# BASAL-CELL CARCINOMA: SPECULATIONS ON POSSIBLE FACTORS INFLUENCING ITS LOW INCIDENCE AMONG THE NON-EUROPEAN RACES IN SOUTH AFRICA*

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Much has been written on the subject of solar radiation and skin cancer since Unna first described 'sailor's skin' in 1896. South Africa with its mixed population of all grades of complexion and colour provides a particularly interesting field of study.

Schrire[19-21] has recently described the activities and findings of a group of radiotherapists, surgeons, plastic surgeons, dermatologists and pathologists who conduct a Clinic at Groote Schuur Hospital, Cape Town, for the diagnosis, prevention and treatment of cutaneous neoplasms. At this Clinic we have been forcibly struck by the great rarity of basal-cell carcinoma in the coloured races. Of 1,193 cases of skin cancer seen in the 8 years from 1949-56, there were 489 European males and 338 European females with basal-cell carcinoma. There were only 61 non-Europeans with cancer of the skin and of these only 29 were cases of basal-cell carcinoma—10 males and 19 females. We had no albinos presenting with skin cancer though their complete lack of pigment should render them very susceptible, particularly if we can accept the theory which has hitherto appeared to satisfy everybody that pigment acts as a screen to ultra-violet light and thus protects people from cancer of the skin. Schrire,[21] however, points out that albino Africans seldom live long enough to reach the age for basal-cell carcinoma because they succumb at an early age to squamous-cell carcinoma.

Our records of cases of cancer of the exposed skin, like those of Hämäläinen[11] in Finland and Paul[16] in Australia, reveal that men, particularly those whose lives have been lived mostly out of doors by day, are far more frequently affected than women. European builders, surveyors, civil engineers, transport workers and policemen are very prone, but the most likely sufferer of all is the Afrikaner farmer, his preponderance of Dutch blood giving him a very fair complexion and his work exposing him throughout his life to the unkind rays of the South African sun.

The members of the Clinic subscribe to the view that the greater protection afforded to women's skins by brimmed hats, cosmetics and indoor occupations is a powerful factor in reducing the incidence of carcinoma amongst them. Gillman, Hathorn and Penn[8] have found that lanoline, a common constituent of cosmetic creams, seems to decrease the incidence of experimentally induced skin carcinoma. Hair protects the skin from irradiation, so that women, who are not ordinarily afflicted with baldness, do not develop basal-cell carcinoma on the scalp; by the same token, bearded men are spared these lesions on the lower portions of the face.

Basal-cell carcinomas tend to arise on sites where the sebaceous glands are most profuse, that is to say, on the scalp but only if it is denuded of hair, on the ears, the back of the neck, the malar regions, the nose and the chin. It is of interest to note that the photosensitivity diseases lupus erythematosus, pellagra and porphyria cutanea tarda also affect some or all of these same areas in people of all degrees of colour.

The neoplastic lesions found on the dorsa of the hands and on the lower lip, regions but poorly supplied with sebaceous glands, are almost invariably squamous-cell carcinomas, not

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basal. Moreover, those parts of the face naturally in shadow, viz. the upper eyelids and the upper lip, shaded by the eyebrows and the nose respectively, are seldom involved. We have never seen basal-cell carcinomas on the palms or soles, areas completely devoid of sebaceous glands, though these have occasionally been described.[15]

Most patients, by the time they seek treatment at the clinic, show on the exposed parts the atrophy, dryness and telangiectasia so characteristic of 'sailor's skin', but a number give a history of acne in youth and, indeed, still show evidence of sebaceous overactivity in the form of seborrhoea capitis, seborrhoeic warts, acne scars and sebaceous cysts. I wonder how wise we are to give our young acne patients prolonged ultraviolet light therapy.

*The Sebaceous Glands*

Modern histochemical techniques have thrown considerable light on the sebaceous glands and their products. The glands are holocrine and usually multiple acinar glands. Lipid accumulation and fragmentation characterize the sebaceous cells. Little is yet known of the mitochondria, but in the beginning of sebaceous differentiation lipid droplets appear first within the mitochondrial filaments. Mitochondria are the most sensitive indices of intracellular change and damage and are the seat of all important biological syntheses. In epidermal neoplasms they become strikingly pleomorphic.[14]

*Sebum* differs from tissue fats in being composed partly or entirely of waxes; thus a number of unusual substances not found elsewhere in the body must be synthesized within the sebaceous glands. Sebum contains free fatty acids, saturated and unsaturated; combined or esterified fatty acids; and unsaponifiable material, viz. cholesterol, squalene, high-molecular-weight alcohol and higher hydrocarbons.[17] The origin of free fatty acids in surface lipids is puzzling but might be explained in terms of lipases, which are known to be present in sebaceous glands and epidermis. The surface lipids, unlike those of any other tissues, contain saturated and unsaturated fatty acids with *odd* numbers of carbon atoms.[14]

The origin and functions of squalene (acyclic triterpine) are unknown, though Gillman *et al.*[8] think that the triterpenoids of sebaceous material may play some part in carcinogenesis. Squalene promotes an increase in $\triangle$-cholesterol and is known to inhibit important intracellular enzymes. Carcinogens may perhaps promote neoplasia by diminishing the inhibitory action of normal skin lipids on the growth and mitosis of epithelial cells.

*Skin Carcinogenesis*

The skin is made up of tissue structures very rich in protein such as collagen, elastin, keratin, albumin, globulin, mucin and melanin. Many amino-acids are also present in the skin and ribonucleoproteins have been demonstrated in the sebaceous glands. Modern work on the nucleoproteins may throw more light on cancer than was formerly available. Boyd[3] points out that the living cell is a mass of seething activity regulated by a system of enzymes and that, under the influence of external factors or hormones, a change may take place in one of the regulating enzymes leading to uncontrolled growth and cell division without reference to the requirements of the organism. The master control lies with nucleic acid, which is conjugated with proteins to form nucleoproteins, thought to be identical with the genes in the cell nuclei. The nucleoproteins possess the unique property of self-duplication within the body. There are grounds for the belief that there is a difference between the normal cell and the cancer cell in the anabolic process of the nucleic acid of the chromosomes. Radiation can produce permanent change in a gene by damaging the chromosome. Gene mutation may give the cell the power of greater reproduction and make it insensitive to normal inhibitory influences.

We know that the regulatory mechanism of the cell can be tampered with and it does not take much to alter the composition of the nucleic-acid regulatory mechanism, thus producing a self-perpetuating and therefore permanent derangement. A very slight change in the chemical structure of an organic substance may convert it from a non-carcinogenic to a carcinogenic agent; for example, the manufacture of methyl cholanthrene from bile salts.[3] It would seem to be possible, therefore, that prolonged actinic irradiation of the pilo-sebaceous apparatus might so alter the nucleoproteins as to lead to the production of carcinogenic substances.

I shall but briefly mention the *carbohydrate metabolism* of the skin, because I think that the answer to the problem of the pathogenesis of cutaneous cancer is far more likely to lie in either the lipid or the protein constituents. Normal sebaceous glands abound in glycogen, which decreases at the same rate as lipid increases. It would therefore appear probable that sebaceous transformation takes place by conversion of carbohydrate to lipid. Diabetics have a higher incidence of tumours in general than non-diabetics. Gillman *et al.*[9] inform us that hypoglycaemia is repeatedly found in cancerous patients. Diabetogenic doses of alloxan fail to provoke diabetes in cancerous individuals and cancerous diabetics need less insulin to reduce the blood-sugar levels. These findings point to the fact that malignant tumours take unto themselves as much carbohydrate as they can get and burn it up voraciously. The higher incidence and growth rate of neoplasms in diabetics is therefore probably due to an increased availability of carbohydrate. One would expect the high sugar content of the skin (Urbach's 'skin diabetes'[24]) to have an effect on the incidence and rate of growth of cutaneous cancers but, while I have no figures available, I am able to state that there have been extremely few diabetics at our Clinic.

THEORIES ON THE AETIOLOGY OF BASAL-CELL CARCINOMA

According to Lever,[12] primary epithelial germ structures differentiate into sebaceous glands, apocrine glands and hair. Tumours arising from the primary epithelial germs show degrees of differentiation into these three. Basal-cell epitheliomas arise only where the primary epithelial germ structures are found. Smith and Swerdlow[22] are impressed by the tendency of the cells in basal-cell epitheliomas to reproduce the pilar apparatus and they think it reasonable to believe that there remain, in the basal layer of the epidermis cells which are anlagen of the pilo-sebaceous structures. They think that basal-cell epitheliomas all arise from hair follicles or hair anlagen.

The cells of the epidermis may undergo sebaceous transformation or metaplasia when irritated.

Gillman *et al.*[7] have found that an excess of pseudo-elastic tissue or basophilic collagen in the dermis plays some part in the pathogenesis of skin cancer in sites of chronic irradiation injuries or in areas repeatedly treated with carcinogens.

They state that skin cancers do not arise from surface epithelium but are 'adnexal tumours'. Regenerating epithelium consistently sends spurs down into the dermis and may form new hair follicles and sebaceous glands, but if the dermis is grossly altered these epithelial spurs may fail to form new appendages and become, instead, papillomatous or even carcinomatous. They postulate that epidermal neoplasia is the consequence of failure of a damaged dermis to differentiate hair-papilla cells in response to pluripotential invasive epithelial spurs derived from a proliferating epidermis. This concept may clarify the obscure relationship of skin cancer to scars, hair regeneration and chronic irradiation injuries of the dermis.

Frumess and Lewis[5] have described a light-sensitive seborrhoeic type of dermatitis of the face, repeatedly provoked by exposure to sunlight.

It is within the bounds of possibility that the sebaceous glands may manufacture or store substances, as yet unidentified, which may be photosensitizers or even carcinogens. In 1933 Roffo[18] suggested that the large amount of cholesterol in the exposed skin prepared the soil for subsequent malignant growth by acting as an accumulator of light. Bergmann *et al.*[1] tried to refute this theory by showing that when they applied irradiated cholesterol to the skin of mice for more than 2 years they failed to produce cancer. Mohs[13] painted the skin of mice with material washed with benzene from human skin affected with multiple precancerous keratoses and failed to produce cancer in the animals. Snapp *et al.*[23] had similar experiences after painting the ears of mice with irradiation products of skin surface fats. I submit that the possible carcinogenic substances in sebum may prove to be species-specific accounting for the failure of these experiments. Greenstein[10] leaves the door open by summing up the present position in the following words: 'It does not appear probable that as a result of the irradiation a carcinogenic agent is formed in the skin which resembles any carcinogen known at the present time.'

The question of smegma might be mentioned here. It is chemically closely related to sebum and is thought to cause cancer of the penis in uncircumcized males and of the cervix in their wives. Solar radiation plays no part here, but the combination of accumulated smegma and repeated mild trauma seems to be a factor in the production of carcinoma.

The mechanism of the production of photosensitivity is not yet known but is thought to depend on the absorption of quanta of energy by molecules of photosensitizing chemicals present in the prickle-cell layer of the epidermis, resulting in chemical changes in this layer.

The work of Coblentz[4] has shown that the parts of the ultraviolet spectrum responsible for ordinary tanning lie between 3,130 and 3,900 Å and that cancer of the skin is produced by wave-lengths between 2,000 and 4,000 Å. Blum[2] found that ultraviolet irradiation caused acceleration of the rate of proliferation of tumour cells, each dose of radiation causing an increase in the relative rate of proliferation proportional to the magnitude of the dose, up to a certain limit set by physiological factors limiting the absolute growth rate. The tumour cells may not differentiate sharply from normal cells but represent those cells and their offspring whose growth rate is most effectively accelerated by the ultraviolet irradiation and which therefore outstrip their fellows and form a tumour. This theory partly accounts for the sudden appearance of tumours after a period, often extremely prolonged, of apparent latency. We, at the Clinic, formed the opinion that by the time basal-cell carcinoma had developed in 'sailor's skin' it was too late to hope for much future benefit from strict protection against actinic radiation.

*Endocrine and Nutritional Aspects*

Androgens stimulate sebaceous activity and mitotic division. They also control the rate of secretion of sebum. There is a pronounced increase in size and activity of the sebaceous glands at puberty and the pituitary is responsible for their proper maintenance. The preponderance of basal-cell carcinoma in European males over European females and all non-European persons may have something to do with a higher secretion of androgens.

By far the most usual type of patient seen at the Clinic is the Afrikaner farmer who, besides exposing his face and hands to the light of the sun throughout his life, probably nowadays lives on a richer, fattier diet than any other class of person in the country. Roffo[18] noted that precancerous skin lesions have a high cholesterol content and are accompanied by hypercholesterolaemia. He also stated that a diet rich in lipoids encouraged the growth of tumours. The question of any possible relationship between increased sebaceous activity and high serum lipids warrants further investigation.

It has always been assumed that the greater cutaneous pigmentation of the Coloured races is enough to explain their relative immunity from solar cancer. I submit that there may be other unexplained accessory factors. It is categorically stated in most text-books that Negroes have more and larger sebaceous glands and more sebum than White people. I assume that this statement applies to the American Negroes, whose culture and dietary habits do not vary greatly from those of their White compatriots. A very different state of affairs exists in South Africa, where the Bantu and Coloured races are on the whole of a very much lower economic and social status than the average European.

In the malnourished non-European, androgen secretion is greatly diminished, sometimes to the extent of producing gynaecomastia and diminution of libido. The Gillmans[6] have most beautifully described certain alterations in the structure and metabolism of the sebaceous glands in the malnourished African. They state that the role of the sebaceous glands in skin metabolism has been incompletely investigated and little thought has been given them in general fat metabolism, though their total volume must be enormous. For normal skin function, a minimal daily amount of fatty acids is essential. There is an interesting but complex relationship between fats, carbohydrates, proteins and sterols in the maintenance of a healthy skin.

In pellagra the involvement of the sebaceous glands is associated with a diet deficient in fats and proteins. The fatty secretions of the sebaceous glands are altered and the lipoids are more easily converted into a black or brown compound accounting for the 'sooty' skin on the exposed parts. The follicular keratosis of malnutrition is probably due to much more than avitaminosis and may well be the result of a general disorder of metabolism arising from a deficiency of biologically useful fats, sterols and proteins.

In malnutrition the sebaceous glands are greatly hypertrophied and the ducts are dilated not because of obstruction to the outflow of secretion but owing to trophic changes in the duct epithelium. After treatment the sebaceous glands

regain their normal size but firm plugs of secretion remain projecting from their orifices. The lipoidal secretion seems to be normal in the alveoli but undergoes some change in the ducts. The abnormal formation of sebum and the acneiform lesions in malnutrition may be manifestations of imbalance of sex hormones.

It is perhaps significant that amongst our 29 non-European patients with basal-cell carcinoma there were more women than men.

It is possible that the abnormal sebum of the undernourished non-European lacks some substance which is present in normal sebum and which may become carcinogenic after prolonged irradiation with ultraviolet light. I venture to suggest that the general low level of nutrition amongst the Coloured races of South Africa plays some part not only in encouraging their pigmentation but in protecting them from over-production of *normal* sebum and therefore, in some way, from basal-cell carcinoma of the skin. The very nature and distribution of basal-cell carcinomas indicate some close relationship between their development and a combined carcinogenic action of ultraviolet light and sebum in otherwise normal individuals. The different dietary habits of the non-Europeans in South Africa may well lead to some alteration in the sebaceous glands and their secretions, producing a lack of the suspected carcinogenic constituents of sebum.

In favour of this theory is that fact that albino Africans, who are usually rejected, neglected and underfed, although very prone to squamous-cell carcinoma of the skin do not in my experience suffer from basal-cell carcinoma in spite of their total lack of protective pigment. Against the theory is the fact that there are many non-Europeans both in South Africa and in America who are well nourished according to European standards and yet do not suffer from basal-cell carcinoma of the skin. By the same token, however, the well-fed African rarely suffers from acne or seborrhoeic dermatitis. It is only the malnourished African who shows evidence of dyssebacia, that is, the secretion of abnormal sebum.


## SUMMARY

The observations of a group of workers at a Clinic conducted at Cape Town for the diagnosis, prevention and treatment of cutaneous neoplasms are discussed, with special reference to basal-cell carcinoma, its nature and its occurrence in sites where the sebaceous glands are most profuse and mainly on the parts of the body exposed to light.

Arising out of these observations and the fact that basal-cell carcinoma is extremely rare in the non-European races in South Africa, the theory is advanced that, in view of the poor nutritional state of most non-Europeans, there may be other factors beyond mere pigmentation which prevent the development of basal-cell carcinoma in these individuals.

One of the commonest manifestations of malnutrition is an alteration in the sebaceous glands and sebum. It is possible that the abnormal sebum of the undernourished non-European lacks some substance which is present in normal sebum and which becomes carcinogenic when it is subjected to prolonged irradiation by ultraviolet light.


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