# AETIOLOGY OF FACIAL CANCER*

## A SPECULATIVE AND DEDUCTIVE SURVEY

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In submitting this theory of aetiology we are able to present for consideration observations made on a group of patients seen at the Combined Clinic, Groote Schuur Hospital, which was established in 1948 to deal with the numerous cases of cancer of the face and mouth which were being encountered.

That exposure to the elements, and more particularly to the sun, for many years is necessary for the development of rodent ulcer has long been accepted; it has been called 'sailor's wart' for years. Thus, the face and nose are the commonest sites for its occurrence for they are the most exposed parts right from childhood. The back of the ear is a very exposed part when the head is turned away from the sun and is also a common site of rodent ulcer. The upper eyelid is in shadow under the brow when the eyes are open and rodent ulcer rarely occurs on it; the lower eyelid is not in shadow and it is a very common site of rodent ulcer. The upper lip is shadowed by the nose and the moustache and seldom develops carcinoma, whereas the lower lip, facing upwards, bears the full brunt of solar irradiation and is a common site of sunburn and epithelioma. So, too, are the dorsa of the hands, where similar lesions develop.

Rodent ulcer on the scalp is rare because the hair has a shading and protecting effect. We have seen only a few cases in hairy areas; those in the scalp occur almost exclusively in bald men. As baldness only comes on in middle age, the bald scalp is not exposed to the sun for as many years as the face and the hands. Most bald men habitually wear hats to prevent sunburn and both these factors may account for the rarity of rodent ulcer of the scalp.

We are now able to present 1,209 cancers of the face and 470 cases of epithelioma of the lip for consideration. The management of these two groups of cases has already been discussed.[1,2] Fig. 1 illustrates the prevalence of the varieties of facial cancer, and shows that rodent ulcer is by far the commonest type encountered. Fig. 2 illustrates the relative frequency of rodent ulcer and of cancer of the lip in male and female and in European and Coloured groups. European and Coloured attendances at the hospital are in about equal numbers, so that the disparity in frequency is highly significant.[1] It is believed that the pigment in his skin protects the Coloured person from the noxious effects of solar irradiation, and it seems that pigmentation, no matter how slight—and some of our Coloured patients are very pale indeed—gives almost complete protection from and immunity to basal-cell carcinoma as well as to cancer of the lip and carcinoma of the exposed skin.

*Age.* The age incidence of rodent ulcer and of cancer of

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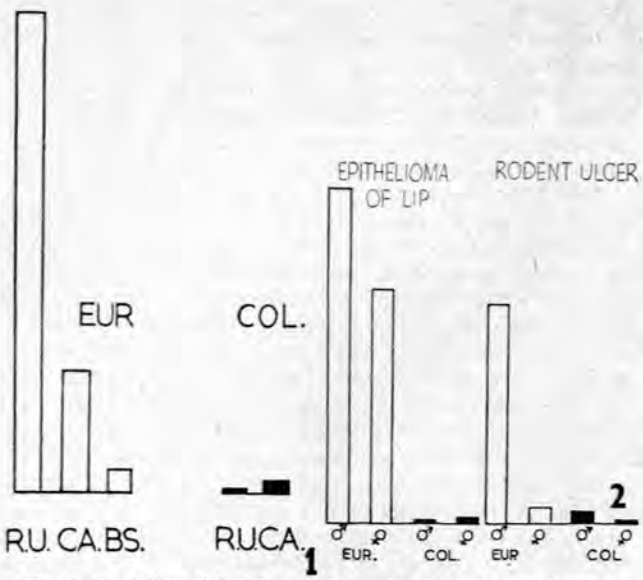


*Fig.* 1. Varieties of facial cancer showing the very much more frequent incidence in Europeans as opposed to the incidence in an approximately equal Coloured population, and the great preponderance of rodent ulcers over epitheliomas of various kinds within the European group.[1] RU=rodent ulcer. CA=epithelioma. BS=basisquamous carcinoma.

*Fig.* 2. Relative frequencies of rodent ulcer and of cancer of the lip in 2 large consecutive series of cases.[2]

the lip is almost the same (Fig. 3). Both occur predominantly in elderly European males of similar diathesis. The typical patient we meet is an Afrikaner farmer, more than 60 years of age, with blue eyes, fair hair and a pale soft skin which does not sunburn and fails to tan. While brown eyes occur occasionally, a sallow complexion rarely accompanies solar keratosis, rodent ulcer and cancer of the lip.

*Sex.* Relatively few women develop the disease. We attribute this to their more sheltered indoor life and to the use of face powder and lipstick, even a light application of which is enough to act as a barrier to the harmful wavelengths. In the Coloured population, where the numbers for analysis are much smaller, the sex incidence is reversed. The fact that the Coloured women rarely uses make-up may be a possible explanation of the reversed sex incidence in Coloured people; this subject is at present under examination.

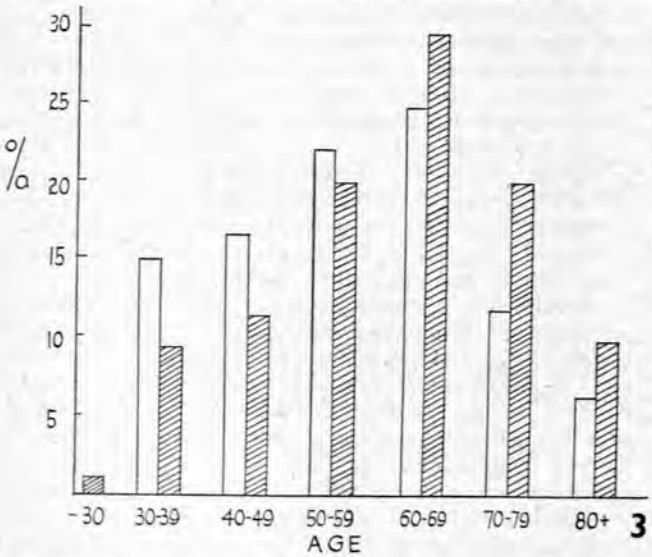


*Fig.* 3. Age incidence of rodent ulcer (white columns) and cancer of the lip (black columns) showing the similarity in the 2 diseases.[1,2]

### THE MODERN THEORY OF CARCINOGENESIS

It is generally accepted today that carcinogenesis is a multi-stage mechanism. Since the work of Deelman[3] has become available, many theories of carcinogenesis have been put forward. Deelman, by a series of experiments, demonstrated that at least 2 factors are essential for the formation of some neoplasms. The neoplasms demonstrated were benign, but equally relevant information soon became available for malignant ones. Deelman showed that if the skin of a mouse was tarred, nothing apparently happened, but if incisions were later made in the tarred (apparently normal) areas, papillomata developed in the lines of the incisions. McKenzie and Rous[4] showed that the same process could be demonstrated in rabbits, and in explanation it was suggested that the first process was an initiating process, which was long, slow-acting and irreversible. The cell, unaltered in its ordinary appearance and behaviour, is brought into a peculiar sensitized state so that a suitable second variety of stimulus, called the promoting process, causes carcinoma to develop. Both processes are necessary for the formation of tumours.

The theory of this two-stage mechanism has been generally accepted, and much work on the subject has been done. Initiation is not always a somatic-gene mutation, as some have suggested, since Berenblum and Shubik[5] have shown that a certain powerful mutagen, sulphur-mustard, is by itself not effective in initiating tumours. In general, the theory of the multi-stage mechanism is acceptable.

While most chemical carcinogens show initiatory as well as promoting functions, some are purely promoting, and others again are purely initiatory.

Many theories have been brought forward to explain what is the characteristic property necessary for a promoting stimulus, and it has been suggested that lymphatic obstruction is one of these properties. It has been shown that artificially induced fibrosis augments the action of skin carcinogenesis, and while fibrosis is not essential in some cancers, such as chemically induced liver tumours, it plays an important part in skin carcinogenesis.

### THE ANATOMICAL BASIS OF RODENT ULCER

Pathologists are unanimous in believing that basal-cell carcinoma can originate in the basal layer of the glabrous skin or in any of the skin appendages. We submit that the basal-cell carcinoma we ordinarily meet almost certainly originates in the sebaceous glands, and a series of observations will be put forward to support this submission. However, by the time the basal-cell carcinoma has become clinically obvious, its microscopic site of origin can no longer be found. As a consequence, the absolute proof cannot be made in the present state of our knowledge of histological technique, and our statements rest on presumptive evidence only. However, several clinical and experimental observations will be brought forward, which we regard as pointing very strongly to the origin of these neoplasms in the sebaceous glands.

Rodent ulcers are commonest in the 'rodent triangle', an

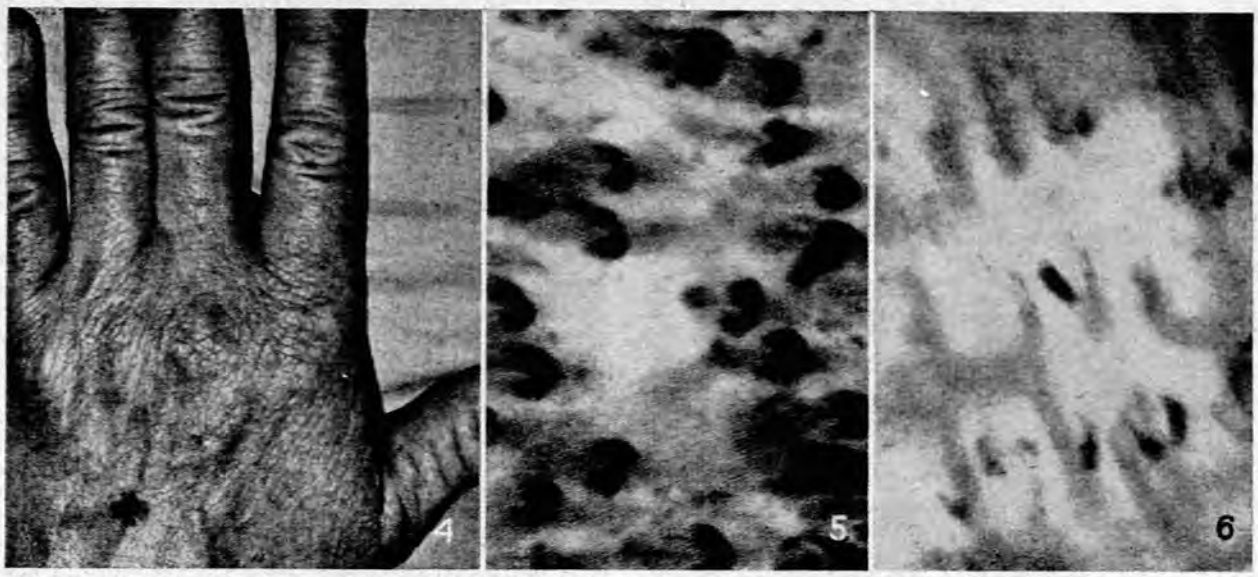

*Fig.* 4. Dorsum of hand in a patient of typical diathesis showing solar keratosis and epithelioma. *Fig.* 5. Normal skin of white mouse, showing sebaceous glands (from Bock and Mund,[8] by kind permission). *Fig.* 6. Skin of white mouse 24 hours after painting with methylcholanthrene, showing the disappearance of the sebaceous glands (from Bock and Mund,[8] by kind permission).

area which is bounded by the two palpebral fissures above, and by a line drawn from each external canthus to the upper lip. In all the body, this area is that in which the sebaceous glands are present in greatest numbers.[6] In the other parts of the face the sebaceous glands, while still frequent, are less common. On the pinna of the ear they are likewise present only in fair concentration, but behind the ear, in the groove between the pinna and the skull, a fair aggregation of these glands seems to occur. Their frequency is so marked in the skin of the rodent triangle that a trained histologist easily learns to recognize whether a portion of skin comes from the face or not by its histological appearance only, mainly because of these numerous sebaceous glands. The frequency of basal-cell carcinoma in these same areas and in about the same relative frequency as the occurrence of the sebaceous glands is surely more than mere coincidence.

Consideration of the histology of the normal skin shows that the pigmented layer lies in the stratum granulosum and a little thought leads to the conclusion that, if pigment protects from the harmful effects of sunlight, the structures that are protected are the ones that lie deep to this pigment layer. These structures are (1) the sebaceous glands, (2) the sweat glands and (3) the hair follicles.

If rodent ulcer arises, as appears to be the case, from a structure that is normally protected from the sun, it must necessarily originate from one of these three structures. Basal-cell carcinoma in a hairy area is exceptionally rare, because the hair has a shadowing effect which protects the skin from direct sunlight, so that although hairy areas are rich in sebaceous glands, each hair follicle being associated with 2 sebaceous glands,[8] the rarity of rodent ulcer can be explained on this physical fact alone. Sweat glands, again, occur as frequently on the forehead, where rodent ulcer is very rare, as on the rest of the face. It appears, therefore, that it is not the hair follicles or the sweat glands that are the sites of origin of rodent ulcer, but that it is to the sebaceous glands that we must look for the genesis and origin of the commoner type of rodent ulcer and evidence will be put forward to support this theory.

The same patient that gets rodent ulcer shows solar keratosis on the dorsum of the hands (Fig. 4). This area also shows roughening and develops neoplasms. Here, however, the neoplasms are almost invariably squamous epitheliomas. The number of sebaceous glands on the skin of the hands is not remarkably high.

The lower lip, which presents a mucous and a cutaneous surface, is the frequent site of neoplasms on its cutaneous aspect in people of exactly the same diathesis as those that suffer from rodent ulcer[2] (Fig. 7). Indeed it is very common to have patients coming up who suffer from both diseases.

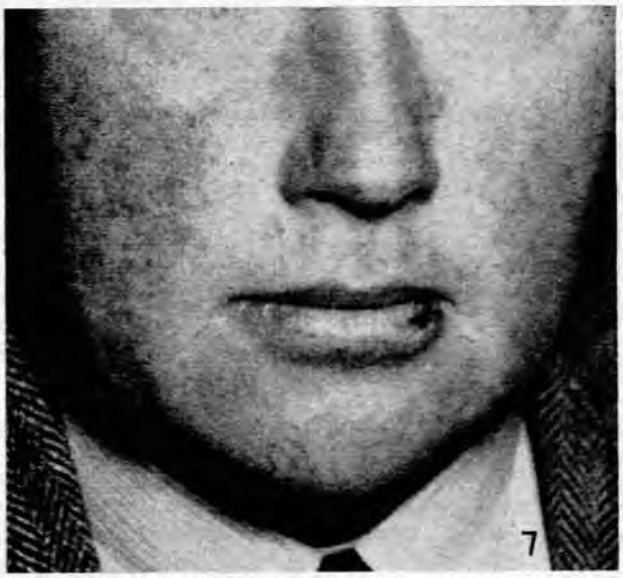

*Fig.* 7. A patient with the typical diathesis showing solar keratosis and epithelioma of the lip.

On the skin of the lower lip, which is by far the most frequent site of epithelioma, the frequency of sebaceous glands is not at all outstanding and the incidence of rodent ulcer is negligible. Here epithelioma is almost invariably the neoplasm encountered (Figs. 7 and 8).

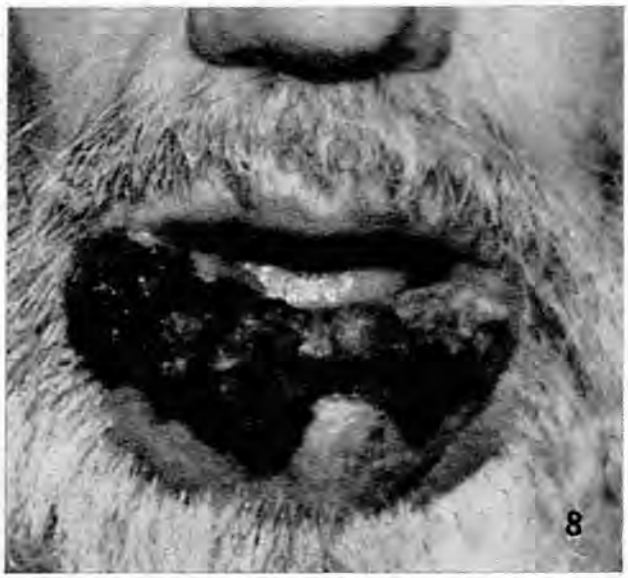


*Fig.* 8. An elderly bearded man with a typical cutaneous variety of epithelioma of the lip. His lower lip has always been shaved; on this unprotected area he developed an epithelioma of the lip with no solar keratosis elsewhere.

THE SEBACEOUS GLANDS AND NEOPLASMS — EXPERIMENTAL EVIDENCE

Experimental work has shown that neoplasms can be produced in rats by exposing their skin to ultraviolet light or to the sun's rays over a long period.[7] These neoplasms are usually squamous epitheliomas and it has been noticed that they occur most commonly on the tips of the ears and on the eyelids. In the human, these situations are likewise common sites for actinic neoplasms.

Bock and Mund,[8] experimenting on white mice, painted their skins with various carcinogenic substances and, using methylcholanthrene, a very potent carcinogen, found that within 24 hours there had been an almost complete disappearance of sebaceous glands from the skin (Figs. 5 and 6). So dramatic and so regular was this response, that these authors have suggested that the suppression of the sebaceous glands from the mouse skin could be used for evaluating the carcinogenic activity of a substance, and they have, indeed, used it for this purpose. In this they confirm Smith *et al.*,[9] who reported that the carcinogenic properties of a certain petroleum fraction could be predicted by its ability to cause disappearance of sebaceous glands from the mouse skin.

Simpson and Cramer[10] have noted that within minutes of painting mice with methylcholanthrene the carcinogen collected in the sebaceous glands. The same workers[11] also demonstrated that solutions of methylcholanthrene in lanolin, which are not carcinogenic, failed to collect in the sebaceous glands in mice, so that concentration in the sebaceous glands follows the carcinogenic activity and is not due to the fatty structure alone. Cambel,[12] repeating this experiment, included the rat and the monkey (in which methylcholanthrene is not a potent skin carcinogen). Here the suppression of sebaceous glands was not observed even though the hydrocarbon was concentrated in them. It appears therefore, that it is by virtue of their carcinogenic activity that carcinogens which are formed in the skin, or are applied to it tend to become concentrated in the sebaceous glands and selectively affect them. The disappearance and suppression of sebaceous glands from the skin is not permanent; after a while the sebaceous glands reappear and apparently become normal again.[13] Since this was written, Bock[19] has reported that the 'sebaceous gland suppression is associated specifically with the benzanthracene structure rather than generally with all phenanthrene-type carcinogens....within the benzanthracene series the parallel between carcinogenic activity and sebaceous-gland suppression is very good'.

Sunlight is well known to act on various sterols and allied polycyclic aromatic hydrocarbons and to alter their chemical constitution. It is thus a commonplace that the ergosterol present in the skin is altered by sunlight to vitamin D2 and, indeed, this is the explanation commonly accepted for the effect of sunlight in preventing rickets. Vitamin D3 can also be formed from 7-dehydrocholestrol as a result of the action of sunlight on the skin, and quite recently Peacock[14] has suggested that cholesterol itself may be transformed to methylcholanthrene. If this assertion proves to be true, it appears that the cholesterol which is present in the skin can actually be the precursor of a very potent carcinogen.

THE NORMAL AND ABNORMAL SKIN REACTION TO LIGHT

That sunlight has a carcinogenic effect on the unprotected skin is common knowledge. As stated above, De Kock,[7] by exposing their skin to sunlight for several hours a day, has produced squamous epithelioma in white rats after some months of such exposure. Epithelioma has been known to develop from ultra-violet irradiation in 'therapeutic' doses, and the wavelengths of the responsible rays has been determined; they lie within the ultra-violet portions of the spectrum.

Normally all brunettes and most blondes develop pigment and tan. This tan is due to the formation of melanin, probably derived from tyrosine by the action of tyrosinase, and the deposition of granules of melanin in the deeper layers of the stratum granulosum; this is the normal reaction. The Coloured races already possess melanin granules in their stratum pigmentosum, but even they show some darkening as a result of long exposure to sunlight. The brunette White man reacts to exposure to the sun by tanning and pigmentation. The Coloured man does not tan, but is protected by his natural skin pigmentation. The blond, blue-eyed White has an imperfect pigment-response to the sun's rays, and fails to tan. Instead, his skin turns red and blisters and, over the years, thickening of the exposed portions of the skin takes place with patchy brownish pigmentation in an obviously imperfect attempt at tanning. Further exposure to the elements results in roughening and dryness of the skin, which has a peculiar dry feel, and clinically there is a notable loss of sebaceous secretion. It is these patients, with a diathesis that affords them no protection against ultra-violet light, who develop rodent ulcers on their face, epitheliomas on their lips and epitheliomas on the dorsum of their hands.

Long before the neoplasms develop the patients show varying degrees of solar keratosis; the skin becomes dry and small painful cracks appear on the projecting portions of the

face, the nose, the cheeks and the ears. There is patchy pigmentation as well, and the cracks heal and constantly break down again; the crusted lesions get traumatized in shaving and the cycle is repeated. It seems that solar keratosis, with its areas of patchy pigmentation, is a *forme fruste* of the frank sun-tan in brunettes. On the lips and on the dorsum of the hands a similar process takes place. Keratosis, however, is represented on the exposed mucosa of the lip by leukoplakia and these lips crack and heal repeatedly. Cigarette smoking additionally traumatizes the lips. The lower lip is 10 times more commonly affected than the upper, because it faces upwards towards the sun and lacks the shade of the latter. Solar keratosis and sunburn are seldom encountered in the upper lip. The dorsum of the hands in these same patients also shows solar keratosis in varying degrees of severity. Neoplasms occur not infrequently, squamous epithelioma being the only type of cancer we have met with in this situation.

### ALBINO BANTU

Although albinism is relatively common in the Bantu, we have not had any personal experience with albinos. However, we know that they always succumb at a youthful age, and we can predict that they would suffer from epithelioma of the skin, rodent ulcer seldom, if ever, developing in them.*

The unprotected albino skin is ideal ground for the development of skin neoplasms because in their natural state these people are unclothed and their skin is unprotected from the sun. The skin cancers which develop in these albinos do so in areas of trauma. Rodent ulcer takes many years to develop in Europeans, and it appears that the albino Bantu may not live long enough for this to happen, but dies at a youthful age from epithelioma of the skin. As both the Bantu and the Coloured man are less hirsute than the White man, and so shave less frequently than the European, their faces are not subjected to the same frequent trauma and this may be another reason for the rarity of rodent ulcer on the faces of members of naturally pigmented races.

### RECURRENCES AFTER RADIOTHERAPY

Two varieties of recurrences are encountered after radiotherapy. Both varieties are rare and both occur months or years after the initial treatment has been given.

*The marginal recurrence* takes place on the edge of an irradiated area, and is the less uncommon condition. It can be explained as being the result either of an incomplete radiation-dosage at the periphery of the treated area, or of ineffective radiation due to a portion of the original rodent ulcer being protected in a bony foramen.[15] A still more likely explanation is that as radiotherapy confers no immunity to rodent ulcer, another area breaks down in a disease which is notoriously multifocal.

*The central recurrence* cannot be so easily explained. In these cases the full dose of gamma rays has almost certainly been delivered and recurrence here—when it is a true recurrence, and not a radiation necrosis—may be due to the persistence of a sebaceous gland more resistant than its neighbours to radiation and to the development of rodent ulcer in this persisting gland. Irradiated areas present as pink, smooth and non-greasy patches, the radiation almost invariably destroying the sebaceous glands together with the other skin appendages.

However, I am informed by our radiotherapists that, while 6,000 r is normally sufficient to destroy most of the sebaceous glands and hair follicles permanently, some of these within the treated area may escape because the destruction is unlikely to be uniformly complete even in the treated area. This is one of the reasons why, while it is possible to get recession of a typical rodent ulcer with a lesser dose than the 6,000 r we usually use, these smaller doses are not usually recommended. The full dose of 6,000 r gives a smooth, clean and satisfactory result, with very much more certain effects. Opinion about this optimum dosage varies among radiotherapists, and I do not feel qualified to enter into this discussion.

### SEBACEOUS ADENOMA AND SEBACEOUS CARCINOMA

The 2 pathological entities of sebaceous adenoma and sebaceous carcinoma must be very rare indeed. Our pathologists have been unable to diagnose a single case of either in any of the 2,000 cases of facial tumours sent to them during 1948-57. We have noted that where the clinical diagnosis of sebaceous carcinoma has been made, the histologist's report is almost always squamous epithelioma; the sebaceous adenoma, clinically diagnosed as such, is usually reported to be a chronic infected sebaceous cyst. Sebaceous carcinoma is probably not the usual form of neoplastic degeneration of the sebaceous glands. It appears that our ideas about these two clinical entities may have to be revised. Senile sebaceous adenoma is a rare disease and a separate clinical entity quite unlike rodent ulcer or what used to be classically described as sebaceous adenoma. It is treated with oestrogens,[16] which effect a decrease in the size and number of sebaceous glands, just as androgens have exactly the reverse effect.[17] Experimentally, basal-cell carcinoma can on rare occasions be produced by painting mice with certain polycyclic aromatic hydrocarbons dissolved in an organic solvent.[18] There is still no direct evidence to link sebaceous glands with basal-cell carcinoma, our own evidence being deductive and based entirely on probabilities.

### DISCUSSION

To be satisfactory in all respects, a theory of aetiology should explain all problems arising from the condition under consideration. However, since the aetiology of facial cancer, as of cancer in general, is as yet obscure, it is not possible to explain every angle of this disease. The theory we are propounding is as follows:

1. The ultraviolet portion of the sun's rays acts on certain sensitive skins which are not protected by pigment.

2. This lack of pigment permits the rays to reach parts of the skin deep to its pigment layer and to react with some substance to form a carcinogen. The substance is probably a sterol allied to ergosterol or to 7-dehydrocholesterol; it may even be cholesterol itself.

3. This carcinogen, which may well be chemically related to the benzanthracenes, is produced in small quantities for

* Mr. S. Kleinot, F.R.C.S., Senior Surgeon at Baragwanath Hospital, who has a large experience with albino Bantus, confirms this prediction. The albinos die early of cancer of the skin at a far younger age than our average patients with rodent ulcer. The majority of their epitheliomas occur on the shoulders and the dorsum of the forearms, areas which are exposed to the trauma of braces and other everyday trauma. In his youth and childhood the albino Bantu lives in his kraal in the natural state and completely unclothed, when his skin is exposed to the sun and undergoes the initiatory phase. In early adult life he migrates to the towns, when he acquires clothes.

many years and is selectively absorbed and concentrated in the sebaceous glands of the area, whose activity it suppresses. The glands recover[13] and the cycle is repeated. Ultimately the glands are altered and prepared for the next process.

4. The process so far described is the initiatory process in which the carcinogen acts very slowly and takes many years to produce its effect, which, however, is irreversible: the sebaceous gland may recover macroscopically and microscopically but it has been brought into a sensitive state, and is ready to undergo a malignant change.

5. Another factor, the promoting factor, now comes into operation, causing basal-cell carcinoma to develop. The promoting factor is probably trauma, repeated and minor in nature, such as may be sustained in daily shaving.

6. The effect of these two factors on sebaceous glands is to cause basal-cell carcinoma to develop.

7. In the glabrous skin no concentration of the carcinogen takes place and the initiatory process is diffuse but still restricted to the exposed areas, which become sensitized, and carcinoma can occur on any part of the exposed skin. The neoplastic response of the glabrous skin is with a squamous epithelioma, as opposed to the basal-cell response of the sebaceous gland.

The theory here propounded explains the following points in connection with facial and other actinic skin cancers.

1. The immunity of the pigmented races to rodent ulcer and epithelioma of the lip and hands.

2. The peculiar anatomical incidence of rodent ulcer, which is explained on the basis of the local frequency of sebaceous glands and not on a mystical basis.

3. The occurrence of rodent ulcer many years after the patient has ceased to expose himself to sunlight.

4. The dry rough skin of solar keratosis.

5. The anatomical incidence of epithelioma of solar origin.

6. The sites of occurrence of epithelioma.

7. The rarity of rodent ulcers in albino Bantu.

## RECOMMENDATIONS FOR PREVENTION OF ACTINIC CANCERS

It will be obvious from what we have written that to tell a man of 70, who has spent all his life in the open air, to pass his remaining days in the shade and under cover is to tackle this problem at the wrong end; the initiating factor has already done its work and many people who carefully abstain from exposing themselves to the sun, or who emigrate to another country, develop rodent ulcer years later.

It is difficult to know what sort of measures to suggest to prevent a disease whose onset is so slow and insidious and which is so wholly dependent on climatic conditions. It is neither practicable nor possible to insist that the whole population at risk, the most active and responsible members of the outdoor workers in the country, should give up their traditional means of livelihood and take to sedentary and indoor occupations. Wearing hats is very little protection; the wearer even of a broad brimmed hat ordinarily has a well tanned face and lower forehead, only the upper forehead remaining pale and protected.

Hair is to a great extent the natural protection against actinic rays and exercises a marked protective effect by virtue of the shadows it throws. However, even bearded individuals possess little hair over the rodent triangle, so that the commonest site of rodent ulcers, viz. the highest points of the cheeks and the nose will still be unprotected even in those with a full beard, though a heavy moustache may well protect some from lip cancer. It seems that it may be possible to devise a protection to the face which in the form of a face lotion could be applied daily after shaving and would cause tanning to develop. Such a preparation already exists[20] and experiments on its use are now in progress, but the investigation is a long-term undertaking and will require careful control and assurance that the application itself is free from harmful effects.

The following recommendations are made.

1. Since the diathesis can be recognized in childhood, school medical inspectors should be taught to recognise the typical diathesis (fair hair, blue eyes and a soft skin) and be instructed to advise that these children should avoid the sun.

2. Boys with this diathesis should be instructed to use a tanning preparation daily after shaving until the face is well tanned. Thereafter, applications should be made at intervals to keep the depth of tan at a satisfactory level. Girls of this diathesis should use lipstick and a brownish face powder.

3. A vigorous campaign to educate the public about the risks of face and lip cancer should be launched. The danger becomes almost negligible if the disease is managed sensibly and treated in its early stages.[1,2]

4. Clinics for treatment should be provided in suitable centres.

## SUMMARY

1. Rodent ulcer of the face, epithelioma of the lip and epithelioma of the dorsum of the hands are actinic diseases.

2. A theory is put forward that the rodent ulcers originate in sebaceous glands and the epitheliomas in the glabrous skin.

3. The various steps in the process of carcinogenesis are outlined.

4. Some suggestions are put forward which may prevent the development of actinic cancers.

My colleagues of the Combined Clinic have had to listen to much rumination while the various steps in this paper have been worked out. I am grateful to them for their patience. I should also like to thank Drs. J. M. Grieve and L. Mirvish for assistance and advice, Dr. B. Lewis for extracting the data on which Fig. 3 is based, and Mr. B. Todt for preparing the photographs.

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