tissue has been very striking. Attention is again directed to those cases which received special comment early in this paper. In Virchow's case of testicular tumour, the only sites of metastasis beyond the lungs were the sternum and an old nodular goitrous thyreoid. In Kaufmann's case of ovarian carcinoma, in Naegeli's case of rectal cancer, in Kettle's case of uterine carcinoma, in Sauer's case of chloroma, and in Prym's case of chorionepithelioma, the metastatic growths in the thyreoid were located in and restricted largely to adenomata, while the more normal thyreoid tissue was uninvolved. In Rost's case of "hypernephroma," a metastasis occupied an area of fibrous tissue in an old goitrous thyreoid. Accepting the metastatic character of Müller's case of haemangio-endothelioma, the metastasis in the thyreoid lay within an old fibrous adenoma. In the case described by Reinhart, chronic tuberculous thyreoiditis co-

existed with a metastasis from a lung carcinoma; and the author suggested that the presence of the tumour predisposed the gland to tuberculous infection. From Reinhart's description, however, it is apparent that the tuberculous disease in the thyreoid was not recent, exhibiting well developed tubercles and areas of fibrosis, and it is improbable that the multiple nodules of secondary growth antedated these chronic inflammatory changes. If, then, a causal relationship existed between the two processes, it is more probable that the tuberculous changes predisposed the organ to the establishment of the metastatic tumours, an interpretation the converse of that suggested by Reinhart.

In my own material, preëxisting abnormalities of the thyreoid tissue were a prominent feature. In Case II the gland exhibited extensive fibrosis and lymphocyte accumulation; in Cases III and VI, adenomatous, cystic and fibrotic changes were present throughout the organ, and several of the smallest chordoma metastases were situated within adenomatous areas. In Case VII the metastatic growth was located in an area of tissue which was the seat of old fibrosis and calcification. In Case IX the thyreoid tissue exhibited advanced fibrosis and adenomatous changes, and several of the metastatic nodules occupied adenomatous areas. In Case X both of the small metastases present lay within adenomata. Thus, in no less than six of my ten cases the metastatic growths present either exhibited a decided preference for adenomatous or fibrosed areas of thyreoid tissue, or else occurred in an organ which was the seat of universal retrograde changes decidedly exceeding normal limits. From the evidence afforded by these observations and with the several striking instances cited from the literature, I cannot avoid the conclusion that the normally slight susceptibility of thyreoid tissue to the development of metastatic growths is decidedly augmented by the presence of adenomatous and other retrograde structural changes in that tissue.

What factors might determine this predisposition of altered thyreoid tissue to metastatic growths? Two possibilities present themselves, (*a*) altered vascular conditions in adenomatous or other abnormal areas may favour the arrest of blood-borne emboli; or (*b*) structurally altered thyreoid tissue may be a chemically more favourable soil than normal tissue for the development of secondary neoplasms. These alternative hypotheses will be discussed briefly.

In support of the first hypothesis might be advanced the observations of Simpson (1913),[49] Monogenow (1913)[50] and others on the impoverished blood supply to thyreoid adenomata. The vascularity of adenomatous tissue is much less than that of normal thyreoid, and the vessels exhibit all grades of degenerative change. It might be argued, then, that the relatively poorly vascularised adenomata with their deteriorated vessels lack the "flushing" action obtaining in normal tissue, so that the effective lodgement of minute emboli is favoured. On the other hand, since the embolic influx into any tissue must be proportional to its blood supply, the diminished vascularity of adenomata necessarily reduces the chances of malignant fragments entering these parts of the organ. Hence while it is *possible* that vascular conditions in adenomatous thyreoid tissue may favour embolic arrest, it is also *certain* that these same conditions minimise the opportunities of embolic entry. Further, it is entirely an assumption that malignant emboli are in general so minute that differences in capillary calibre or velocity of blood flow in different tissues will influence to any great degree the chances of embolic lodgement. We know that the average diameter of the capillaries in various tissues is approximately equal to the diameter of a single red blood corpuscle and that the highly plastic red corpuscles frequently suffer great deformation in traversing the narrower capillaries (Krogh, 1929).[51] Malignant embolic fragments must be much less deformable than blood corpuscles, and their size must usually be much larger than that of a single erythrocyte; often, indeed, neoplastic emboli certainly consist not of single cells but of clumps of cells or of fragments of thrombus bearing malignant cells. Such fragments must certainly suffer arrest in the arterioles or capillaries of any tissue. For these reasons therefore it is improbable that vascular deterioration is the principal factor determining the different incidence of metastatic tumours in healthy and in altered thyreoid tissue.

The second hypothesis, that altered thyreoid tissue is more suitable than normal tissue as a nidus for malignant growth, is suggested by (*a*) the peculiar characters of the thyreoid parenchyma, which, with its large content of iodine-rich colloid, is a chemically unique tissue, and by (*b*) the high oxygenation of that tissue. Malignant cells have a relatively anaerobic metabolism (Warburg, 1930).[52] It is possible then that the thyreoid and other well arterialised tis-

sues are poor soils for malignant growth partly because of their high oxygen tension, while poorly oxygenated organs like the liver offer a metabolically more favourable nidus for the proliferation of arrested cancer cells. Now adenomatous and other retrograde changes result in atrophy of the thyreoid parenchyma and its replacement by poorly vascular fibrous tissue, and the increased vulnerability of adenomatous or fibrosed areas to malignant metastasis may be due to the partial loss of those parenchymatous and metabolic qualities which antagonise neoplastic development.

Some support for this hypothesis is afforded by consideration of the tumour types most frequently responsible for thyreoid metastases. Our review of 57 neoplasms has shown that, next to mammary cancer (15 cases), two relatively rare forms of malignant growth, melanoma (9 cases) and lung cancer (8 cases), were the most potent in producing metastatic deposits in the thyreoid gland, while many commoner neoplasms, *e. g.*, the alimentary carcinomata, are relatively ineffective in this respect. These observations strongly suggest that some metastasising neoplasms, notably melanoma and lung carcinoma, manifest a decidedly greater inherent capacity than others for colonising the thyreoid. It is difficult to see how the different incidence of thyreoid metastasis by different tumour-types can depend on any local vascular conditions in the organ. That it is determined rather by a variable metabolic relationship between thyreoid tissue and the various types of malignant elements which effect lodgement therein, appears much more probable. Some kinds of tumour cells, *e. g.*, those of melanoma suffering embolic arrest in the thyreoid gland, find their chemical environment suitable to continued extravascular multiplication, while to other kinds of malignant cells thyreoid tissue is an uncongenial soil, in which, therefore, these cell deposits become sterile. This sterility, however, is only relative, and continued proliferation of the malignant cells may ensue should they chance to lodge in an adenomatous or other abnormal area of the gland where retrograde processes have deprived the tissue somewhat of its inhospitable metabolic qualities.

Another striking point emerges on further consideration of those recorded cases in which thyreoid metastases have exhibited some notable association to other lesions of the organ. The responsible tumours in these cases were carcinoma of testis (Virchow), carcinoma of ovary (Kaufmann), carcinoma of rectum (Naegeli), carcinoma of

uterus (Kettle), chloroma (Sauer), carcinoma of lung (Reinhart), haemangio-endothelioma (Müller), "hypernephroma" (Rost), chorionepithelioma (Prym), carcinoma of rectum (my Case II), carcinoma of breast (Case III), chordoma (Case VI), carcinoma of stomach (Case VII), carcinoma of breast (Case IX) and carcinoma of skin (Case X). Observe that in these 14 cases, carcinoma of the lung is represented only once and melanoma not at all, despite our finding that, next to mammary cancer, these two forms of tumour are most frequently responsible for metastases in the thyreoid. It is notable in this respect that the only one of our own seven cases in which the thyreoid parenchyma was entirely healthy was one of melanoma, and this was also the case in other recorded examples of melanoma in which details are given concerning the thyreoid gland, those of Chalier and Bonnet, Mori, and Girdwood. Evidently then, those very tumour-types which possess a maximum propensity for colonising thyreoid tissue seldom exhibit any remarkable association with other abnormalities of that tissue; while, on the contrary, such notable associations are encountered frequently in the case of other growths which seldom produce metastases in the thyreoid. This strongly suggests that these latter growths find healthy thyreoid tissue an infertile nidus and hence tend to remain sterile therein, while such infertility is less in adenomatous and other diseased areas, which therefore are frequently present in association with metastases from neoplasms of small thyreoid-colonising capacity. These considerations confirm the predisposition of altered thyreoid tissue to metastasis, and support the metabolic rather than the vascular hypothesis regarding this predisposition.

In pondering these problems, it occurred to me that a study of other non-neoplastic embolic processes in the thyreoid tissue might shed light on the questions under discussion. Accordingly a search of the literature for records of pyaemic and other metastatic inflammatory lesions of the gland was made. Only one reference to the association of such a lesion with a thyreoid adenoma was discovered. Benelli (1912)[53] described a case of mycotic infection of the gastric mucous membrane. The thyreoid gland contained a metastatic mycotic abscess, and this was located within a thyreoid adenoma. This observation might appear at first to support the vascular rather than the metabolic hypothesis of the predisposition of adenomata to metastatic processes, but further consideration suggests an alterna-

tive and precisely opposite interpretation. Practical medicine recognises the curative influence of iodine in mycotic infections, and it is possible that in Benelli's case the mycotic organism found the iodine-deficient adenomatous tissue a more favourable soil than the normal iodine-rich parenchyma. This case indeed may be interpreted as actually illustrative of the biochemical conception of tissue predilection for metastatic development.

For the various reasons outlined above, I believe that the frequent association of secondary tumours in the thyreoid with other abnormalities of the organ is not to be explained as merely coincidental, but that structurally altered thyreoid tissue is indeed predisposed to metastatic developments, and that this predisposition depends on the chemical or metabolic qualities of the recipient tissues with respect to the requirements of malignant cells arrested therein. We return then to the view of Fuchs and Paget mentioned in our introduction. To adopt Paget's simile, malignant seed, though necessarily sown less lavishly in the altered than in the normal tissue, germinates more readily in the former.

ENDOCRINE DISTURBANCES OCCASIONED BY METASTASES IN THE THYREOID

Thyreoid deficiency resulting from neoplastic destruction of the thyreoid gland is exemplified by my Case V, reported in detail elsewhere. A remarkable observation made first by Hirschfeld (1906)[26] and later by Mori (1913)[31] is that exophthalmos, tachycardia, tremor and other thyreotoxic symptoms may result from a metastatic tumour in the thyreoid gland; Ewing (p. 949)[3] has observed the same event. In three such cases Mori found this organ to be the seat of colloid goitre with plentiful deeply staining secretion; while in another case of metastasis in the thyreoid without thyreotoxic symptoms the gland was poor in colloid. Mori concluded that the thyreotoxic state was due to excessive absorption of secretion from active thyreoid tissue subjected to mechanical pressure by the enlarging metastasis and its stroma. This conclusion appears to me to be based on inadequate data, and not to be supported by the observations of other writers. In many of the other cases reviewed in this paper colloid goitrous changes were recorded, and in my own material abundant colloid-rich tissue was present in Cases III, VI and VIII, yet no thyreotoxic symptoms had been present.

CONTIGUITY-INVASION OF THE THYREOID GLAND

Though strictly not falling within the scope of this paper, it is desirable to refer briefly to the phenomenon of direct invasion of the thyreoid gland by contiguous neoplasms. Primary tumours of the pharynx, larynx, oesophagus or thymus may infiltrate the thyreoid, and this event is a frequent finding in cases of extensive cervical glandular metastases from carcinoma of the lip, tongue and pharynx. In a series of 35 autopsy cases of epidermoid carcinoma of the head and neck [54] I found the thyreoid invaded by growth in nine cases. In one remarkable case of this kind [55] the extensive cervical metastases from a lingual cancer had almost completely destroyed the gland, and compensatory hyperplasia of an accessory lingual thyreoid had occurred.

Primary endothelioma of the cervical lymph nodes may invade the thyreoid gland, as in Flournoy's case (1907)[56]; and the same may be observed in Hodgkin's disease of the cervical region (Osler, 1885).[41] The writer has seen an enormous anaplastic carcinoma of the parotid gland, the peripheral extensions of which infiltrated the thyreoid; and malignant intrathoracic neoplasms may extend into the neck and directly invade this organ (Jacobs, 1927).[57]

Summary and Conclusions

1. Forty-seven collected records of metastatic growths in the thyreoid gland are reviewed, and ten personal cases are added and described.

2. Secondary tumours occur more frequently in the thyreoid than is generally recognised, and a plea is made for more thorough pathological examination of this organ in cases of malignant disease.

3. There are good grounds for believing that different types of tumours possess different intrinsic capacities for establishing metastases in the thyreoid, and that melanoma and lung carcinoma are the most potent in this respect.

4. There is strong evidence that adenomatous and other abnormal areas of thyreoid tissue are predisposed to the establishment of metastatic neoplasms, and that this predisposition depends on chemical or metabolic rather than on vascular changes in the altered tissues.

5. In the case of those neoplasms which display a maximum propensity for metastasising to the thyreoid (melanoma and lung can-

cer) notable association of the metastases with other abnormalities of the gland are observed only infrequently. Conversely, thyreoid metastases from growths of low thyreoid-colonising tendency exhibit remarkably frequent association with preëxisting abnormalities of the organ.

NOTE: I am indebted to Professor P. MacCallum of the Department of Pathology, Melbourne University, for his stimulating criticism and interest, and to members of the Honorary Staffs of the Austin and Alfred Hospitals, Melbourne, for their consent to my utilising the histories of the cases.

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DESCRIPTION OF PLATES

PLATE 38

FIG. 1. Case II. Vertical sagittal section of the right lobe of the thyreoid showing the metastatic growth at the upper pole (A). The fibrotic condition of the gland elsewhere is evident. (Natural size.)

FIG. 2. Case II. Photomicrograph of the metastasis shown in Fig. 1. A clump of loosely aggregated anaplastic tumour cells, some of signet ring type, are seen amidst thyreoid parenchyma which exhibits lymphocyte accumulation. × 180.

FIG. 3. Case III. Two sagittal sections of the right lobe of the thyreoid, showing the infiltrating metastatic growth, indicated by arrows. Observe the advanced adenomatous and cystic changes in the gland elsewhere. (Natural size.)

FIG. 4. Case III. Photomicrograph of the metastasis shown in Fig. 3. Mucoid adenocarcinoma is seen invading thyreoid tissue, which exhibits fibrosis, distortion of vesicles and aggregation of lymphocytes. × 80.

FIG. 5. Case III. Another area of the same growth, showing infiltrating carcinoma simplex. × 180.

FIG. 6. Case VI. Vertical sagittal section of the left lobe of the thyreoid, showing two translucent chordoma nodules denoted by arrows. Notice the conspicuous adenomatous, cystic and fibrous changes throughout the gland. (Natural size.)

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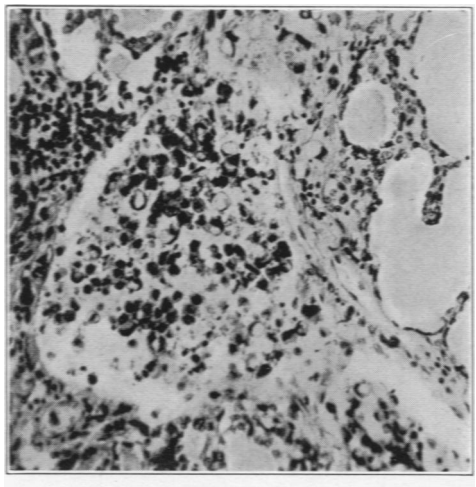

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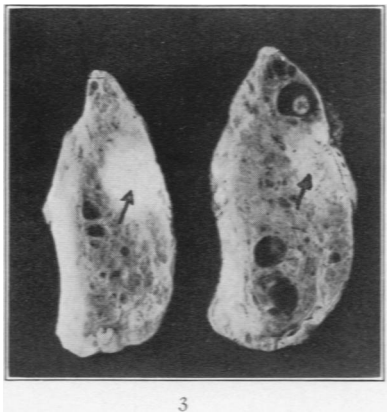

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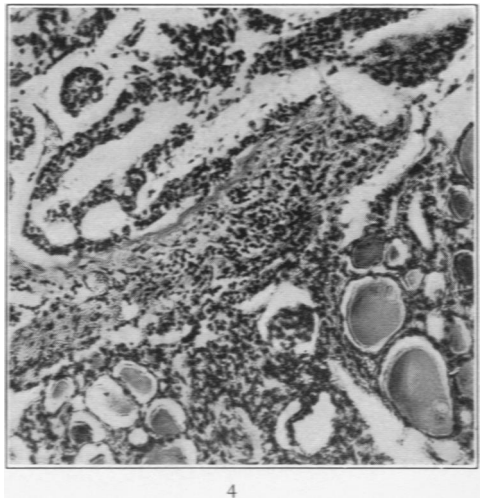

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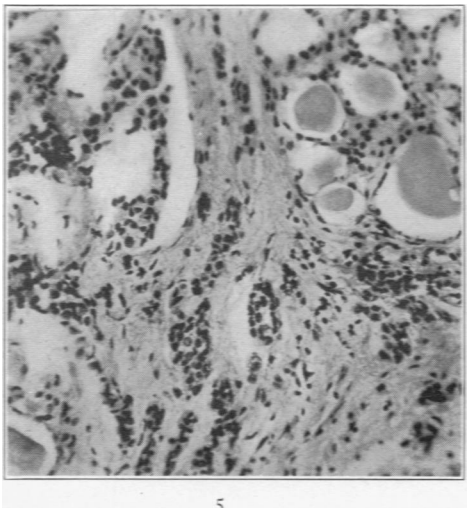

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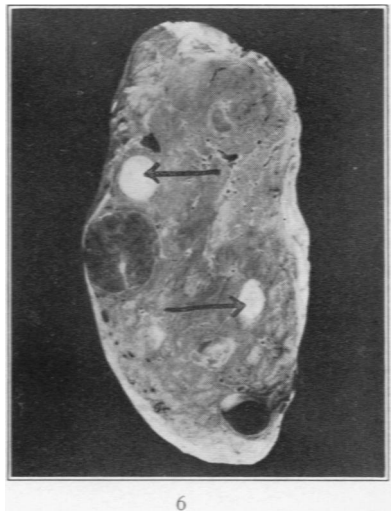


6

Willis

Metastatic Tumours in Thyreoid Gland

PLATE 39

FIG. 7. Case VI. Photomicrograph of junction of thyreoid and chordomatous tissue. The latter stains deeply because of its high mucoid content. The thyreoid exhibits advanced fibrosis, lymphocyte accumulation and atrophy of the parenchyma. × 80.

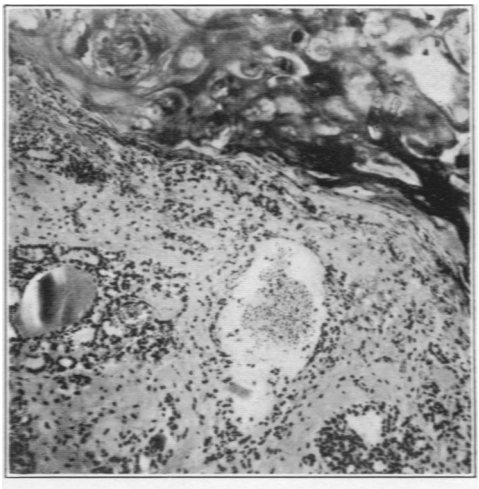
FIG. 8. Case VII. Photomicrograph from periphery of metastasis, showing thyreoid tissue penetrated by a large irregular acinus of adenocarcinoma. × 80.

FIG. 9. Case VIII. Vertical sagittal section of the right lobe of the thyreoid showing the irregular metastasis with satellite nodules in the caudal parts of the gland (A). (Natural size.)

FIG. 10. Case VIII. Photomicrograph showing the periphery of the clear-celled renal carcinoma invading thyreoid tissue. × 100.

FIG. 11. Case IX. Diffuse invasion of fibrosed thyreoid tissue by carcinoma simplex. × 60.

FIG. 12. Case X. Small adenoma of thyreoid containing a diffusely infiltrating metastasis denoted by the arrows. × 12.



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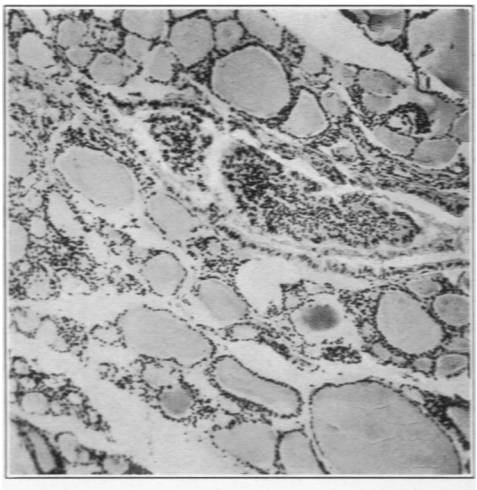

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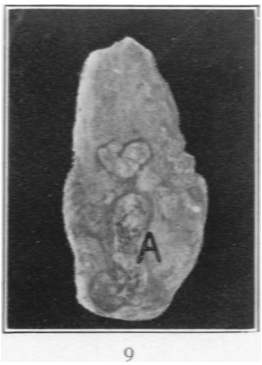

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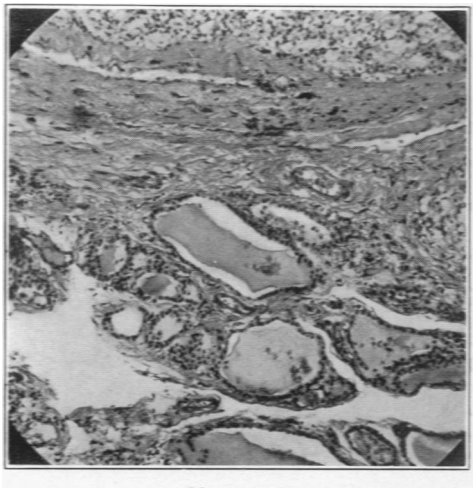

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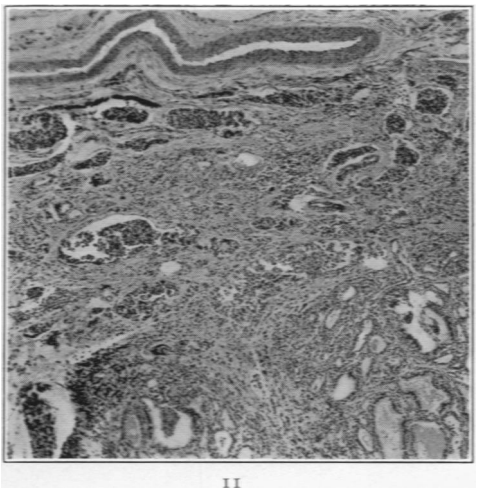

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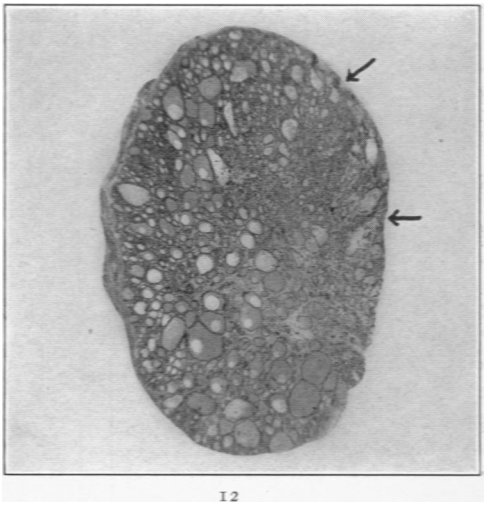

12

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Metastatic Tumours in Thyreoid Gland