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ORIGINAL ARTICLES

✓ RECENT ASSESSMENTS IN THE AETIOLOGY AND THERAPY OF SKIN CARCINOMAS

by

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AETIOLOGY

Skin cancer in Australia (of which the great majority of lesions are rodent or squamous carcinomas), comprises approximately 60% of all cancer, which is the highest incidence in the world. As a contrast, the incidence in Texas (among the highest in the United States of America) is approximately 33% of all cancer.

Solar keratoses, which are the commonest accepted precursors of skin cancer, comprise approximately 12.5%, and skin cancers comprise approximately 14.4% of all dermatoses seen in the writer's hospital and private practice. When all premalignant lesions are included, they, together with skin cancers, comprise approximately 30% of all dermatoses seen.

This high incidence is due mainly to the effects of the carcinogenic rays of the solar spectrum, which lie between 2900 and 3341 Å for humans, in a people of predominately British and Northern Continental origin, with fair skins and usually, light-coloured eyes. (Belisario, 1959).

HEREDITY

As far as is known, heredity is not directly concerned in the handing on of actual skin cancer tendencies. It can and does however, play an important role in providing a suitable palubum (e. g. in the form of a fair skin) for the appearance of skin cancer. A too low actinic tolerance to sunlight, possibly aggravated by wind, may also play an aetiological role.

SEX

Men are more often affected than women, due to the overall greater degree of exposure to the sun in the former.

Lip cancer occurs in Australia in the approximate proportion of 10 males to 1 female. The lower lip, (the one most exposed to sunlight) is almost always the one affected. The protection against the sun's rays afforded by lipstick in women is considered to be the main reason for the higher incidence in males (Molesworth, 1927, 1934, 1944). It is unlikely that smoking plays much if any part since many women smoke more heavily than men over the last decade at least, and indoor workers rarely exhibit lip cancer. In addition, the incidence of lip cancer has been decreasing over recent years (Lancaster, 1954, 1955) in spite of fact that smoking generally, particularly in women, has markedly increased.

COMPLEXION

The incidence of skin cancer has been found by numerous authorities to be lower in people with darker skins (and usually with darker coloured eyes) owing to the protection their skin pigment offers against the causative ultraviolet radiations of the solar spectrum.

For example Oettle (1963) has found the incidence of skin cancer to be approximately 11 times higher in whites than in the African or United States Negro.

Khanolkar (1954) found skin cancer in Bombay comprised only 3% of all cancer. Shanin (1951) found skin cancer comprised from 8% to 9% of all cancer in Russia and that 89.4% occurred in people with fair skin and hair.

Takulov (1959) found skin cancer in Russia comprised 22.9% of all cancer and that 88.8% occurred on the head and neck. Also, Piyaratn (1959) found skin cancer in Thailand comprised 4.9% of all cancer.

Grieve (1961) noted that skin cancer comprised 35% of all cancer in White South Africans and only 2.5% in coloured South Africans.

Ten Seldam (1953) and Ingram and Brain (1957), among others, noted that rodent carcinomas are rarely found in dark-skinned races, but squamous carcinomas are relatively more common in the dark-skinned races.

White-skinned races are also more often affected by malignant melanoblastomas than dark-skinned races, but less so than with skin carcinomas (Cohen et al. 1952, Ten Seldam 1953). In addition, the mortality from malignant melanoblastomas is lower in the dark-skinned races, which suggests that, as well as the aetiological effects of sunlight (McGovern, 1952, 1956, 1957 and the writer) other factors may be operating e. g. the frequency of junction naevi (Oettle, 1963).

The incidence of rodent carcinomas is higher than that of squamous carcinomas in people of European descent, whereas the reverse appears to be the case in dark-skinned races (Ten Seldam, 1950, 1953; Hazen and Freeman, 1950; the writer and others). Pigment is present in the outer layers of the epidermis as well as in the

basal layer in the dark-skinned races such as the Australian Aborigine or American Negro, thus affording greater protection than in the case of the white-skinned races in whom the pigment is almost entirely in the basal layer. Thus, Aborigines or Negroes in general, are found to be about 10 times less sensitive to sunlight than whites, with the yellow and olive-skinned races occupying a position somewhere between the two. The African Johannesburg Bantu may be a little less sensitive than even Aborigines or American Negroes (Oettle 1963).

AREAS OF PREDILECTION

The great majority of skin cancers (from 90 to 93% or more) in whites, occur on the exposed parts of the head and neck, with the dorsum of the hands and forearms next in line (Cooper, 1955, Limberger et al. 1960; Belisario 1959, 1962).

The incidence of rodent carcinomas in Australia is between three and four times that of squamous carcinomas, and the commonest precursors of both are the solar keratoses.

HABITS OF SPORT AND WORK

The high incidence of skin cancer in Australia is due mainly to the fact that the population is of predominantly British, Irish or Northern Continental descent, with fair skins, combined with the practice of sunbathing both in and out of the surf or still sea water or fresh water swimming pools, and the habit of working outdoors (particularly in the case of males) without hats, and frequently without shirts and the wearing of short trousers.

SKIN PIGMENT PROTECTION

Mackie and McGovern (1958) performed experiments which indicated that the pigment content of the skin was the main protective factor against the carcinogenic radiations of the solar spectrum. They claimed that these radiations were responsible for collagen degeneration in the dermis, which brought about profound carcinogenesis. They found that squamous carcinomas of solar origin were always preceded by collagen degeneration as also were most cases of rodent carcinoma on exposed areas. In some cases however, there could be a naevoid tendency. The alteration in the nutrition of the epidermis, due to the carcinogenic effects of ultraviolet radiation on the dermis, also predisposed to the development of solar keratoses and keratoacanthomas. It is also thought by some that a degree of added protection may be obtained by a subsequent thickening of the horny layer in fair-skinned individuals, whose skins absorb radiations with a wave length of less than 3000 Angstrom units.

Blum (1962), in experiments with albino mice, found that when exposed repeatedly to ultraviolet radiation the exposed skin of these mice, transmitted much less of this radiation than did the normal, unexposed skin. This decrease in transmission was obviously not due to increase in melanin, because albino mice do not possess that pigment. Consequently, the decreased transmission probably

represents an increased opacity of the stratum corneum as a result of thickening, this layer being an excellent absorber of ultraviolet light.

Also, the erythematous radiation is strongly absorbed by the protein component, absorption being enhanced in the corneum by light scattering presumably at optical boundaries in its flake-like structure.

In exposed areas in humans, where ultraviolet radiation is aetiologically significant, tumours are in the greater majority epidermal, i. e. rodent and squamous carcinomas. This might be expected since ultraviolet radiation is principally absorbed in the epidermis and exerts its photochemical action there.

In contrast, Blum (1959) found that in the mouse, approximately the same wavelengths produced a high proportion of sarcomas. These wavelengths penetrate to the dermis to a considerable extent and are much less absorbed in the epidermis. With shorter wavelengths (0.2537 μ) which are principally absorbed in the epidermis of the mouse, Kelner and Taft (1956) produced only epidermal carcinomas. These two findings indicate that cancer is produced in the tissues in which the radiation is absorbed, and militate against the concept that epidermal cancers in man result from ultraviolet light acting at deeper sites e. g. the dermis (cf. Mackie and McGovern, 1958).

SUNLIGHT

The number of hours of exposure of the skin to sunshine is of considerably greater aetiological significance than the intensity of each exposure. A contributory role however, may be played by the degree of brightness of the sunshine and reflection from the sea or snow.

Actual heat is of no aetiological significance or ships' deck hands would show a lesser incidence of skin cancer than stokers, and dark-skinned races living in hotter climates near the equator would be more affected than whites in cooler climates, neither of which is the case (Belisario, 1959).

The significance of the number of sunshine hours is also seen in the finding of Cipollaro (1947) that only 12.5% of all cancer in whites in Chicago involved skin whereas 46.5% did so in Dallas which is further south towards the equator, thus exposing the inhabitants to a greater number of sunshine hours.

Wilson, cited by Black and Jolly (1953) found cancer of the skin to be four times as frequent in Dallas and Fort Worth in the Southern state of Texas, as in the more northern state of Michigan with less sunshine hours.

Minty (1961) found skin cancer comprised approximately 33% of all cancer in the southern city of Melbourne (Victoria). Others have found that the incidence rises to 50% in Adelaide (South Australia) which is further north towards the equator, 60% in Sydney (New South Wales) still further north (Belisario, 1959), and 70% in Brisbane (Queensland) the most northern capital in Australia. In the

most northern part of Queensland, the incidence rises to 75% (Cooper, 1959; 1960). Dorn and Cutler (1954) found the incidence of skin cancer per million in the United States of America, was 292 in the North, 1333 in the South and 785 in the West.

With the exception of malignant melanoblastomas, cutaneous cancer and precancerous lesions comprise 8% of all dermatoses seen in Wellington, New Zealand (Park, 1957), 12% in Hamilton further north (Purdy, 1957), 14% in Melbourne (Australia), still further north (Rosanove, 1952; Summers, 1955), 20% in Adelaide (Hakendorf, 1956; Linn and Linn, 1956, 1957), 30% in Sydney (Belisario, 1959) and 32% in Perth, Western Australia (MacMillan, 1956). These figures again indicate a general increase in incidence as the equator is approached from the south.

Rollier and Pelbois (1960) found the incidence of rodent carcinomas to be higher in Moroccan than in European women in spite of the darker skins of the Moroccans. This was considered (and rightly in the opinion of the writer) to be due to the lack of cosmetic protection and the greater exposure to the sun, while performing manual outdoor work, in the Moroccan women.

Cooper (1959) stated that it had been reported from the U. S. A. that the incidence of skin cancer in whites living between latitudes 42° north and 30° north doubles for every 4° south. He also pointed out that in spite of the fact that the total possible sunlight in Queensland averaged from 60% to 80% of that in Dallas (Texas, U. S. A.) it is likely that the intensity of ultraviolet radiation in Queensland sunshine is greater since the patients there are drawn from an area between latitude 16° south and 28° south. Those reported from Dallas are centred in an area on latitude 23° north. From 1945 to 1957 he found a yearly average of 31.3% of patients with skin cancer or approximately 25 cases per million per annum, or 1% of new patients in Queensland.

In 1960, Cooper showed that the incidence of skin carcinomas exceeded 350 new cases per 100,000 in Queensland, and that this figure was halved in more southerly latitudes. The highest incidence he was able to find in the literature was 140 per 100,000 in Dallas (Sannal and Schour, 1957).

In 1955, Cooper reported a case of an engine driver who had stood on the left side of his cab for years, thus exposing the left side of his face to the sun. He eventually developed five rodent carcinomas on his left cheek.

Corson (1962) observed a rodent carcinoma on the right side of the nose in a man who drove a car to and from work, 30 miles, for 30 years, with that part of his nose exposed to the sun both going and coming back.

POSSIBLE MISCELLANEOUS FACTORS OF AETIOLOGICAL SIGNIFICANCE

Wetzel (1959) considers that a photochemical reaction due to ultraviolet radiation, which causes a secondary reaction attributable to absorption of tyrosine

and tryptophan (melanin can be formed from the latter) is an important factor in the development of photogenic cancer.

Everett et al. (1960) observed a significantly higher number of individuals with atrophic skin changes in a carcinoma group than in a control group. Due to a greater ability to tan, a greater degree of skin tanning was present, as indicated by standard applications of ultraviolet rays in the control group in spite of the fact that more individuals in the cancer group had considerable sun exposure.

They suggest decreased melanin in exposed skin and a reduced ability of unexposed skin to tan, reflect some more profound physiochemical alterations than can be attributed to "basic skin type".

Carson (1960) biopsied the margin of a pigmented macule on the forearm of an albino Negro female. On examination under the microscope, he found striking sun damage in the non-pigmented area, and protection from damage in the area where there was pigment in the epidermis.

EXTRANEIOUS FACTORS OF ACTUAL OR PROBABLE AETIOLOGICAL SIGNIFICANCE

1. White people who live in the tropics do not unduly expose their skins to the sunlight because of the intense degree of heat. They take the precaution of wearing hats and covering clothes and hence they show a lower incidence of skin cancer than that observed in sub-tropical areas.

2. Variations in the quality and intensity of the carcinogenic ultraviolet radiations.

3. Customs of dress for sport or work coupled with the practice of sunbathing and swimming, as evidenced more particularly in Sydney and Brisbane (Australia).

4. Variations in the amount of water vapour in the atmosphere.

5. Seasons of the year in relation to variations in solar distance from the sun.

6. The altitude above sea level.

7. The time of the day as evidenced by the zenith distance of the sun.

8. The absorptive effect of ozone in the atmosphere on ultraviolet radiation which is increased as the distance from the sun to the zenith increases.

9. Prolonged exposure to arsenic or occupational hazards such as the presence of foreign bodies.

10. Prolonged application of tar preparations to the skin may be of aetiological significance (Rook et al., 1956).

11. Repeated prolonged local irritation or trauma (Laycock, 1954., Word, 1955 and 1956).

12. Clinically normal looking skin, which has been "prepared" by prolonged and/or repeated exposure to sunlight, may be the site of a skin cancer following a single injury or trauma.

13. Ionizing radiations in medical practice or industry.

14. Long periods up to 10 to 30 years may be required for the development of skin cancer due to frequent and/or prolonged periods of exposure to sunlight.

15. Walker (1959) suggested that the low incidence of rodent carcinomas in non-European South Africans might be accounted for in part by both skin pigment and poor nutrition. He found that one of the commonest manifestations of malnutrition was an alteration in the sebaceous glands and sebum, and that this abnormal sebum might take some substance which could become carcinogenic when exposed to prolonged ultraviolet radiation.

In Australia, the average period of time in which the writer has observed skin cancers to have arisen in resident immigrants is 25 years, with the outside limits from 10 to 45 years.

PRECURSORS

The commonest precursors of both rodent and squamous carcinomas are the solar keratoses which occur mostly on the normally exposed areas. The writer has not (with 3 exceptions in the case of the palms) observed solar keratoses on the palms, soles or bathing trunk area, but has seen squamous carcinomas arising *de novo* on these areas and 2 rodent carcinomas in the last-named area.

Many solar keratoses may show no malignant changes for years or may never become malignant at all.

Carmichael (1961) stated "there is a tendency for both basal and squamous cell cancer to occur in the absence of hyperkeratosis" and "that solar keratosis is not an important pre-malignant lesion but rather that it occurs independently".

Lancaster (1962) however, pointed out that Carmichael had used an unjustifiable procedure in arriving at his conclusions, and that a study of Carmichael's paper does not support the conclusions drawn.

The writer likewise disagrees with Carmichael's conclusions entirely, since he has observed, over a period of more than 30 years, numerous solar keratoses which have become either rodent or squamous carcinomas, while under observation.

In addition, the writer has questioned numerous authorities throughout the world, and all have agreed that the solar keratosis is the most common precursor of skin carcinomas which have arisen in a precursor lesion. Of the numerous lesions which are recognized as precursors of skin carcinomas (for a list of which the reader is referred to "Cancer of the Skin", Belisario, (1959) Butterworth & Co., London) the following (when present) are among the next most common after solar keratoses:-

Xeroderma pigmentosum, Leucoplakia, cutaneous horns, chronic actinic dermatitis, arsenical keratoses, burn scars, chronic suruses fissures, fistulae and ulcers and X-ray and radium dermatitis and ulcers.

THERAPY

Scalpel Surgery

This is preferred by most surgeons and even some dermatologists for small lesions. *Its advantages* include the following:-

- (a) It is the treatment of choice for lesions in the scalp as removal can be effected without leaving a bald patch.
- (b) It is the method of choice over irradiation for lesions on the back of the hand or dorsum of the foot (bad healing areas) in manual workers in whom an accidental injury to the treated area may cause it to break down into an actinonecrotic ulcer.
- (c) A lesions is removed at one sitting and heals in 2 to 3 weeks.
- (d) Resort can be had to surgery in the event of failure of other forms of therapy, and plastic repair can be performed when large areas are concerned.
- (e) In doubtful cases, the whole growth can be presented to the pathologist for microscopical examination.

The disadvantages are seen in :-

- (a) The inherent fear or dislike for the "knife" in the majority of individuals.
- (b) Lesions require wider removal than is the case with chemosurgery or topical chemotherapy so that the cosmetic results are usually not as good. The cosmetic results are also not usually as good as those obtainable by irradiation for lesions on the lips, eyelids, nose and ears, and in the case of the latter two areas, as those obtainable by chemotherapy.
- (c) For larger lesions, the patient has to be hospitalized.

Electrosurgery (Cautery, Electrodesiccator or Electrocoagulator). Among the *advantages* may be included:-

- (a) Treatment is carried out at one sitting and no sutures are required as a rule.
- (b) Healing occurs, in small lesions, in 2 or 3 weeks.
- (c) There is no bleeding.
- (d) It can be used to remove the main areas of a growth prior to irradiation. In this way, each modality is employed to a lesser degree than if either were used alone, with consequent improvement in the cosmetic result. Likewise, this combined therapy can reduce the likelihood of damage to the nasolacrimal duct for lesions in the inner canthus area.

- (e) Like scalpel surgery, it can be used for failures and recurrences following other forms of treatment.
- (f) For smaller lesions, particularly in conjunction with a curette, the cosmetic results can be quite good and it can be used for chemosurgery.

Disadvantages include the following:—

- (a) It leaves bald patches after removal of scalp lesions, and healing may take longer than with scalpel surgery.
- (b) Some individuals have an instinctive dislike for the “electric needle or knife”.
- (c) The cosmetic results are usually not as good as those obtainable by scalpel surgery for large lesions, or those obtainable by irradiation for the eyelids, lips, nose and ears, or in the latter two areas, as those obtainable by chemotherapy, combined or alone.
- (d) The cosmetic results are not in the overall as good when electrosurgery is used alone as when it is combined with chemotherapy since more destruction of tissue is necessary with electrosurgery alone to guard against recurrence. This extra amount of destruction of peripheral cells, is taken care of by chemotherapeutic agents when employed.

IONIZING RADIATION

X-Rays have the following *advantages* :—

- (a) There is no discomfort or pain associated with their administration.
- (b) Hospitalization is not necessary.
- (c) They can be used in one dose of 2500 “r” (2200 rads) or 1800 “r” (1580 rads approx.) following electrosurgery and curettage, or 1200 “r” (1050 rads approx.) on 2 consecutive days, or 1000 “r” (880 rads) on 3 consecutive days or 800 “r” (700 rads approx.) on 5 consecutive days. These dosages should only be used for people who live long distances away or who cannot attend more often.

The likelihood of radiation sequelae is decreased in direct proportion (within therapeutic limits) to the increase in fractionation. The best results have been obtained by the writer with a total dosage of from 4500 “r” (3960 rads) to 5000 “r” (4400 rads), delivered over 21 days in increments of from 250 “r” (220 rads) to 350 “r” (310 rads).

- (d) X-rays are the method of choice for the edges of the eyelids and the lips both because the best cosmetic results are obtainable by X-radiation in these areas and because proper shielding of surrounding or neighbouring structures (e. g. the eye) can be obtained. This protection is not readily obtainable with radium or radon (Belisario, 1969).
- (e) Cosmetic results are almost always better than those obtainable by scalpel or electrosurgery when the cartilage of the nose or ears is involved.

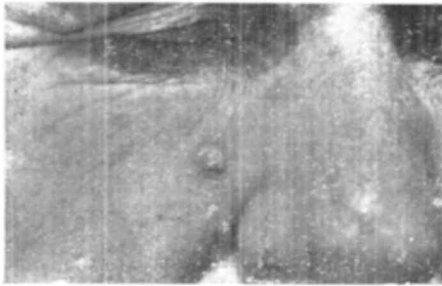


Fig. 1. Cherry type rodent carcinoma. This appearance is more often seen with a keratoacanthoma or squamous carcinoma.



Fig. 2. Squamous carcinoma showing involvement and destruction of the ear cartilage.



Fig. 3. Same patient as in Fig. 2, cured after 15×300 "r" (275 rads) by cross-fire over 21 days (total 4500 "r" or 3960 rads).

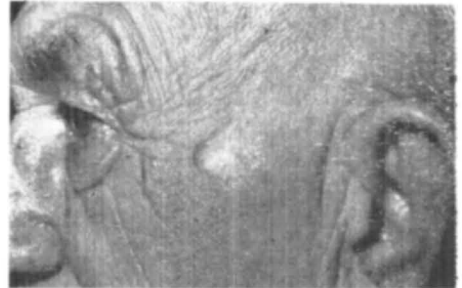


Fig. 4. Rodent carcinoma of left side of face.

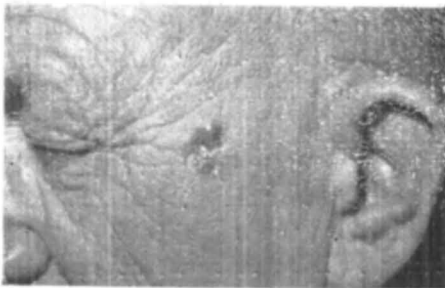


Fig. 5. Same patient as in Fig. 4 cured by cauterly-curette-synkamine (Vit. K5) technique.



Fig. 6. Rodent carcinoma to the right lower side of the vulva (very rare).



Fig. 7. Same patient as in Fig. 6, cured by cauterly-curette-Synkamine (Vit. K5) technique.



Fig. 8. Rodent carcinoma involving cartilage of right ear.



Fig. 9. Same patient as in Fig. 8 showing erosion after 3 weeks topical application of 0.5% methotrexate ointment.



Fig. 10. Same patient as in Figs. 8 and 9 cured after topical therapy with 0.5% methotrexate ointment for 4 weeks, followed by bi-daily application of neotracin ointment.

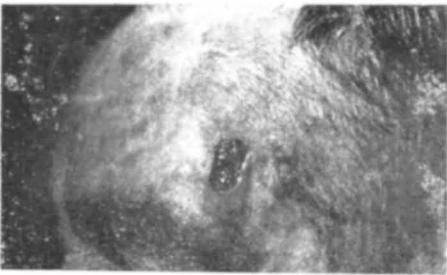


Fig. 11. Rodent carcinoma of left temporal region.



Fig. 12. Same patient as in Fig. 11 showing erosion of carcinoma area after 3 weeks topical therapy with 0.25% each of colcemid and methotrexate ointment.

The factors commonly employed by the writer are 110 KV, 15 cms. F. S. D., 6 MA., and H. V. L. 1.5 mm. Al., with which, an average of approximately 70% of the surface dose (depending on the depth of underlying tissue and the size of the irradiated area) will reach the base of the lesion. For deeper lesions, the estimated dose to the base of the lesion is employed and may approximate 3500 "r" (3100 rads) approx. (Belisario, 1959).

The following *disadvantages* may be associated with X-ray therapy :

- (a) Telangiectasia, atrophy and pigmentation may supervene within a period of years even up to 10 or more. Also an actinonecrotic ulcer may arise, particularly on areas of poor blood supply like the dorsum of the hand or foot where an accidental injury may be the trigger factor.
- (b) Bald patches are left in hairy areas such as the scalp.
- (c) Later sequelae may be embarrassing in such individuals as a physician, actress, model or a beauty specialist, particularly on exposed areas.

RADIUM OR RADON

The same applies for radium or radon as in the case of X-rays except the following *advantages* :—

- (a) The slow even delivery of a dose obtainable with a radium or radon mould with from 0.6 to 0.8 mm. of platinum filtration (Paterson and Parker, 1934), is better tolerated by normal tissues than the fractionated delivery X-rays, with consequent lessening of the degree of later sequelae. Consequently, if irradiation is to be employed on areas such as the dorsum of the hand or foot, a radium or radon mould should be employed providing a distance of 0.5 to 1.0 cm. between the radiation source and the surface skin, to give 6000 "r" (5800 rads) over 14 days. This dose can be given over 7 days in areas where the blood supply is good.
- (b) A patient does not have to report daily for treatment and treatment can be carried out in the home or a hospital in the case of a bed-ridden, invalid or crippled patient.

The *disadvantages* lie mainly in the fact that neighbouring tissues cannot easily be protected as with X-radiation (e. g. the eyes), and interstitial radiation (in areas where surface radium therapy is impracticable) may not be favoured by the patient because of dislike for "the needle" or the local anaesthetic. Interstitial radiation can also be followed by necrosis if employed over cartilage such as the nose or ear.

RADIUM AND COBALT BOMBS AND RADIO-ACTIVE ISOTOPES

So far, these modalities have shown no significant advantages over conventional irradiation therapy for cutaneous carcinomas, and also are not usually readily obtainable at other than large treatment centres.

CHEMOSURGERY

Moh's Technique (1947). This procedure comprises the destruction of surface carcinoma tissue by the application of dichloroacetic acid followed by the application of zinc chloride fixative and covered with a water-tight dressing. About 1.5 mm. depth of tissue is removed each day with a scalpel then cut into sections and examined microscopically. This routine is continued until all cancerous tissue has been removed.

The *advantages* include:—

- (a) It can be employed when other methods have failed.
- (b) It ensures complete removal of all cancerous tissue when this is possible.
- (c) It can be employed for patients who are too ill or old to undergo surgery and anaesthesia.

The *disadvantages* are seen in the following factors:—

- (a) The method is very time-consuming and tedious,
- (b) The inherent dislike of "the knife" in some people may prove an obstacle.
- (c) Thorough training under expert supervision is necessary to obtain proficiency in this form of therapy.

The Writer's Technique (Belisario, 1959, pp. 152-157 and 160). Under a local anaesthetic, the main mass of a growth is softened or destroyed with a cautery knob or diathermy needle or knob. All friable material is then removed with a curette and haemostasis is effected by lightly touching over the treated area with the cautery or diathermy. The area is then covered with 50% of podophyllin in tincture of benzoin compound or Vitamin K5 powder (Synkamine, Parke Davis Ltd.) or both, and protected with a gauze or Telfa dressing (Bauer and Black, Chicago, Ill.) and adhesive tape for 48 hours.

The area is then dressed once or twice daily with a steroid ointment, containing neomycin, 5 mg./gm. of base, or from 1% to 2% of hexachlorophene until it is healed. This application reduces the reaction caused by podophyllin (which resembles that following irradiation) and Vitamin K5 and also obviates any likelihood of possible super-added coccal infection (Belisario, 1961).

The *advantages* of this form of therapy include:—

- (a) The treatment is performed at one sitting.
- (b) There is no use of "the knife" which appeals to most patients.
- (c) The treatment can be performed in the patient's home or hospital if necessary.
- (d) The final cosmetic results are better in the overall than with the previously mentioned methods of treatment, since the antimitotic or cytotoxic effect of the podophyllin and/or synkamine destroys peripheral carcinoma

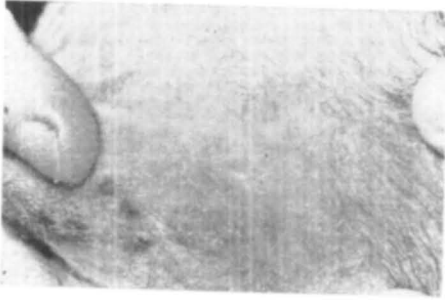


Fig. 13. Same patient as in Figs. 11 and 12, showing cure of the rodent carcinoma after 4 weeks treatment with colcemid and methotrexate followed by 2 weeks bi-daily application of neotracin ointment.

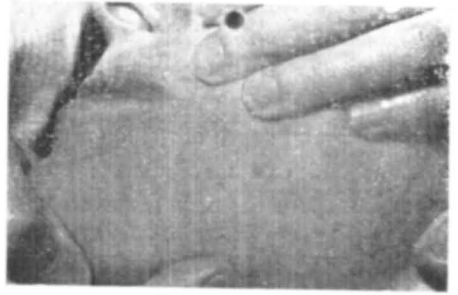


Fig. 14. Superficial cicatricial rodent carcinoma of the left side of the chin.



Fig. 15. Same patient as in Fig. 14, showing erosion (wide of apparently clinically involved area) after 3 weeks topical therapy with colcemid and methotrexate ointment, containing 0.25% of each.

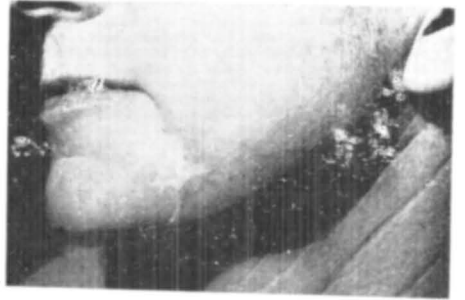


Fig. 16. Same patient as in Figs. 14 and 15 showing cured lesion with slight scar formation after 4 weeks treatment with the cytotoxic ointment followed by 3 weeks bi-daily application of neotracin ointment.



Fig. 17. Multiple lesions of Bowen's disease on the posterior aspect of the right leg.



Fig. 18. The same patient as in Fig 17 showing a degree of erosion increasing from above downwards, after 2 weeks topical with 0.5% methotrexate ointment, 0.5% colcemid ointment, 0.5% thio-colciran ointment and 0.2% each of the 3 combined in the one ointment.

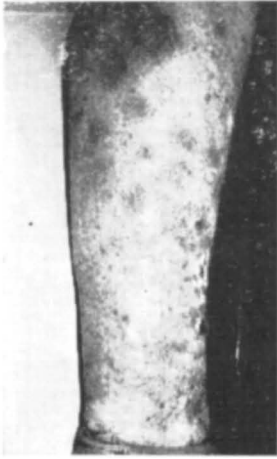


Fig. 19. The same patient as in Figs. 17 and 18 showing treated areas healed with mild temporary pigmentation



Fig. 20. Crusty reaction produced by topical therapy with 0.5% colcemid ointment on multiple keratoses when irradicated only without covering,



Fig. 22. Same patient as in Fig. 21 showing erosion after 3 weeks topical therapy with 0.5% colcemid ointment.

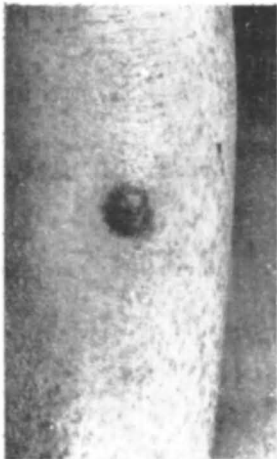


Fig. 21. Kerato-acanthoma on the anterior aspect of the left leg in a female patient.

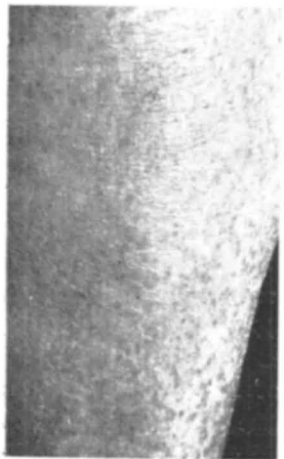


Fig. 23. Same patient as in Figs. 21 and 22 cured, 2 weeks after cessation of treatment colcemid ointment (for 4 weeks) and the bi-daily application of neotracin ointment.

cells making less tissue destruction necessary with the cautery or diathermy than if either were used alone.

- (e) The cure rate compares favourably with the previous methods of treatment.

Of the *disadvantages* the following may have to be considered :

- (a) An occasional patient has an aversion to the use of needles as required for local anaesthesia.
- (b) The method should not be employed on the edges of the eyelids because of the irritant effect of podophyllin, and to a lesser extent, synkamine on the conjunctiva. This also applies to the mucous membranes of the lips with podophyllin. This chemosurgical technique has been employed by the writer over a period of 10 years, during which period, over 1500 cutaneous carcinomas (of which 65 have been squamous carcinomas) have been treated in this manner.

The cure rate for small to medium-sized rodent carcinoma lesions, is in the region of 90% or over since retreatment of recurrences, (which vary from about 15% down to 5% depending on the degree of experience of the physician in the performance of the technique), is permissible.

With the exception of larger lesions, all the squamous carcinomas were early to medium-sized lesions (from 0.5 to 2.0 cm. diameter). Of the 4 larger lesions, one remained clear after one treatment and 3 recurred. One of these cleared up after a second treatment and 2 failed to respond to X- and Cobalt radiation, and resort was then had to scalpel surgery. One of these developed metastases. Also, one of the medium sized lesions was followed by metastases although the primary lesion cleared up permanently. In the early days of this form of therapy, if a lesion did not disappear clinically, or there was early recurrence (5 of 12 cases), resort was had to irradiation or surgery. Over recent years however, a number of observers have cast doubt on the aetiological significance of an increase in the presence of cancer cells in the blood from scalpel and electrosurgery and manipulation of the primary lesion, and on their ability to metastasize to other areas except in the case of those growths from which metastases would have occurred any way. The vast majority of cancer cells in the blood stream (which can be very difficult to differentiate from megakaryocytes and a number of other large benign cells), are destroyed, and it is only a relatively very small number that can survive to form metastases (Engel, 1959, Sandberg et al. 1960, Alexander and Spriggs, 1960, Scheinin et al. 1962, Pruitt et al. 1962.).

Because of these findings, the writer has more recently treated recurrences a second time by his chemosurgical technique (in one case a third time), and also any lesions which did not disappear clinically after the first treatment.

In addition to those previously mentioned there have been 5 of the former and 3 of the latter. These patients have remained clear until now for periods of from 2 to 7 years. The case treated a third time has remained clear for 5 years.

It is realized that recurrences and/or metastases could still supervene, but not necessarily with any greater frequency than that following other forms of therapy.

LOCAL CHEMOTHERAPY

This can be performed by intralesional injections or topical application.

For *intralesional injections* the writer has used:-

1. Analogues of vitamin K (2 injections weekly up to 8) in the form of (a) *Synkamine* (4-amino-2-methyl-1-naphthol hydrochloride, Parke Davis and Co.), 1 mg/cc. of diluent (b) *Synkavite* (tetra-sodium 2-methyl-1:4-naphtho-quinone diphosphate, Roche) 1 mg./cc. and (c) *Menadione* (menaphthone sodium bisulphate, Drug Houses of Australia), 10 mg. and 75 mg./cc. of diluent, with reduction in size and even disappearance of some lesions but with no visible effect in others. Of the lesions which benefit by this form of therapy, the squamous lesions appear to be more affected than rodent carcinomas.

2. *Colcemid* (*demecolcine* or *omain*) or N-desacetyl methyl colchicine, a cytotoxic or antimitotic and radiomimetic agent, which was isolated by Santavy and Reichstein (1950) in association with Ciba chemists from the meadow saffron plant. They found that it was 30 times less toxic than its parent substance colchicine which is also a derivative of the meadow saffron.

Colchicine has also been employed by Hirsch (1951), Martinotti (1954) Wiedemann (1957) and others in ointment form for the topical therapy of skin carcinomas in strengths of from 0.5% to 3.0%.

Menshikov, Ber and Kiselev also isolated N-desacetyl methyl colchicine (which they called *omain*) in 1950 from *colchicum speciosum* and *colchicum vernum* (Musin, 1959). *Colcemid* has been employed since that time intralesionally (although not so successfully) and in ointment form in strengths of from 0.1% to 1.0% or more (Santoianni, 1956, Wermel and Kramorenko, 1958, Schramchenko, 1960, Belisario, 1960, 1961, 1962., Kramorenko et al. 1962).

Colcemid exerts a selective action on tumour cells by inhibiting mitosis in the metaphase (Schar et al., 1954 and others). *Methotrexate* (Lederle) or 4-amino-N10 methyl pteroglutamic acid, acts on a different stage of mitosis since it prevents the commencement of this process by interference with the synthesis of desoxyribonucleic acid (Van Scott, 1962). Because of this, the writer combined these two cytotoxic agents both in solution and in ointment form and found that in this way they exerted a synergistic effect which increased their therapeutic action.

The effects of *Intralesional-therapy* on both rodent and squamous carcinomas were found by the writer to be equivocal in that only some lesions disappeared or were reduced in size and others appeared to be little if at all affected.

TOPICAL THERAPY

The application of colcemid in 0.5% strength has been found by the writer to be beneficially effective on rodent carcinomas, Bowen's disease, leucoplakia and solar keratoses. This efficacy is increased by the addition of methotrexate, which on its own, is not as beneficially effective as colcemid. When combined, they can be used in 0.25% strength of each due to their synergism, and any bland base may be employed. The one used by the writer consists of Cetomacrogol emulsifying wax (B. P. C.) 20 gm., soft white paraffin 40 gm., and liquid paraffin 200 gm. Vermel (1962) considers the addition of ephedrine 1% and hyaluronidase 80 U./ml. to the ointment base increases its efficacy.

More recently the writer has been using *thio-colciran* N-desacetyl thiocolchicine chlorhydrate or R261 (Roussel Drug Co., Paris), and has found it to be as or almost as effective as colcemid, to which it has a similar action in stopping mitosis in the metaphase (Bassel and Montfort, 1955, 1959). It appears clinically to enhance the therapeutic action of an ointment containing colcemid and methotrexate, and all can be employed in strengths of from 0.2% of each in the same ointment or 0.5% when used alone.

Like colcemid and methotrexate, it has little to no clinically observable effect on squamous carcinomas (Belisario, 1961, 1962). This has also been noted by Temime et al. (1962).

The ointment is applied twice daily and covered with a Telfa dressing (Bauer and Back, Chicago) and adhesive tape. Within the first week erosion of the abnormal tissues occurs, (selective effect) while the clinically normal looking adjacent tissues are usually unaffected. Little to no discomfort experienced by the patient, but should there occasionally be any inflammation of surrounding tissues, these can be covered with zinc paste. The average optimum time of treatment has been found to be four weeks, but a few lesions may have to be treated for a little longer. At the conclusion of treatment with the cytotoxic ointment the area is dressed with a mild antiseptic or antibiotic (e. g. neotracin) ointment until healed.

Recurrences have been relatively minimal in small to medium-sized lesions and can be retreated so that an over-all cure rate around 90% should be obtainable.

Larger lesions or indurated nodules may require superficial destruction with a cautery or electrodesiccator to allow the ointment to act, and in the case of the former, should be treated piecemeal to improve the cosmetic result (Belisario, 1940, 1942, 1952, 1959).

As in the case of other forms of therapy, the superficial cicatricial, or fibrous lesions, or lesions occurring in a scar, have the highest recurrence rate. These should be assisted with a cautery and/or curette (Vide Figs. 14, 15 and 16).

Recently the writer has successfully treated 6 consecutive kerato-acanthomas with similar therapy to the above. This phenomenon could become an additional

helpful point in the differential diagnosis of a kerato-acanthoma from a low-grade squamous carcinoma.

ADVANTAGES

- (a) The use of an ointment instead of the knife, electrical apparatus or even a needle, has a strong appeal for most patients.
- (b) The treatment can be used for a scalp lesions without causing hair loss.
- (c) The cosmetic results when the cartilage of the ears or nose is involved, can be better than those obtainable by other forms of therapy.
- (d) The treatment can be repeated and/or used when other methods have failed or in the case of recurrence.
- (e) It can enhance the use of irradiation and lessen the size of the dose required. This also applies to the scalpel and electro-surgery by reducing the degree of physical destruction required.
- (f) The cosmetic results are on the whole, better than with other forms of treatment.

DISADVANTAGES

- (a) So far, the drugs are expensive.
- (b) The area requires dressing twice a day.
- (c) The treated area is "raw" and eroded for several weeks, and occasionally a little uncomfortable and a little unsightly to the patient.

SUMMARY

1. The incidence of the skin cancer in Australia is the highest in the world, comprising approximately 60% of all cancer, due mainly to the effects of the ultraviolet radiation in the solar spectrum on fair-skinned people who expose their skins more than others, both at work and in sporting activities.
2. Aetiological factors include heredity, complexion, habits of dress, lack of skin pigment protection, thickness of the horny layer of the epidermis, the number of hours of exposure to the sunlight, miscellaneous and extraneous factors which are enumerated.
3. The commonest precursors of both rodent and squamous carcinomas are the solar keratoses.
4. Therapeutic methods include (a) scalpel surgery, (b) electrosurgery, (c) radiotherapy (d) chemosurgery and (e) local chemotherapy.
5. The advantages and disadvantages are indicated.
6. The majority of patients prefer the idea of being treated by an ointment.
7. The cytotoxic drugs colcemid, thio-colciran and methotrexate and their methods of use are described.

8. Cosmetic results have been found by the writer with local chemotherapy to be generally better than with other forms of therapy, and the cure rate with small to medium-sized lesions compares favourably. ✓

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