Summary

Five cases of generalized peritonitis secondary to perforating lesions of the gastro-intestinal tract were benefited by treatment with aureomycin. Four of these received the drug post-operatively; the fifth recovered without surgical intervention.

REFERENCES

- Altemeier, W. A. (1949). *J. Amer. med. Ass.* **139**, 347.
 Bryer, M. S., Schoenbach, E. B., Chandler, C. A., Bliss, E. A., and Long, P. H. (1948). *Ibid.*, **138**, 117.
 Knight, V., McDermott, W., and Ruiz-Sanchez, F. (1949). *J. clin. Invest.*, **28**, 1052.
 Pulaski, E. J., Voorhees, A. B., and Seeley, S. F. (1949). *Ann. Surg.* **130**, 242.
 Smadel, J. E., Bailey, C. A., and Lewthwaite, R. (to be published).
 Woodward, T. E., Smadel, J. E., and Ley, H. L., jun. (1949). *J. clin. Invest.* In press.
 Yeager, G. H., Ingram, C. H., and Holbrook, W. A. (1949). *Ann. Surg.*, **129**, 797.

EPITHELIOMA AND PAPILLOMA ARISING ON RECENTLY IRRADIATED SKIN

REPORT OF THREE CASES

BY

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[WITH PHOTOGRAVURE PLATE]

Hyperkeratosis and epitheliomatous degeneration are well recognized as late complications of chronic radiodermatitis following treatment. Typically they develop on a basis of obvious skin damage such as atrophy, telangiectasia, epidermal thickening, etc., though they may at times be caused by repeated irradiation over several years without obvious skin reaction. The latent interval is usually several or many years; MacKee and Cipollaro (1937) state that x-ray epithelioma has been seen as early as two years after excessive irradiation. The same authors (1946) refer to epithelioma shown to occur within a year after the healing of a third-degree reaction—that is, an “acute necrosis” involving the true skin (dermis).

The following cases, occurring a very few months after x-ray reactions of only moderate severity (second degree, with shedding of epidermis only), therefore seem to be worthy of record.

Case 1

Mr. A., aged 65, had carcinoma of the larynx involving the left cord and anterior commissure. Biopsy from the cord had shown a Grade 3 squamous epithelioma (Plate, Fig. 1). No secondary nodes were felt.

Treatment was given by x rays at 200 kV, H.V.L.=1.5 mm. Cu, filter of 1 mm. Cu and 1 mm. Al, 40 cm. F.S.D.; output (for 8 by 6 cm. field, including backscatter) 60 r per minute. Two principal parallel fields were used, with the aid of a wax mould which served the double purpose of acting as a “beam director” and filling in the air gaps. From December 28, 1946, to January 21, 1947, these two fields were treated daily to a total of 3,450 r incident dose on each (initial dose of 300 r, then 9×350 r)—24 days overall; treatment was continued from January 23 to 28 by an 8 by 6 cm. field from the back, to 1,200 r incident (3×400 r). Total treatment time was therefore 31 days, the estimated tumour dose was 4,600 r, and the skin dose at the sides of the neck approximately the same. The skin reaction proceeded to a deep erythema with dry desquamation and a few small moist patches. Healing was rapid and uneventful.

Seven weeks after the end of treatment there was no trace of the primary lesion, the site of which was marked by a pale scar; the case notes record “little skin change” in the neck. In June, 19 weeks after treatment, “a little atrophy and pigmentation in the treated region” was noted; in the middle of the field on the right side was a skin nodule 7 mm. across, which according to the patient (an intelligent observer) had been present five weeks. A month later it had grown to 9 mm.; the accompanying photograph (Fig. A) shows its appearance at that time. It was therefore excised and sectioned; the histological report stated: “The section shows the structure of a simple squamous papilloma, which has been completely removed” (Fig. 2). The patient has remained well to date, after 26 months.

FIG. A.—Case 1. External lesion in July, 1947: simple squamous papilloma.

Case 2

Mr. B., aged 72; carcinoma of hypopharynx (right arytenoid region), with a hard fixed secondary mass of nodes 4 by 2.5 cm. below the angle of the jaw on the right side. A “needle biopsy” (Ellis and Hermitte, 1947) from the nodes showed “several portions of a Grade 2 squamous epithelioma, in a mixture of blood and acute inflammatory exudate” (Fig. 3).

Treatment.—The same factors were employed as in Case 1. Two parallel fields were used, each 10 by 8 cm. to include primary and nodes. Between February 14 and March 19, 1947, 3,000 r was given to each field, by treatment on alternate days (12×200 r, then 2×300 r), both fields being irradiated at each session; the overall time was 33 days. The skin dose was estimated to be 3,900 r, and the dose at the primary about the same. The skin reaction was an erythema of moderate depth. Primary and nodes regressed to a considerable extent, but 11 weeks after the end of treatment a nodule 1.5 cm. across was noted within the treated field on the left side. This was excised, and the section report stated: “Grade 1 squamous epithelioma which appears to be primary skin growth. Completely removed” (Fig. 4). One year after treatment the patient died from the effects of the primary lesion.

Case 3

Mr. C., aged 76; secondary nodes in neck, primary uncertain. There was a large hard fixed mass of nodes below the angle of the jaw on the right, 6 by 3.5 cm. Needle biopsy showed “rather undifferentiated malignant cells, probably anaplastic squamous carcinoma” (Fig. 5).

Treatment, with the same general factors as above, was by the "wedge field" method described by Ellis and Miller (1944), using two fields of 8 by 6 cm. at a right-angle. Daily treatment between August 31 and September 23, 1948, gave a total of 3,500 r incident on each field (17×200 r, 1×100 r); the depth dose was about 3,500 r and the skin dose approximately the same; the overall time was 23 days. A moderate erythema developed, and the mass decreased in size to 3 cm.

Seven weeks after the end of treatment a nodule 2 cm. across was noted on the lower part of the right cheek within the treated skin area, which showed no gross changes; the patient thought it had been present for two weeks. A biopsy was taken, which showed "a portion of a cornifying Grade 1 squamous epithelioma" (Fig. 6). It was decided to treat by x rays, at 100 kV, H.V.L.=2 mm. Al; filter of 1 mm. Al, F.S.D.=15 cm., with a circular field of 3 cm. diameter. 500 r was delivered twice weekly to a total of 3,500 r in 23 days in seven fractions. A moist reaction followed, and healing was complete after a month. The patient is well to date, with a residue of the secondary mass still present.

Discussion

All three cases show very similar features, with squamous skin lesions appearing within weeks after moderate radiation reactions. If the patients' own observations be accepted, the intervals between the end of the treatment and the first appearance of a definite nodule were 14, 11, and 5 weeks respectively. Various possible explanations of these lesions have to be considered.

(a) *They May be Skin Secondaries.*—The clinical appearances were typical of primary skin tumours and unlike nodules of secondary growth, which are usually subepidermal or subcutaneous. In Case 1 the histological grade was lower than that of the primary lesion, and in Cases 2 and 3 it was lower than that of the secondary nodes. It is often said that a metastasis is invariably of the same grade as the primary, or a higher grade; if so, this is a strong argument against the possibility of the lesions being skin secondaries in these cases (though I have observed one case in which a Grade 2 epithelioma of the tongue gave rise to a secondary node in the submaxillary region which was of a highly cornifying Grade 1 character). But the most convincing argument against this possibility is the actual microscopical appearance in each case, which is perfectly typical of a primary skin tumour and quite unlike that of a skin secondary (see Figs. 2, 4, 6).

(b) *They May be Coincidental.*—If an early microscopic skin tumour was present before the start of radiotherapy the dosage given to the skin in each case would be expected either to be curative of such tumour or at least to delay its appearance very considerably. If, on the other hand, the tumours originated after the radiotherapy had been completed, then the latent interval before their clinical appearance would be extremely short, especially in the third case, in which the interval was seven weeks at most, more probably five. In pitch or tar workers the shortest latent period in the series of Henry (1947) was eight months for a papilloma and ten months for an epithelioma. Once initiated, however, epitheliomas can grow very rapidly; Winternitz (1947) mentions a squamous carcinoma in a pitch worker that had apparently grown from microscopic size to 0.7 cm. in diameter in a fortnight at most. A carcinogenic "stimulus" which would take many months or years to produce an epithelioma on "normal" skin might perhaps produce the same effect in a few weeks in the case of skin that had undergone the abnormal changes of acute radio-dermatitis. If this were so, cases similar to ours should not be extremely rare, yet they do not appear to have been recorded.

(c) *They May be "Late" Radiation Effects.*—Late radiation effects typically follow definite overdosage, leading to gross skin changes, both naked-eye and microscopical. Histologically there is dense fibrosis of the corium, with thickening and obliteration of blood vessels. In none of these respects do the present cases correspond.

(d) *They May be "Early" Radiation Effects.*—(i) A possible explanation might be based on the action of x rays upon chromosomes. It is well recognized that mutations can be produced experimentally by radiations, and such a mutation in one or more cells due to the radiation treatment might theoretically be the starting-point of a new growth. The whole question of somatic mutations as possible factors in carcinogenesis is still speculative; but if this explanation were correct then radiation-induced epitheliomas would not be excessively rare after the scores of thousands of skin fields treated by x rays. Much more convincing evidence would be required before such an explanation could be entertained. (ii) The radiation itself may be responsible for the tumours—that is, act as an "acute" carcinogen in the same way as other carcinogenic agents. The latent periods of 7, 11, and 19 weeks are surprisingly short for human carcinogenesis, but exceptionally early cancers have been known to occur—for example, the case recorded by Bang (1923) in which a carcinoma appeared on a workman's nose 16 days after a splash of hot tar. This explanation also faces the same difficulty as the last—that is, the extreme rarity of the sequence. (iii) One may also consider the possibility of an associated carcinogenic irritant such as a local application to the skin. Attention has been drawn to the possible carcinogenic effect in humans of prolonged application of liquor picis carbonis (Berenblum, 1948); the combination of two irritants might have a more rapid effect than either separately. The only local application used in our cases was penicillin cream, for periods up to about two weeks.

Summary

In this paper are described two cases of squamous epithelioma and one case of papilloma, appearing on the skin at intervals of 7, 11, and 19 weeks after completion of radical x-ray therapy, with moderately severe skin reactions. Several possible explanations are discussed.

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REFERENCES

- Bang, F. (1923). *Bull. Ass. franç. Cancer*, **12**, 184.
 Berenblum, I. (1948). *British Medical Journal*, **2**, 601.
 Ellis, F., and Hermitte, L. C. D. (1947). In *Recent Advances in Clinical Pathology*, edited by S. C. Dyke, p. 324. Churchill, London.
 — and Miller, H. (1944). *Brit. J. Radiol.*, **17**, 90.
 Henry, S. A. (1947). *Ibid.*, **20**, 149.
 MacKee, G. M., and Cipollaro, A. C. (1937). *Cutaneous Cancer and Pre-cancer*. American Journal of Cancer, New York.
 — (1946). *X-rays and Radium in the Treatment of Diseases of the Skin*, 4th ed. Kimpton, London; Lea and Febiger, Philadelphia.
 Winternitz, J. G. (1947). *Brit. J. Radiol.*, **20**, 158.

The Ministry of Health has sent a circular to hospital boards and committees asking them to help tuberculous persons find suitable work, whether as nurses or otherwise, in tuberculosis sanatoria. This has already been done at many tuberculosis institutions. Though there may be some administrative disadvantages in employing tuberculous nurses or other staff in sanatoria, the Minister considers that the advantages outweigh them. Patients nursed by these people find an exceptional degree of sympathy and understanding.

J. WALTER: EPITHELIOMA AND PAPILLOMA ARISING ON RECENTLY IRRADIATED SKIN

FIG. 1.—Case 1. Original Grade 3 squamous epithelioma of the left vocal cord. ($\times 80$.)

FIG. 3.—Case 2. Original Grade 2 squamous epithelioma. ($\times 80$.)

FIG. 5.—Case 3. Original anaplastic squamous carcinoma. ($\times 80$.)

FIG. 2.—Case 1. Simple squamous papilloma of neck after radiotherapy. ($\times 10$.)

FIG. 4.—Case 2. Grade 1 squamous epithelioma after radiotherapy. ($\times 75$.)

FIG. 6.—Case 3. Grade 1 squamous epithelioma after radiotherapy. ($\times 50$.)

F. I. POWELL: FRACTURE OF THE FIRST RIB

FIG. 1.—Case 1. Complete fissure of first rib with no widening medially.

FIG. 2.—Case 2. "Oblique" fissure of first rib with fissure line widened out medially.

FIG. 3.—Old fracture of first rib with callus formation (buttressing appearance).

FIG. 4.—Old ununited fracture of first rib, suggestive of pseudo-arthritis.