METASTASIS IN SQUAMOUS CARCINOMA

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INTRODUCTORY

Secondary deposits of squamous carcinoma, with the possible exception of those in the local lymphatic glands, are of somewhat rare occurrence. Nevertheless, they are sufficiently common to be worthy of record. It is true that several cases of such metastases have been recorded in the literature from time to time, but it is generally agreed that, in comparison with the spheroidal- and columnar-celled tumours, those arising in squamous epithelium relatively rarely give rise to metastases.

The problem as to what factors determine the development of secondary deposits in one case of squamous carcinoma, and their absence in another clinically similar case, has not been satisfactorily solved, and it is with a view to correlating the results of pathological investigation with the available clinical data that the present series of clinical cases is recorded.

Ewing (1) states that "squamous epithelioma rarely produces bulky metastases," but he offers no adequate explanation as to the difference in behaviour of different tumours arising in various anatomical sites and developed in the ectodermal and entodermal layers of the embryo. As he points out, the appearance of a secondary tumour at some distance from the primary growth may arise in one of three ways: by multiple origin of primary growths; by continuous extension of a primary growth; by true metastatic growth arising from tumour-cell emboli. Naegeli (2) gives a statistical analysis of 190 cases of primary carcinoma of the skin and aural mucosa seen at Bern. No metastases, however, were observed in the internal organs. Crile (3) found secondary cancer foci in distant organs and tissues in less than 1 per cent of a series of 4,500 cases of cancer of the head and neck, all of squamous epithelial origin.
On the other hand, Halberstaedter and Simons (4) found metastases in 19.3 per cent of the infiltrating types of skin tumour when first seen. This was in a series of 556 cases. They draw attention to the importance of the character of the skin which is the seat of carcinoma, and point out that the outlook is more unfavourable in cases where the tumour arises in skin which is already altered by x-ray burns, lupus, old scars, or other factors. They fail to state, however, whether tumours arising in such altered skin are more prone to give rise to metastases than are tumours arising in normal skin. Nevertheless, they point out that the location of tumours is important in relation to direct infiltrative spread, for in positions directly over bone or cartilage, as in the eyelids, the internal and external auditory canal, the nose, on the forehead, or over the malar region, relatively little infiltrative growth can take place before the barrier of periosteum or perichondrium is reached.

I propose to give an account of a number of cases of squamous carcinoma with true distant metastases in the internal organs which have come within my own experience, and among which are examples of dissemination by infiltration, by vascular and lymphatic embolism, and by transplantation. In the series under consideration, regional spread to neighbouring lymphatic glands and direct extension of the primary growth to soft tissues or to bone in the vicinity are not regarded as true distant metastases, which alone are included. By the term, “distant metastases” is meant progressively growing autonomous deposits in the lungs, liver, kidneys, or other organs remote from the primary site.

During the past four years, I have had the opportunity of making post-mortem examinations on a large number of hospital patients with advanced malignant disease. In a high proportion of these cases the primary site of new growth was in squamous epithelium, either on the
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skin or on mucous membranes. Of these cases, only a small percentage (about 10 per cent) showed macroscopically visible metastases in the internal organs (Figs. 1, 2, and 3).

In a series of 158 consecutive autopsies which were carried out in The Glasgow Royal Cancer Hospital on cases of squamous carcinoma of various regions of the body, the primary site and the distant metastases were found to be distributed as shown in Table I.

TABLE I: Distribution of Primary Tumours and Distant Metastases in a Series of 158 Consecutive Autopsies on Cases of Squamous Carcinoma

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Metastases in</th>
<th>Total Autopsies</th>
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<tbody>
<tr>
<td>Tongue</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>Lip</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Fauces and pharynx</td>
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</tr>
<tr>
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</tr>
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<td>Vulva</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>32</td>
<td>3</td>
</tr>
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<td>1</td>
</tr>
<tr>
<td>Skin</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Nasal duct</td>
<td>1</td>
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</tbody>
</table>

158 with metastases in 19

In addition to these cases of undoubted squamous epithelial origin, there came to autopsy, during the same period, 10 cases of bladder carcinoma and 5 cases of "nasal carcinoma," some of which were of
squamous character, but in none of these were macroscopic signs of distant metastases found.

Referring to Table I, it is plain that in this series the primary squamous epithelial tumour showed a tendency to form metastases more commonly when it arose in certain situations. Though primary carcinoma of the tongue is acknowledged to be a rare source of distant deposits, in this series it furnishes 6 examples in 40 cases. Brief outlines of the clinical histories of those cases in which metastases were found at autopsy are set forth below.

**Case Reports**

**Case 1**: D. C., male, aet. 63, gave a history of dysphagia of five months' duration. On examination, an area of ulceration could just be seen at the root of the tongue on the right side; it was about the size of a shilling. There was bleeding from the surface. Enlarged nodes were present below the mandible on the right side.

![Fig. 3. Hemisected kidney, from Case 6, showing solitary cystic squamous deposit in the upper pole](image)

Post-mortem: An extensive ulcerative carcinoma involved the base of the tongue, extending down into the larynx as far as the vocal cords. Multiple small white nodules of growth were found in the liver, lungs, and kidneys, and a massive growth was invading the bodies of the 7th and 8th thoracic vertebrae. The right supraclavicular nodes were enlarged. (The nodules in the liver and kidneys were discovered only by cutting the organs into multiple thin slices, each not more than a quarter of an inch in thickness.)

Histology: A keratinizing squamous carcinoma. There is a considerable degree of polymorphism and dedifferentiation in the metastatic deposits in the lungs, liver, and kidneys.

**Case 2**: J. S., male, aet. 78, was admitted to hospital with a seven months' history of ulceration of the tongue, which spread, on the left side, from the tip to the junction of the anterior two-thirds and the posterior third, and down to the floor of the mouth, involving the mucous membrane. The submaxillary nodes were palpable. Death occurred from septic bronchopneumonia.

Post-mortem: There was a fungating mass of growth in the mouth, extending down to the pharynx just above the epiglottis. Enlarged nodes were found at the hilum of the lungs.
The liver contained a number of white metastatic nodules, the centres of which were liquefied, forming thick-walled cysts of malignant tissue. These nodules varied in size from a millet seed to a hazelnut, and contained serous fluid.

**Histology:** The primary growth is a highly cellular and rapidly growing squamous carcinoma. The liver nodules are extremely polymorphic. The central zone of the nodules has undergone colloquative necrosis. The liver cells in the neighbourhood of these deposits are greatly congested and show some degree of compression and atrophy, as well as being infiltrated and destroyed by growth.

**Case 3:** F. M., male, aet. 51, was admitted to hospital with enlarged submaxillary and cervical nodes. Four months prior to admission, a partial excision of the tongue had been performed. Treatment was by deep x-ray therapy, after injection of calcium phosphotungstate. Massive ulceration occurred, and death was due to haemorrhage.

![Fig. 4](image)

**Fig. 4. Case 6: Metastatic Involvement of Submaxillary Region and Cervical Nodes, the Latter Showing a Fungating Massive Growth Which Has Ulcerated Through the Skin**

Deposits were present in lungs, and left kidney (Fig. 3).

**Post-mortem:** A large ulcerated mass occupied the region of the left anterior triangle of the neck, immediately under the body of the mandible. Masses of enlarged submaxillary nodes were present. There was no destruction of bone in the vicinity of the tumour, which was ulcerated towards the surface. There had been much haemorrhage into the tumour before death, but its origin could not be determined.

**Histology:** The lungs showed no gross pathological change of note, but, microscopically, small embolic nodules of malignant squamous epithelium were found in the peribronchial lymphatics. The primary tumour is a very diffuse type of growth, with much keratinization and some calcification.

**Case 4:** H. M., male, aet. 71, was admitted to hospital with a history of having noticed, seven months previously, a small pimple on the left side of the tongue. Death occurred from septic bronchopneumonia.

**Post-mortem:** The tongue showed, on the left side, a small, shallow, depressed area, lined by hypertrophied, finely formed papillae, and showing no ulceration. The base of the depressed area was firm but not hard, and there was no sign of tumour extension into the neighbouring structures. The larynx and oesophagus were normal. However, at the bifurcation, the anterior wall of the trachea was perforated by a soft fungating growth,
extending forward from a hard mass of tumour in the retrotracheal glands. This mass formed a solid block of elastic and partly necrotic tissue, spreading down along the oesophagus below the tracheal bifurcation and through the diaphragm into the abdomen. Below the diaphragm, the nodular mass was situated between the liver, the lesser curvature of the stomach, and the pancreas, binding all these structures together but not, apparently, invading them. There was syphilitic aortitis.

**Histology:** A highly keratinizing squamous carcinoma, showing many cell nests. The mediastinal nodes were very fibrotic and showed many squamous deposits. All sections showed vast post-mortem degeneration.

**Case 5:** D. McD., male, aet. 68, in February 1933 complained of a sore throat and had some dysphagia. On admission, April 16, 1932, the tongue could be protruded for about an inch beyond the front teeth. The posterior dorsum was swollen and firm. There were two ulcers with indurated edges, one on the right side and the other on the mid-line. The fauces and alveolar margin, and floor of the mouth were not affected. No nodes were palpable. Radium was inserted May 2, 1932. Death occurred May 5.

**Post-mortem:** There was extensive sloughing of the tongue and mouth. One nodule was found in the apex of the right lower lobe; secondaries.

**Case 6:** D. M., male, aet. 55, was admitted to hospital with a fungating ulcer of the tongue, of twelve months' duration. This was situated on the left side, near the base, and extended onto the alveolar margin. Radium needles were inserted, but the growth became infected, and there was extensive sloughing of the tissues. The patient died three months later, from septic bronchopneumonia.

**Post-mortem:** The left side of the tongue was almost completely destroyed by a fungating, ulcerating growth. A nodule was found at the upper pole of the left kidney, about 1.5 cm. in diameter, showing central necrosis and liquefaction. A few small nodules were found in the lungs. (Figs. 3 and 4.)

**Histology:** The primary tumour and the renal deposit, as well as the lung nodules, show the histology of a well differentiated squamous carcinoma, with epithelial pearl formation. The primary tumour is considerably more keratinized than are the metastatic deposits.
Case 7: A. B., male, aet. 64, gave a history of lumps appearing on the left side of the neck, followed, after four months, by ulceration of the floor of the mouth. The tongue and mandible became involved. Death occurred from gangrene of the lung nine months after the first manifestations of disease. (Fig. 5.)

Post-mortem: There was a tumour arising from the floor of the mouth, which had produced a swelling over the mandible, with a discharging sinus. The bone was exposed over a wide area and eroded by growth, which had produced multiple fractures. The floor of the mouth and the under surface of the tongue were ulcerated, and the submental and submaxillary nodes were suppurating. The pleura was thickened over the whole surface of the right lung; over the apex its thickness was about 1/10th of an inch. It was infiltrated by growth and, apparently, by lymphatic spread. The left apex had a similar appearance. There was gangrene in both lower lobes.

Histology: Squamous carcinoma; lymphatic dissemination in lungs.

Case 8: J. McN., male, aet. 72, was admitted to the hospital with a history of having noticed a swelling on the left side of the neck six months previously. An epitheliomatous patch was seen on the left soft palate. Enlarged nodes were present behind the angle of the mandible on the left side. Death was due to septic pneumonia. (Fig. 6.)

Post-mortem: A large tumour was found, extending from above the angle of the mandible about half-way down the neck. The overlying skin was not involved. On separating the rather dense adhesions between parietal and visceral pleurae, a peculiar carcinomatous spread was found extending over the parietal pleura. Groups of flat round nodules, with raised edges, were scattered over the pleura, the largest group occupying the right apical region in the angle between the diaphragm and pleura, where a glandular mass was present in relation to a large flat plaque, similar to those described above. A few similar masses were present on the visceral pleura, on the left side.

The bronchial and retrotracheal nodes were enlarged and showed whitish deposits of growth. The interior of the larynx was free from tumour, but the entrance was surrounded by a ring of tumour tissue. The left soft palate, tonsil, and oropharynx were all involved in the carcinomatous process, and showed massive necrosis. The growth encroached on the tongue, on the left side, at its middle third. There was partial erosion of the left common carotid artery, but the intima was quite soft.

Histology: A highly keratinizing squamous carcinoma, with well formed cell-nests; similar appearance in the lung nodules.

Case 9: Mrs. A. C., aet. 70, was admitted to hospital with an eight weeks' history of pain in the cheek. There was a fungating, cauliflower-like mass on the buccal surface of the
the left cheek, about the size of a florin. It extended from the cheek onto the left alveolar margin, and, posteriorly, into the fauces and tonsil. Radium gave great improvement for a while, but the condition ultimately progressed and the patient came to autopsy six months after admission.

Post-mortem: The patient was an adipose woman. Deposits of growth were found in the lung, pleura, and diaphragm, and a few small deposits under Glisson's capsule.

Histology: Squamous carcinoma.

Case 10: J. McC., male, act. 58, was admitted in an exhausted condition, but was fully conscious. He stated that for the past few days he had been unable to swallow anything but sips of water. There was no visible or palpable disease in the neck, but nodules were palpable in the liver. Death occurred four hours after admission.

A communication from the patient’s doctor states that he began to have pain in the throat, on swallowing, in January 1932. The oesophagus was practically completely obstructed; there was hoarseness, with bronchitis in the right chest.

Post-mortem: The patient was an adipose woman. Deposits of growth were found in the lung, pleura, and diaphragm, and a few small deposits under Glisson’s capsule.

Histology: Squamous carcinoma.

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Histology: Squamous carcinoma.

Post-mortem: The patient was an adipose woman. Deposits of growth were found in the lung, pleura, and diaphragm, and a few small deposits under Glisson’s capsule.

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Histology: Squamous carcinoma.
which were quite fixed. There had been some bleeding from the oesophagus for six months prior to admission.

Post-mortem: A small oval mass of nodes was found on the left side of the neck, below the angle of the mandible. There was an extensive carcinoma of the oesophagus behind the larynx, extending upward on the left pharyngeal wall to the back and upper surface of the tongue on the left side, where there was a raised ulcer the size of a shilling. The ulceration involved the upper part of the left side of the larynx, above the vocal cords, the left half of the epiglottis being also ulcerated. There was also complete obstruction of the upper end of the oesophagus. A mass of nodes was found in the left side of the neck, the size of a walnut. The liver showed a few small secondary nodules in the region of the gallbladder.

Histology: Squamous carcinoma.

CASE 13: W. McP., male, aet. 65, admitted to hospital with a year's history of dysphagia, was found to have a growth of the oesophagus. There was a hard nodular mass in the right supraclavicular region, with oedema of the suprasternal notch. Death followed a severe haemorrhage from the mouth.

Post-mortem: There was a large ulcerated area occupying the entire lower third of the oesophagus and extending into the cardiac end of the stomach, where there was a second mass the size of a plum. There was also a small flat papilloma near the pylorus. The oesophageal mass was adherent to the aorta and to the hilum of the right lung, where there was a large abscess. There was a necrotic mass of nodes in the right side of the neck. Multiple secondary deposits were found all over the liver and throughout its substance, with plaques of tumour on the under side adherent to the stomach. One large nodule was found on the lower pole of the left kidney. The lungs were the seat of septic bronchopneumonia and a lung abscess.

Histology: The primary growth in the oesophagus was a very cellular type of squamous carcinoma. The kidney showed a large deposit of keratinizing squamous carcinoma of the cortex, with a fibrous stroma. Groups of malignant cells, which retained their squamous characters and which were definitely hyperchromatic, could be seen permeating
down the pyramids along the line of the straight tubules. They appeared to be lying in lymphatics, and to be causing compression of the tubules. (Figs. 7 and 8.)

**Case 14:** Mrs. S. O'H., female, aet. 51, was admitted to hospital Nov. 17, 1931, complaining of difficulty in passing urine and faeces, and of pain in the right iliac fossa and across the abdomen, of at least six months' duration. She never had any abnormal vaginal discharge. She had had four children, the last nineteen years before. On examination, a swelling of Bartholin's gland, on the right side, was found, with a small patch of ulceration. There was a deep ulcerated crater in the posterior vaginal wall, with some involvement of the cervix.

**Post-mortem:** The body of the uterus was almost entirely destroyed by a fungating growth arising in the cervix. There was a sloughing fistulous communication between the vagina and the bladder. The growth was very extensive and compressed the ureter in the region of the trigone. It had infiltrated the pelvic wall and the sacrum. There was a large, suppurating inguinal gland on the right side, and the para-aortic glands were enlarged, firm in consistency, white in colour, and obviously infiltrated with growth. At the upper pole of the right kidney, a white nodule, the size of a hazelnut, was found. No metastases were found in the other organs.

**Histology:** Squamous carcinoma, with a deposit in the kidney. Deposits were also found in lung and nodes.

**Case 15:** Mrs. I. C., female, aet. 34, was admitted to hospital in August 1931, complaining of a watery discharge from the vagina, continuous since the birth of her last child, eight months before. There was never any pain. The patient had had eight pregnancies (one breech presentation). On examination, a large fungating pedunculated mass was found growing from the cervix.

On Jan. 15, 1932, the patient complained of left-sided pain and backache. Rectally, a large mass could be felt bulging backwards, which seemed to extend upwards towards the iliac crest. On Feb. 13, 1932, phlebitis developed in the left leg; this spread into the external iliac vein, and the thigh was swollen and discoloured. On May 13, 1932, an x-ray plate showed extensive disease of the chest. Death occurred June 7, 1932, from septicaemia and confluent bronchopneumonia.

**Post-mortem:** A fungating carcinoma of the cervix was found, extending along the lymphatics to the para-aortic glands. The wall of the pelvis and the three lower lumbar vertebrae were invaded by a direct extension of the growth. The left external iliac vein was thrombosed, and there was some compression of the ureter, causing hydronephrosis of the left kidney.

A large nodular growth, the size of a walnut, was found at the apex of the left lower lobe of the lung. There was no appreciable pleural effusion. No pathological change was seen in the brain or spinal cord.

**Case 16:** Mrs. H. F., female, aet. 40, was admitted with a seven months' history of vaginal discharge and lumbar pain. On examination, the cervix was found to be fixed and ulcerated, and a mass of growth extended round the vaginal vault, filling the posterior fornix and extending down the vaginal wall. Two months later a pedunculated strawberry-red growth, the size of a cherry, appeared on the inner aspect of the right ankle. A month later this had increased to a lobulated mass, one lobe being the size of a grapefruit and the other the size of a pippin. Death occurred three months after admission.

**Post-mortem:** In its upper two-thirds the vagina was infiltrated by a tumour, giving it a fairly rigid wall about one-third of an inch thick. The cervix and vagina were ulcerated, and there was a vesico-vaginal fistula at the trigone. The body of the uterus was unaffected. Several metastases were found in the liver, varying in size from 1/4 to 3/4 inch. The renal pelvis and the ureter were dilated from the obstruction by a mass in the pelvis. The kidney tissue was very anaemic. There was destruction of the ischium and largely of the acetabulum, but the head of the femur was not affected. There was an extensive bony destruction of the pelvis on the right side, but not on the left. There was a fluctuant swelling of the right knee. Two large pedunculated swellings, ulcerated on the surface, were found growing from the inner aspect of the right foot, one about 4 1/2 x 3 x 2 inches, and the other about 3 x 2 x 1 1/2 inches. They were soft in consistency and necrotic in the centre. The mid-tarsal bones, the metatarsal bones, and the tarsal end of the tibia were found to be extensively destroyed by tumour.
**Histology:** The tumour is composed of large masses of cells, which are mainly spheroidal in character, the masses showing central necrosis. In other places the tumour is less defined, being composed of fairly uniform areas of spheroidal cells resembling a sarcoma. However, the general appearance of the tumour shows the condition to be an encephaloid type of squamous carcinoma. There is no obvious keratinization. Tissue from the foot, the liver, and the vagina presents the same histological picture.

**Case 17:** Mrs. M. C., female, age 52, was admitted to hospital with a nodular enlargement of the right breast. There was an extensive deep ulcer, about 3 inches in diameter, above and external to the upper outer quadrant. No nodes were palpable. The history dated from four and a half months prior to autopsy. A lump appeared in the right breast and, on admission to hospital, ten weeks before death, the whole upper half of the right breast was swollen, plum-coloured, and hard. Induration and swelling extended back to the axilla, where there was a small secondary nodule, about the size of half-a-crown.

**Post-mortem:** The right parietal pleura was studded with a number of nodules of growth, apparently by direct lymphatic extension. There was no involvement of the vertebrae, ribs, or sternum.

**Histology:** The histology is that of a squamous carcinoma of the skin of the breast. The tumour is composed of masses of oedematous squamous cells, showing many areas of focal necrosis and calcification. Post-mortem degeneration is marked. The pleura shows deposits of squamous cells in the peri-arterial lymphatics.

**Case 18:** A. S., male, age 71, was admitted to hospital nine months before death, with a carcinoma of the left side of the tongue, involving the fauces and mandible. The chief symptoms were difficulty in opening the mouth and gradual swelling of the left side of the face.

**Post-mortem:** There was a large ulcerated mass in the left tonsillar area, with extensive spread to the adjacent structures. There was ulceration extending to the adjacent surface of the cheek, and the mandible had undergone pathological fracture.
The left ventricle showed a secondary nodule of growth. There were a few small nodules in the liver. At the lower pole of the left kidney a small tumour mass was found. The pancreatic tissue and the suprarenals were almost replaced by tumour tissue.

**Histology:** There is an extra-renal tumour on the capsule of the kidney, which has infiltrated the renal parenchyma. The malignant cells show a good deal of polymorphism, and mitotic figures are abundant. There is considerable keratinization and some focal necrosis and pyknosis. In some places the malignant cells have an almost alveolar arrangement. (Fig. 9.)

In the heart muscle groups of malignant cells can be seen in the perivascular lymphatics and spreading along the interfascicular fibrous trabeculae. (Fig. 10.)

In the suprarenals there is a wide permeation of all the zones by columns of malig-
CLINICAL ASPECTS

An integral part of the present enquiry consisted in the collection of clinical data with a view to correlating these with the pathological findings, and, although the results of such correlation are disappointing, in that they yield no consistent features applicable to any particular clinical type of tumour, they are set forth for what they are worth. The purely pathological investigations relating to the problem of the metastasis of squamous epithelial tumours have been described elsewhere (Price, 5). From the clinical standpoint, tumour-bearing pa-

![Image](https://via.placeholder.com/150)

FIG. 11. EPITHELIOMATOUS ULCER AT ANGLE OF THE JAW, FOLLOWING LUPUS PRESENT SINCE CHILDHOOD

The patient was a male, aged forty-four. There were no metastases in the internal organs.

tients were examined in respect of the following criteria, with a view to their possible etiological significance on the development of metastases: (1) age, (2) duration of disease, (3) sex, (4) rate of growth of primary tumour, (5) interval between the appearance of the primary tumour and the development of metastases, (6) general condition of patient, (7) severity of destruction of normal tissues.

Age of Patient: It is often stated that cancer in the aged tends to run a comparatively benign course, and indeed there are many examples on record to support this theory. Conversely, cancer in the very young tends to be exceptionally malignant. The truth of these broad statements, however, is confined within certain ill-defined limits. Randall (6), for example, describes several cases of carcinoma of the prostate in patients over seventy-five years of age, with no metastases in the internal organs, whereas in a large series of younger patients, bone metastases and deposits in the pelvic, para-aortic, and retroperitoneal lymphatic glands were common. However, in the case of malignant squamous epithelial tumours, such benign tendencies in the aged are not borne out in the series here reported. It is true that the majority of tumour-bearing patients come within the fifth and
sixth decades of life, but individual cases show wide variations with regard to age of onset of malignant disease, both within and outside these limits. Furthermore, there are considerable variations in the estimated duration of the disease prior to its fatal termination. Table II is an analysis of the cases which are the subject of the present

<table>
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<tr>
<th>Case</th>
<th>Age and Sex</th>
<th>Duration of Disease (months)</th>
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<th>Metastases</th>
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<td>40 F</td>
<td>11</td>
<td>Cervix</td>
<td>Liver, pelvic bones, tibia, tarsus</td>
</tr>
<tr>
<td>17</td>
<td>52 F</td>
<td>14½</td>
<td>Skin of breast</td>
<td>Lung</td>
</tr>
<tr>
<td>18</td>
<td>71 M</td>
<td>9</td>
<td>Fauces</td>
<td>Heart, kidney, suprarenal</td>
</tr>
<tr>
<td>19</td>
<td>7 M</td>
<td>15</td>
<td>Penis</td>
<td>Lung, aorta</td>
</tr>
</tbody>
</table>

investigation. From the table, it would appear that the age of the patient and the duration of the disease are very variable and bear no constant relationship to the incidence of metastasis.

Sex of Patient: The sex of the patient, from general observations, is in itself of little consequence, except in so far as the female genitalia provide a source of many primary tumours of squamous epithelial origin. This, however, is fully compensated for in males by the much greater incidence of tumours of the mouth. In this connection, it is noteworthy that of females with carcinoma of the tongue or mouth a high proportion are found to be pipe-smokers, a fact which adds evidence in favour of chronic trauma as a potent factor in determining the site of election for the development of malignant disease.

Rate of Growth of the Primary Tumour: The rate of growth of the primary tumour plays an inconstant part in the development of metastases. Secondary deposits are sometimes widespread and advanced, and may announce their presence clinically before the existence of the primary tumour is suspected. It might be expected that the slowly growing tumours would tend to give rise to metastases more freely than the fulminating types, for such inherent regional resistance to malignancy as the tissues initially possessed would tend to diminish with the passage of time. This hypothesis, in my estimation, finds some support in clinically observed facts. Muir (7), however, states
that widespread metastases are present equally frequently in the hard
cancers and in the soft rapidly growing varieties. Extremely rapidly
growing tumours may give rise to very widespread deposits in the
course of a few weeks, as also may small slowly growing primary
tumours.

Interval between Appearance of Primary Growth and Development
of Metastases: The interval elapsing between the appearance of the
primary tumour and the development of metastasis proves to be of no
prognostic importance. It varies from a few weeks to many years in
different cases in which the primary tumours may be clinically and
histologically similar. Biopsy examination, therefore, is of little help
in computing the probable clinical course of individual cases, as far
as the formation of metastases is concerned. From such examinations,
however, it is sometimes justifiable to venture on a tentative prognosis
as to the probable clinical progress of the tumour, for cytology is an
index of the rate of growth, and anaplasia often forebodes metastasis.

General Condition of Patient: In the absence of specific signs or
symptoms, the general condition of the patient frequently affords no
cue as to the certain presence of metastases in the internal organs.
The great majority of cases that come to autopsy present a typical pic-
ture of cancerous cachexia; the disease is advanced and there are often
much sloughing and destruction of tissue, in addition to which there
may be intercurrent infection, such as septic bronchopneumonia, pyel-
tis, or meningitis. In some cases cachexia would seem to be of a spe-
cific nature, dependent entirely on the presence of a neoplasm, and
associated with a degree of wasting out of all proportion to the physical
destruction of tissues or to mechanical interference with alimentary
functions. Nevertheless, in such cases as these, distant metastases are
by no means invariably present. On the other hand, there are some
patients whose general condition is comparatively good, but in whom
widespread malignant dissemination has taken place. Natural re-
sistance to malignant disease and regional resistance to metastases
are thus seemingly independent of general bodily health.

Severity of Destruction of Normal Tissues: Here, again, there is no
correlation with the presence or absence of metastases. There may be
extensive destruction of tissue in the neighbourhood of the primary
growth, with erosion and pathological fracture of the mandible, verte-
bræe, or other bones; yet such destructive growth is not necessarily
associated with the presence of distant metastases. In other clinically
similar cases, however, metastases may be found. On the other hand,
comparatively insignificant primary tumours may give rise to the most
extensive metastatic deposits in the internal organs.

Conclusions

1. The evidence available from the foregoing general considerations
as to the relationship of clinical and pathological data is sufficient to
indicate that there is no correlation between the clinical condition of
the patient and the development of distant metastases.
2. There is no constant relationship between the site of the primary tumour and the site of the distant metastases. The commonest sites for metastases in this series are lungs, 13 cases; liver, 7 cases; kidneys, 5 cases. Less frequently metastases were formed in other situations.

3. From a wider consideration of the development of metastases from numerous primary tumours of various types, the only consistent feature that emerges is that tumours arising in certain primary sites have a tendency to form metastases in certain tissues of predilection. There is a peculiar relationship between the site of the primary tumour and the site of the secondary deposits.

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REFERENCES