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GENERAL PRACTICE

Observations on the Natural Course of Skin Cancer

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ABSTRACT

The variations in the natural course of skin cancer are discussed in detail. Basal cell carcinoma (when properly classified) and squamous cell carcinoma have a reasonably predictable course; malignant melanoma and mycosis fungoides do not. Histological examination may not provide sufficient evidence on which to base a prognosis concerning a particular tumour; clinical evaluation may be of much greater value. The different rates of growth of any one tumour appear to be more closely related to host factors than to tumour virulence.

SOMMAIRE

L'auteur expose en détail les variations de l'évolution naturelle du cancer de la peau. Les épithéliomes épidermiques (à condition d'être classés convenablement) et les épithéliomes pavimentaux ont une évolution qui est raisonnablement prévisible. Par contre, les mélanomes malins et les mycoses fongoïdes ont une évolution imprévisible. L'examen histologique peut se révéler insuffisant pour y fonder le pronostic d'une tumeur particulière; l'évaluation clinique peut avoir une valeur bien plus considérable. La vitesse de croissance d'une tumeur donnée est davantage fonction de facteurs personnels que de la virulence de la tumeur.

"To know the natural progress of diseases is to know more than half of medicine."—ARMAND TROUSSEAU†

AS MANY members of the profession, particularly those in Saskatchewan, will recall, in addition to 42 years of private practice in Welwyn and Regina, Dr. Frederick Dennis Munroe was for five years Minister of Health in the Provincial Legislature. During that time he organized the Saskatchewan Cancer Commission, the first of its kind in the British Commonwealth, and cancer clinics were subsequently established at Regina and Saskatoon.

Like so much of modern medicine, the expert management of patients with cancer calls for sophisticated knowledge and techniques which are beyond the scope of any one individual. The team approach is employed in the care of skin cancers in the Ottawa Clinic of the Ontario Cancer Treatment and Research Foundation. A radiotherapist, a plastic surgeon, and a dermatologist all participate in such care with the close co-operation of a pathologist. The various members of the team do not always agree, but the opinion of each is invited and respected. Follow-up examinations are carried out by the entire team so that each sees the good and the bad results of all types of therapy. It is our belief that the patients get better care as the result of this team effort. It seems to me that Dr. Munroe was anticipating this type of modern consultative cancer clinic 30 years ago.

Very little is known about the natural course of cancer, including skin cancers, because for obvious reasons these lesions can rarely be left untreated. However, by close and intelligent clinical study much can be learned about the natural course of skin cancer. Skin cancer, although rarely causing death—except in the case of malignant melanoma—is the most common type of cancer. In 1962 the Ontario Cancer Treatment and Research Foundation[1] and the Saskatchewan Cancer Commission[2] reported that about 25% of all the new cancers registered were skin cancers. The actual number of patients with skin cancer is quite large; for example, 1676 new patients with skin cancers were treated at the Ontario Cancer Clinics, and 611 were admitted to the Regina and Saskatoon Clinics in that year.

The natural course of skin cancer can be discussed under four headings, *viz.* rodent ulcer (basal cell carcinoma), squamous cell carcinoma, malignant melanoma and mycosis fungoides.

RODENT ULCER

Rodent ulcer (basal cell carcinoma) often presents as a small elevated pearly nodule with central ulceration (Fig. 1). The vast majority of these tumours slowly increase in size over a number of years. Schrek and Gates,[3] in an excellent study of several hundred cases, found that lesions of this nature had a median size of 1.9 cm. and a median duration of 3½ years. Warren, Gates and Butter-

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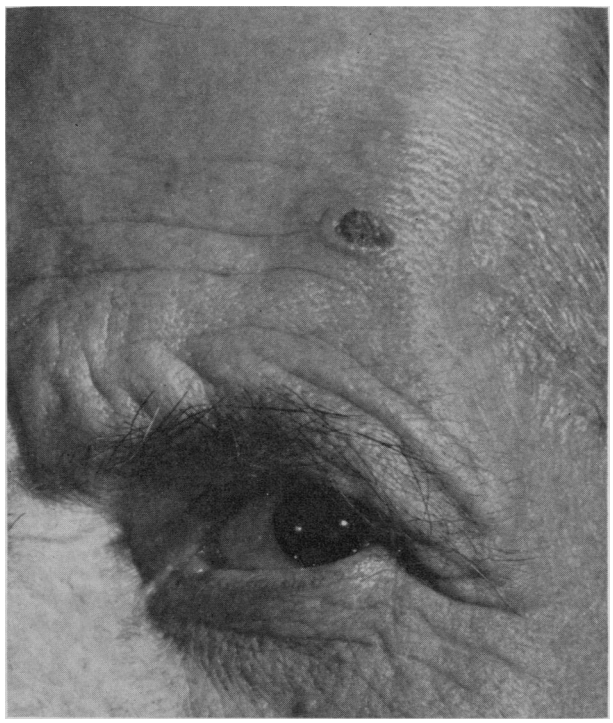

Fig. 1.—Rodent ulcer on forehead. Note pearly, raised border with central area of necrosis.

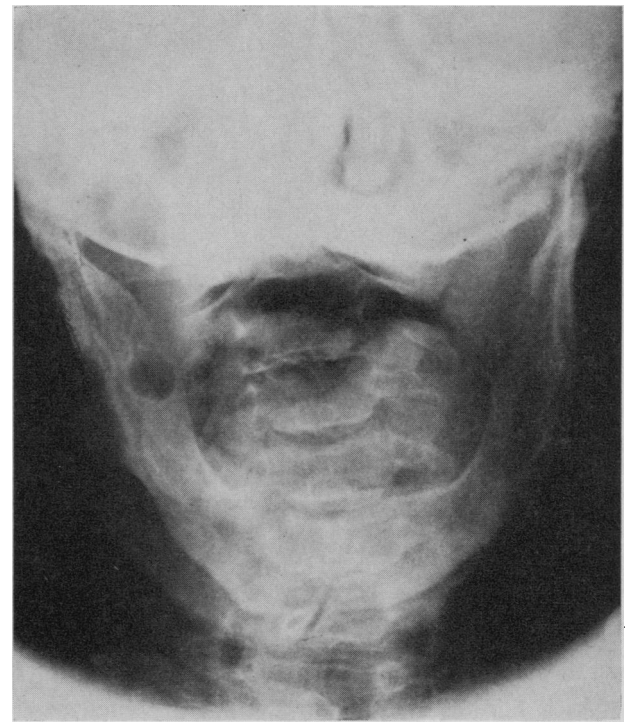

Fig. 2.—Case 1. Basal cell nevi syndrome. Jaw cyst in right mandible.

feld[4] described the average size as 2.5 cm. and the average duration as five years. That the growth rate of these lesions is approximately ½ cm. per year is a good approximation in most cases. Unless these tumours are near an orifice, their treatment is neither urgent nor difficult. For the vast majority, I use electrodesiccation and curettage,[5] which gives results equal to radiotherapy and surgical excision. The reason that these tumours can be successfully treated with relative ease is that they are not highly invasive. However, in view of the radical forms of treatment often proposed for these small tumours, it is one of the most overtreated of locally malignant cancers.

Not all rodent ulcers can be controlled by simple electrodesiccation and curettage, and the experienced clinician may often be able to diagnose these unusual cases when they are first seen. One group of these unusual rodent ulcers is the Gorlin-Goltz syndrome (hereditary basal cell cancer of the skin, or the basal cell nevi[6] syndrome). This syndrome consists of multiple basal cell cancers, jaw cysts and congenital rib abnormalities; palmar keratoses and frontal bossing are associated findings.

CASE 1

A.T. died at the age of 65 with a brain abscess secondary to a penetrating basal cell carcinoma of the external auditory canal. In addition, he had multiple (about 50) basal cell carcinomas on his head, neck and torso, jaw cysts (Fig. 2) and a bifid rib. One son (R.T., aged 34) has had five rodent ulcers and one squamous cell cancer removed from his face. He also has jaw cysts and a patch of superficial multicentric basal cell carcinoma on his left flank. One daughter (L.T., aged 38) had a bifid rib, jaw cysts and palmar keratosis. Another son (E.T., aged 45) has jaw cysts, and three rodent ulcers have been removed from his face.

Another son (H.T., aged 46) had about 14 basal cell cancers on his face and torso; some were of the superficial multicentric type. Multiple jaw cysts have been removed by his dental surgeon. Histological examination of these jaw cysts showed a cystic cavity lined by normal-appearing stratified squamous epithelium. He also has palmar and plantar keratoses and webbing between the second and third toes on both feet.

His son, aged 12 (A.T.'s grandson), has undergone enucleation of jaw cysts on three occasions. He has no basal cell carcinoma at the present time.

The rodent ulcers in the Gorlin-Goltz syndrome have three important clinical features: (1) the multiplicity of tumours; (2) their onset between 20 and 40 years; and (3) their occurrence on skin that has not been damaged by the sun.

A second group of unusual rodent ulcers is that small percentage (perhaps one or two cases out of 100) which are virtually uncontrollable. Some of this group may show metastatic disease.

CASE 2

J.E.W., aged 70, had a growth on the right side of his neck which started at age 61. At age 66, a 5 x 3 cm. ulcerative lesion was biopsied and showed a basal cell carcinoma of the skin; tumour was present in the adjacent lymph nodes. Two radical operations and cobalt therapy failed to control the local disease. He died in hospital of massive intracerebral hemorrhage.

Canad. Med. Ass. J.
Mar. 13, 1965, vol. 92

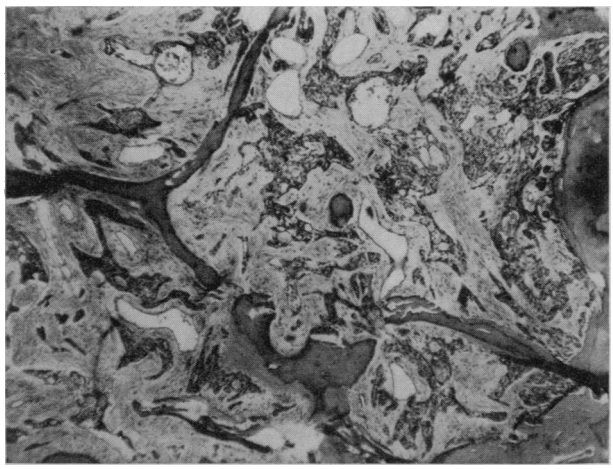

Fig. 3.—Case 2. Metastatic basal cell carcinoma in vertebrae. (Hematoxylin and eosin, approximately × 100.)

Postmortem examination showed, in addition to residual local disease, basal cell carcinoma in vertebrae (Fig. 3), ribs, skull and retroperitoneal and cervical lymph nodes. The total duration of the disease was nine years.

It is hard to imagine any treatment which would have been successful in this case.

It is important to note that histological examination of the three types of rodent ulcers previously described (i.e. the common, the basal cell nevus and the metastasizing rodent ulcer) shows no significant histological differences. It is remarkable that three histologically similar rodent ulcers will have completely different clinical courses. In this regard, studies by Teloh[7] and Thackray[8] are interesting. Teloh attempted to establish a correlation between the histological characteristics of basal cell carcinomas and their rates of growth. He found that only the degree of inflammation and the extent of invasion could be statistically related to the rate of growth. However, these two histological characteristics may well be the result of host resistance. Thackray studied the histological features of basal cell carcinoma, comparing those cured with those not cured by radiotherapy. The only significant histological feature he noted was the extent to which the growth was "infiltrative". From an examination of his photomicrographs I conclude that by "infiltrative" he means "sclerosing". It is a well-known clinical fact that sclerosing (or morphea type) basal cell carcinomas are difficult to cure, no matter what type of treatment is used. Rodent ulcers, like men, cannot be fully understood if they are viewed only after they have been pickled in formalin, coloured and cut in pretty little slices.

In addition to the two above-mentioned rare and unusual rodent ulcers (the basal cell nevi syndrome and the metastasizing basal cell cancer), there are other types of basal cell carcinoma which have reasonably characteristic clinical courses. The sclerosing rodent ulcer is an extremely slow-growing tumour requiring 10 to 15 years to reach 2-3 cm. in diameter. Another slow-growing rodent ulcer is the superficial multicentric type, which sometimes appears following long-term exposure to arsenic. It has the interesting characteristic of usually remaining attached to the epidermis and penetrating less than 1 mm. into the dermis. Familiarity with both these types is essential in planning rational therapy.

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma is the second most common skin cancer and is a moderately slow-growing tumour. In a review of several hundred squamous cell carcinomas, Schrek and Gates[3] found the median size to be 1.9 cm. and the median duration to be 1 1/5 years. Almost nothing is known about the genesis of those squamous cell carcinomas which arise from solar keratoses (Fig. 4) on

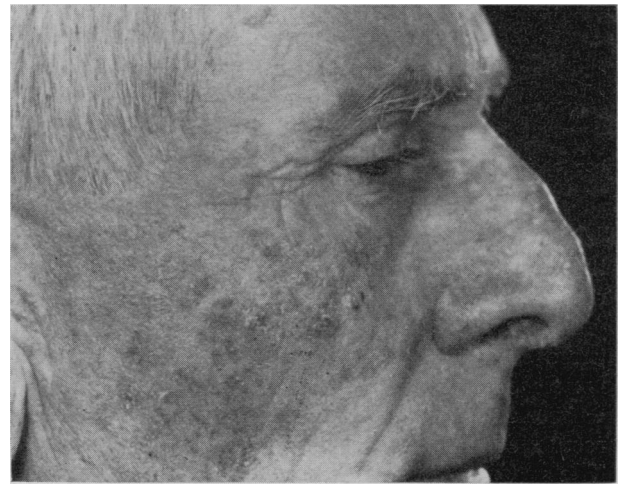

Fig. 4.—Sun-damaged skin showing numerous solar keratoses.

sun-damaged skin on the face, neck or dorsum of the hands and forearms. The percentage of solar keratoses (which histologically are carcinomas *in situ*) that progress to squamous cell cancers must be very small. I believe this transformation occurs more frequently in severely sun-damaged skin; the latter, incidentally, may show a striking clinical and histological similarity to radiodermatitis. The paucity of knowledge about the natural progress of solar keratoses makes it impossible to plan any sort of rational preventive therapy. Treatment should be instituted when lesions show clinical evidence of rapid growth or ulceration.

The shortcomings of the histopathological examination should be emphasized. The pathologist often cannot determine whether a particular lesion is a true cancer or merely an "active" solar keratosis.

Squamous cell carcinoma of the skin rarely metastasizes. In our review of 108 cases[9] only six showed evidence of metastases and all of these were large lesions (from 3 to 7 cm. in diameter) and of long duration (four to five years).

MALIGNANT MELANOMA

The experienced clinician can predict with reasonable accuracy what most rodent ulcers and squamous cell cancers will do. The situation with respect to malignant melanomas is quite different. From 96 malignant melanomas that we have seen at the Ottawa Civic Hospital over the past 10 years, four have been chosen which illustrate some aspects of the natural course of this type of skin cancer.

CASE 3

G.R., aged 91, was admitted to hospital *in extremis* and died as a result of arteriosclerotic cardiovascular renal disease. He had a seven-year history of a superficial black lesion on the right inner arm with enlarged lymph nodes in the right axilla (Fig. 5). At

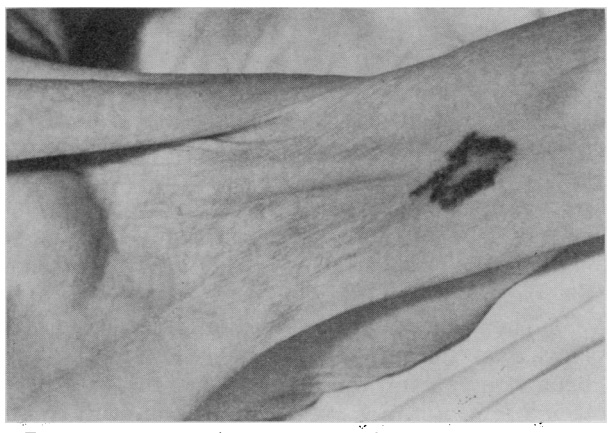

Fig. 5.—Case 3. Active compound pigmented nevus on arm with metastatic melanoma in axillary lymph nodes.

postmortem examination, only the lymph nodes in the right axilla showed metastatic melanoma. The histology of the primary lesion was compatible with that of an active pigmented compound nevus.

CASE 4

Mrs. H.W., aged 55, had a flat black-brown freckle on the right instep which had been there at least since she was 30 years of age. For four months before biopsy,

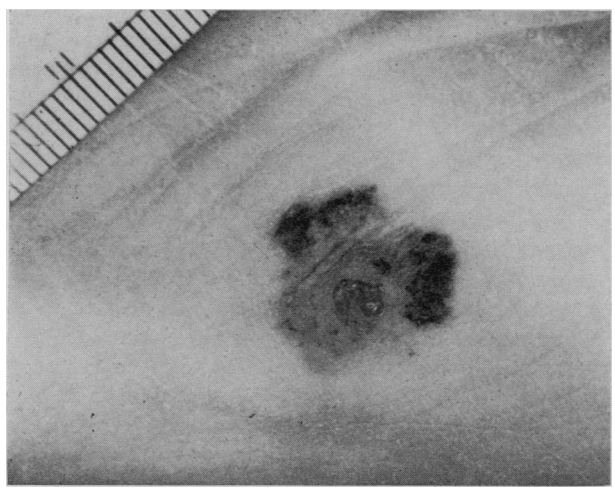

Fig. 6.—Case 4. Active junctional nevus with central area of malignant melanoma in right instep. (Scale in mm.)

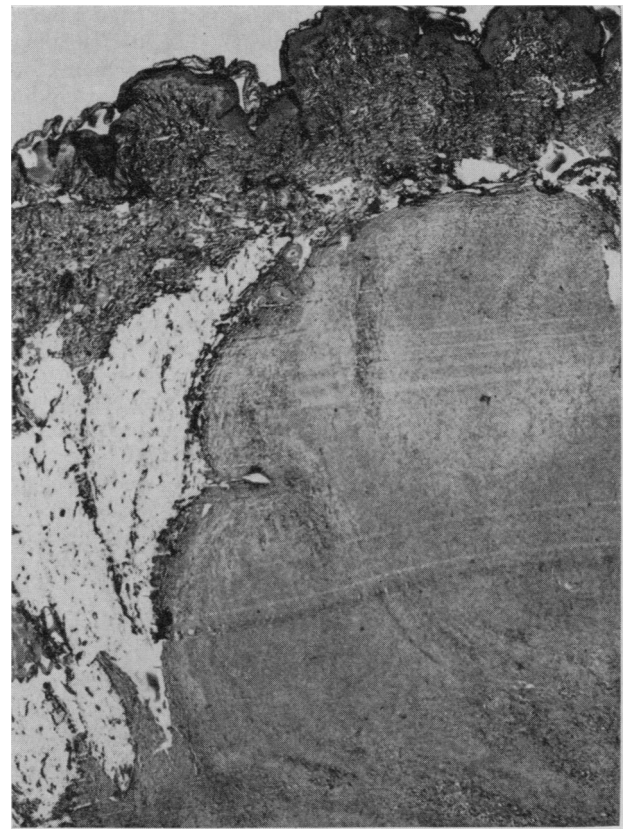

Fig. 7.—Case 5. Malignant melanoma locally recurrent 15 years after initial excision. Note extensive fibrosis. (Hematoxylin and eosin, approximately × 15.)

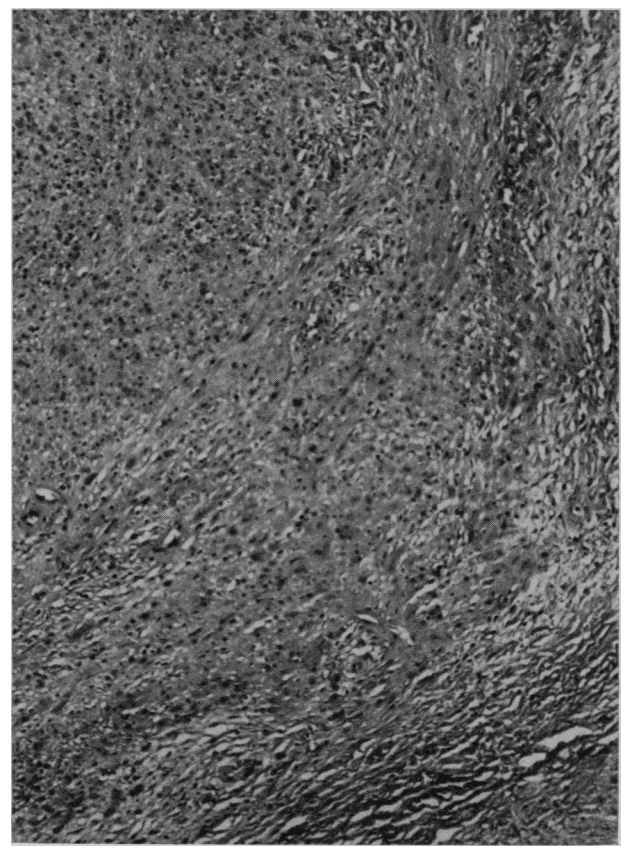

Fig. 8.—Case 5. Detail of Fig. 7. Note fibrosis in right lower corner and malignant melanoma cells in central area. (Hematoxylin and eosin, approximately × 120.)

Canad. Med. Ass. J.
Mar. 13, 1965, vol. 92

some bleeding and crusting had appeared from a 6-mm. nodule in the centre of the freckle (Fig. 6). Histological examination showed that malignant melanoma was present only in the central nodule; the surrounding tissue was made up of active junctional nevus. With a small superficial lesion and such a short duration the prognosis seemed good. However, the patient died of generalized malignant melanoma in 2½ years.

CASE 5

Miss E.I., aged 55, had a malignant melanoma of two years' duration which had been widely excised from the outer portion of the right lower leg at age 40. Fifteen years later she noted a nodule beneath the site of the primary excision, and a swelling in the right groin. Re-excision and subsequent histological examination revealed malignant melanoma at both sites. The recurrent subcutaneous local lesion showed extensive fibrosis (Figs. 7, 8 and 9) which was similar to that described by Sumner[10] in a case of apparent spontaneous complete regression following pregnancy.

CASE 6

Mrs. P.L., aged 49, had always had a "birthmark" on her left lower leg. She said that at age 39, when feeding chickens, "a hen pecked her exactly on the birthmark". At age 41 she had a black, slightly elevated, nearly circular mole slightly larger than a 5 cent piece. It had been bleeding. Two small lymph nodes were present in the left groin. She refused all treatment and went to a female lay "physician" who applied a "plaster to draw out" the tumour. The patient said that the treatment was successful because all the "roots" came out. Four months after this procedure her family physician noted a pale non-indurated scar at the site of the original tumour and again the lymph nodes were noted in the groin. At age 49 she presented with enlarged lymph nodes in the left groin and widespread multiple ulcerating subcutaneous and cutaneous nodules which on histological examination were secondary malignant melanomas. The original tumour site was marked by a thin white atrophic scar. There were no metastatic nodules near this scar. She died in the same year of disseminated disease. This malignant melanoma had been present for 10 years, during which the patient had virtually no treatment.

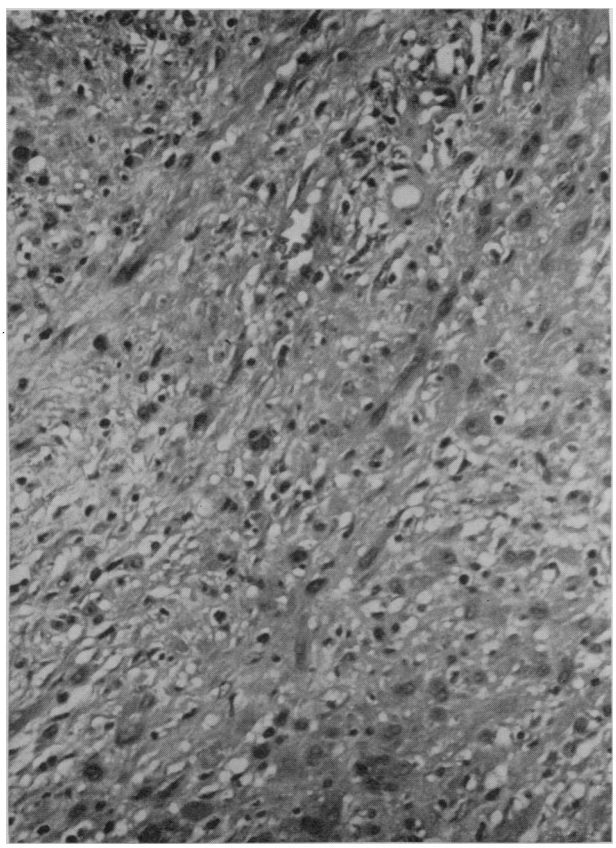

Fig. 9.—Case 5. Detail of Fig. 8, showing malignant cells with interspersed fibrous tissue. (Hematoxylin and eosin, approximately × 250.)

A discussion of the natural history of malignant melanoma is made difficult in view of the following inconsistencies:

1. The patient may have metastases with no obvious primary tumour. In this instance it is possible that the metastases caused the primary lesion to disappear.

2. The patient may have metastases from a comparatively innocent-looking lesion which histologically is not a malignant melanoma—these lesions might be thought of as benign metastasizing melanomas (Case 3). Perhaps the ultimate criterion for malignancy should be the presence of metastatic disease.

3. The patient may develop metastases from small (less than 1.0 cm.) superficial lesions which have been present for only a few months (Case 4). Whether or not metastases are present at the initial examination is obviously of crucial prognostic importance. In my opinion, if no metastatic disease is present, wide local excision of the primary tumour will almost always result in successful treatment; if metastatic disease *is* present, the prognosis is poor, and in many of these cases, innate host resistance will determine the course of the illness. The difficulty is that there is no way of identifying the presence of microscopic metastatic deposits of tumour in the adjacent lymphatics, in the regional lymph nodes or in a distant organ at the time of the original examination.

4. The patient may die of disseminated disease within one year; he may develop numerous local and distant metastases which have little apparent effect on his general health (Case 6); he may develop late (10 or more years) local or systemic disease (Case 5); or the tumour may undergo partial or complete spontaneous regression.

5. The tumour may arise from melanocytes in a pre-existing pigmented nevus (Case 6), from melanocytes in a lentigo maligna which has been present from five to 40 years (Case 4), or from the melanocytes in apparently normal skin. No malignant melanoma arises overnight. Lund and Kraus[11] believe that this tumour "evolves from a precancerous stage to a so-called superficial or *in situ* stage and then to a frankly malignant neoplasm." The passage of many years may be necessary for this evolution.

Certainly all malignant melanomas do not present with these bizarre features. Of the 96 melanomas we have studied, 20 had one or more of the above-mentioned unusual features. There is obviously no such entity as a typical or classic malignant melanoma. Because it is impossible to determine whether or not metastatic disease is present at the initial examination, and because of the wide variation in its natural progress, one cannot be dogmatic about the treatment of this skin cancer. Furthermore, to speak of curing malignant melanoma is a trifle presumptuous.

Malignant melanoma is the only skin cancer that has been reported to have undergone complete spontaneous regression.[10, 12, 13] Some sclerosing rodent ulcers may show central healing, but I have never seen a rodent ulcer or a squamous cell carcinoma disappear spontaneously. However, once again it is wrong to be too dogmatic. Perhaps we are so absorbed in treatment that the possibility of regression is never considered and the body is never given a chance to show what it might do to the tumour. Hundreds of keratoacanthomas were treated as squamous cell carcinomas up to 10 years ago, and were never allowed to follow their natural course to complete spontaneous regression without treatment. In this instance, the physician was relying on histological criteria which were not biologically valid.

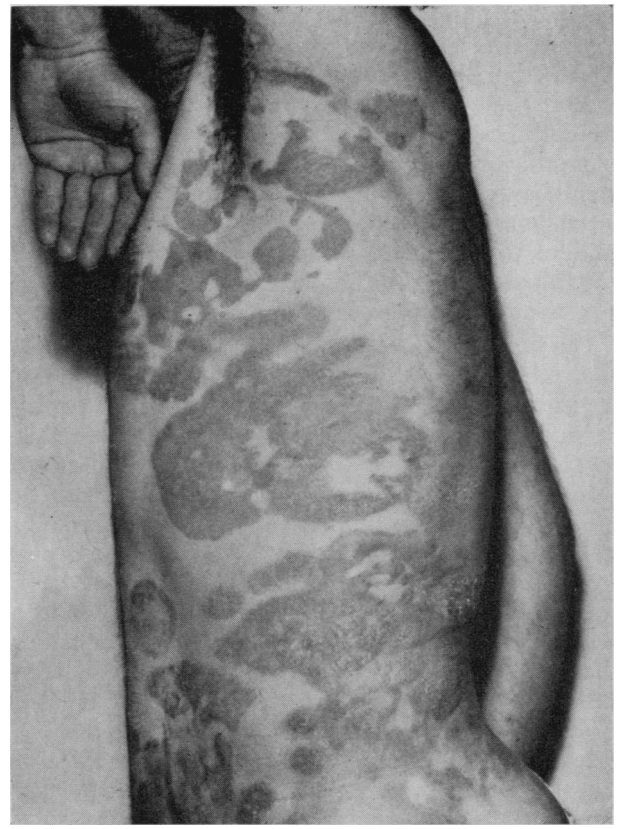

Fig. 10.—Parapsoriasis *en plaque* with mycosis fungoides.

MYCOSIS FUNGOIDES

The tremendous variation in the natural progress of mycosis fungoides (Fig. 10) and the other lymphomas of the skin is well known.

CASE 7

Miss G., aged 75, had parapsoriasis *en plaque* that had started at the age of 28. Mycosis fungoides was diagnosed on biopsy of a nodule at age 59. The patient still has lesions of parapsoriasis and mycosis fungoides. All search for associated systemic disease has been fruitless. The total duration of her disease is almost 50 years.

CASE 8

Mrs. L.C., aged 58, first noticed psoriasiform patches at the age of 49. Biopsy of a tumour nodule at age 56 showed mycosis fungoides (Fig. 11). She died with widespread skin lesions two years later. Postmortem examination showed extensive mycosis fungoides in lymph nodes, lungs, kidneys and breast. The total duration of the disease was nine years.

This degree of variation in the natural progress of mycosis fungoides is similar in many respects to that noted in Hodgkin's disease, both from the clinical and pathological points of view.

Factors Influencing the Course of Skin Cancer

As has been illustrated in this paper, the histological findings in skin cancer may be of little value in establishing a prognosis. Clinical examination—that is, determining what the tumour has done locally and whether or not metastases are present—can in many cases provide a reasonable basis for predicting the future course of the tumour. In

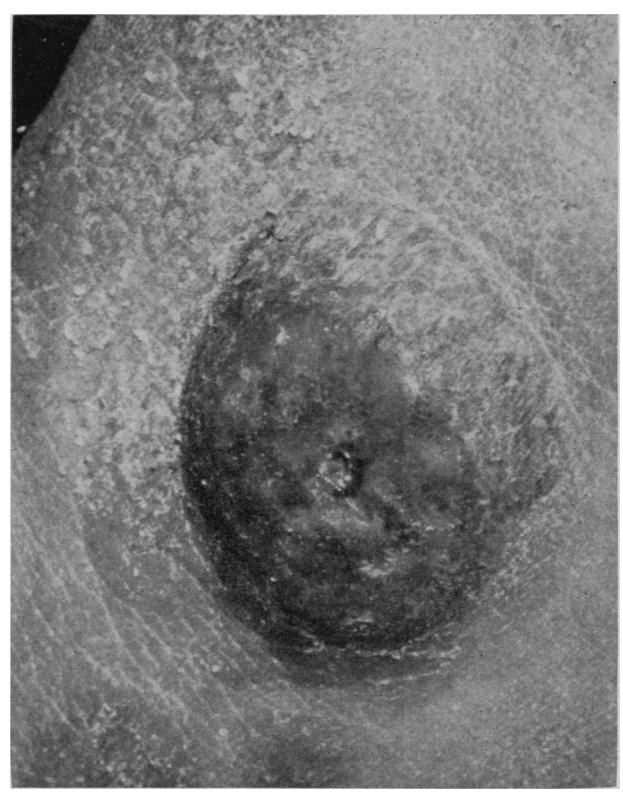

Fig. 11.—Case 8. Mycosis fungoides tumour.

Canad. Med. Ass. J.
Mar. 13, 1965, vol. 92

other words, malignancy (which is a relative term) is primarily a clinical or biological concept. For this reason, the physician should not be surprised to find that there is considerable variation in the biological response to skin cancers. This response is more variable with malignant melanomas and lymphomas than with basal and squamous cell carcinomas of the skin. As with all disease, knowledge of the range of the biological response of the individual patient to the particular disease is necessary in order to plan treatment.

The biological factors which determine the course of a particular skin cancer in a particular patient are virtually unknown. Age does not appear to be an important factor; but in view of the fact that skin cancers are unusual in the 20-40 year old group (except for malignant melanoma) it is difficult to make any general statement on this point. Certainly most basal cell carcinomas in this younger age group are not difficult to treat. However, we have seen a few patients in this age group with rodent ulcers that defied all therapy. On the other hand, I have seen elderly infirm patients in whom large rodent ulcers developed relatively quickly. It used to be said that malignant melanomas were aggravated by pregnancy. Two recent reports suggest that pregnancy probably has no effect on these skin cancers.[14, 15] The role of other host factors such as general health or co-existing disease is unknown.

SUMMARY AND CONCLUSIONS

An attempt has been made to outline the natural course of various forms of skin cancer based on the author's experience.

There is a considerable, usually predictable, variation in the natural course of basal and squamous cell carcinomas of the skin.

There is a considerable, frequently non-predictable, variation in the natural course of malignant melanoma and lymphomas of the skin.

There are definite limitations to the value of the pathological examination of these skin cancers as a guide to their natural course. In many instances information obtained from clinical examination is just as important as that obtained by pathological examination.

It is probable that the different rates of growth of any one tumour are due more to host factors as yet unknown than to differences in the virulence of the tumour.

Intelligent therapy of skin cancer must be based on what is known—or *not* known—about the natural course of the lesion, even though this knowledge is at times grossly inadequate.

The photographs and photomicrographs were prepared by the Department of Medical Photography, Ottawa Civic Hospital.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

GAS GANGRENE IN 1915

We have had five cases of gas gangrene in this series of which two have died; two have been saved after having their arms amputated and one, the case of fracture of the femur, is convalescing and has kept his leg. In all these cases the bacteriologist has found in the pus the bacillus aerogenes capsulatus, and on one or two occasions it has been cultivated from fragments of clothing adhering to the fragment of shell on its removal. In both of the arm cases the metal was removed from the forearm and the track curetted and cleansed with tincture of iodine. The next day the temperature had risen and the pulse was quicker, the wounds discharged bubbles of gas of the peculiar odour and thin reddish pus, and the arms above were discoloured. The arms were opened with large incisions and irrigated with 10 per cent chloride of zinc. Dr. Depage prefers this solution to one of carbolic. The next day the discolouration had increased proximally and distally, and the arms were amputated at the shoulder joint. During the last week or so we have almost been in despair as gas gangrene has appeared on several wards in apparently simple wounds, which had been thoroughly scraped and cleaned out with iodine under anæsthesia, and simple rifle bullet wounds of the forearm and leg have not been immune. Practically all the cases of gas gangrene have been in men wounded at Nieuport. The quarters are dirty there and the men often live huddled together in cellars, which may account for the infection. In Constantinople during the Balkan war, Dr. Depage says that they did not find it necessary to curette every simple rifle bullet wound. We have lost several cases lately (not included in this series) even after amputation of the limb. Now we are endeavouring to stay the spread of the infection by opening the wound widely, employing irrigations of zinc chloride and injections of oxygen into the tissues, and by making circular incisions of the skin, and subcutaneous tissues above the areas of discolouration. Gas gangrene and not tetanus is the problem with which we have to contend.

On our ward in the first one hundred cases we had only one of tetanus. This developed in a boy on the twenty-first day after having been wounded by a shell which caused a compound fracture of the thigh. With injections of the serum he soon recovered, and at most only had slight stiffness of the neck and jaw muscles. There have been four cases all told so far in the hospital out of four hundred cases treated, and only one has died.—T. A. Malloch, *Canad. Med. Ass. J.*, 5: 362, 1915.