Previous experimental studies (1) in mice and histologic studies of specimens from human patients were interpreted to suggest that squamous cell carcinoma arises by malignant transformation of a segment of squamous epithelium and not as a result of such changes occurring in one cell or a small nidus of cells. Furthermore, the experimental evidence recorded was interpreted by the authors to indicate that while the principal factor in the increase in size of such lesions was the increased number of cells resulting from continuous mitotic activity another factor, namely, progressive malignant change in the normal epithelium immediately apposed to the malignant epithelium, also contributed to lateral spread of the process. This hypothesis is not a new one (Ribbert, Adami) and admittedly has few adherents today. Still another observation in the study just referred to, which was made on mice bearing methylcholanthrene squamous cell cutaneous carcinomas, was that when the carcinoma was bisected, one-half of it removed, and normal skin approximated to the cut edge of the growth by suture with subsequent spontaneous separation of the wound to produce a chronic ulcer, healing of the latter was attempted by epithelial growth from the side of the normal epithelium and not from the margin composed of malignant cells. However, the neoplasm did increase in size in the direction away from the cut edge; that is, lateral spread went on over the continuously intact margins of the growth.

A patient presenting a squamous cell carcinoma of the dorsum of the left hand was recently observed, in whom an experiment similar to the last one mentioned above in mice was carried out. A summary of the history is as follows:

J.J.M. (67485) 62 years of age in 1932. Admitted September 9, 1932, with an ulcerating lingual carcinoma (biopsy) involving the right anterior margin, and rather extensive leukoplakia of the tongue. The Wassermann reaction was ++++. On December 2, 1932, the right anterior half of the tongue was resected. On March 6, 1933, a small ulceration in the wound was resected and found to be carcinoma. On April 19, 1937 a more radical partial glossectomy was performed for the third recurrence. He was seen at intervals until 1940, no recurrences being observed.

He was readmitted November 20, 1943, now 73 years of age, presenting an oval, fungating, and ulcerating lesion on the dorsum of the left hand, that had been present for a year and had been treated elsewhere by x-ray on several occasions. There was no evidence of recurrent carcinoma in the tongue or of lymph node metastases in the neck. Biopsy of the lesion on the hand revealed squamous cell carcinoma, and at the junction of the malignant and normal epithelium at the edge of the lesion a typical “zone of continuity” was present, i.e., a narrow zone in which malignant and nonmalignant cells could not be morphologically differentiated.

The Wassermann reaction was still ++++ in spite of considerable antiluetic therapy. His mentality was impaired and he had been living a parasitical existence for several years, depending entirely upon a daughter who herself was now incapacitated because of multiple sclerosis.

On November 22, 1943, the lesion was bisected under local anesthesia and the usual aseptic surgical precautions, and one-half was removed together with a semicircular patch of skin. A fresh wound was thus created, one margin of which was composed of malignant epithelium (Figs. 1 to 4). Vaseline dressings were applied and the progress of the area was noted until January 31, 1944, when the whole area was excised. No metastases were palpable in epitrochlear or axillary nodes. Later, when the area of excision had partially healed, and required only a small dressing, the patient was discharged to an institution.
Fig. 1.—Dorsum of left hand of J.E.M., day of operation. C, bipected squamous cell carcinoma; U, surgical ulcer; T, partially exposed extensor tendon; this is stationary marker to gauge closure of ulcer margins from normal skin edges.

Fig. 2.—Eighteen days after operation. Little change in size of carcinoma. The ulcer has become smaller because of healing from margin composed of nonneoplastic tissue. No tendency of malignant epithelium to cover ulcer.

Fig. 3.—Thirty-five days after operation. Further healing of ulcer from normal skin margins. Increase in size of carcinoma away from ulcer. No tendency of malignant neoplasm to extend over ulcer.

Fig. 4.—Fifty-three days after operation. The neoplasm has extended appreciably away from ulcer. The latter is almost healed by growth from nonneoplastic margins. No evidence of proliferation of malignant epithelium over ulcer; indeed, center of segment of tumor, N, bordering ulcer margin has become necrotic.
During the period of observation measurements of the flat, ulcerated area and of the neoplasm were made at intervals (Table I). After the 18th day the lesion exhibited fungations that overhung the actual base of its nontraumatized margins. Thus it appeared larger when the extent of these fungations was included in the measurements. In the Table the dimensions of the base and dimensions including the fungations are recorded separately.

Microscopic examination revealed typical squamous cell carcinoma. At the intact margins (Fig. 5) there was the typical zone of continuity between malignant and normal epithelium. Sections through the tumor bordering the ulcer revealed downgrowth of columns of cells into the subcutaneous tissues and no apparent evidence of the mechanism that prevented these cells from growing over the chronic ulcerated area. Indeed, the histologic appearance was similar to that of the ulcerating border seen in routine biopsy sections of squamous epithelial lesions. The border of advancing normal epithelium was typical for the margins of a nonspecific ulcer.

From the tabulated data it is seen that little change occurred in the size of the tumor and of the surgical ulcer during the 8 days following operation. By the 18th day increase in length of the lesion was noted and fungations had developed. Progressive increase in size then occurred. However, the spread was at the margins not traumatized by the operation. There was no evidence of even attempted spread of the malignant epithelium over the ulcer. Indeed, that portion of the tumor bordering the ulcer eventually became necrotic. From the eighth day onward the ulcer progressively decreased in size, healing taking place from the margins composed of nonneoplastic epithelium. A partially exposed extensor tendon (T in Figs. 1 to 4) served as a stationary marker in the subcutaneous tissues and study of the four accompanying illustrations shows the “healing in” of the ulcer from the normal skin margins.

Table I and Diagram: Diagrammatic Representation of Bisected Squamous Cell Carcinoma on Dorsum of Hand of Patient J.J.M. and Measurements of Traumatic Ulcer and Adjacent Neoplasm Made at Intervals Following Operation

<table>
<thead>
<tr>
<th>Date</th>
<th>Area of resection, ulcer Length × Breadth</th>
<th>Area of tumor (base) Length × Breadth</th>
<th>Area of tumor (including overhanging fungations) Length × Breadth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov. 22-43</td>
<td>58 × 21 mm.</td>
<td>35 × 18 mm.</td>
<td>41 × 28 mm.</td>
</tr>
<tr>
<td>Dec. 1-43 (8th day)</td>
<td>58 × 22 &quot;</td>
<td>38 × 19 &quot;</td>
<td>40 × 28 &quot;</td>
</tr>
<tr>
<td>&quot; 10-43 (18th day)</td>
<td>48 × 23 &quot;</td>
<td>41 × 18 &quot;</td>
<td>40 × 28 &quot;</td>
</tr>
<tr>
<td>&quot; 22-43 (30th day)</td>
<td>30 × 18 &quot;</td>
<td>40 × 20 &quot;</td>
<td>40 × 28 &quot;</td>
</tr>
<tr>
<td>&quot; 30-43 (38th day)</td>
<td>26 × 15 &quot;</td>
<td>40 × 24 &quot;</td>
<td>40 × 35 &quot;</td>
</tr>
<tr>
<td>Jan. 9-43 (48th day)</td>
<td>20 × 10 &quot;</td>
<td>40 × 33 &quot;</td>
<td>43 × 35 &quot;</td>
</tr>
<tr>
<td>&quot; 30-44 (69th day)</td>
<td>19 × 9 &quot;</td>
<td>43 × 33 &quot;</td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

The course of events in the human patient thus paralleled closely the observations previously reported in similar experiments with cutaneous squamous cell carcinomas produced by methylcholanthrene in mice; that is, the wound-healing stimulus obtained by the surgical excision of tissue did not stimulate locally the growth of the neoplasm. Similar conclusions were reached in studies with methylcholanthrene sarcomas in rats (2). Indeed, the malignant squamous epithelium appeared strikingly indolent toward such a stimulus, and seemed to have lost the property of purposeful proliferation to cover denuded areas. On the other hand, growth was progressive in areas that were undisturbed and the histologic findings here, as emphasized in a previous report, were consistent with the hypothesis (not, however, widely accepted) of progressive cancerization of normal cells as a factor in the lateral spread of squamous cell carcinomas. The intactness of the original junctional zone between malignant and nonmalignant squamous epithelium appeared to be a factor contributing to the lateral spread of this type of malignant process.

SUMMARY

Bisection of a squamous cell carcinoma in a human patient, with the production of a cutaneous defect adjacent to the portion of the tumor remaining in situ revealed: (a) lack of stimulation of the carcinoma along the incised margin; (b) healing of the cutaneous defect from the normal skin borders, with no evidence of retention of purposeful (healing) proliferation in the malignant epithelium; (c) continuous lateral spread of the carcinoma at the margins of the growth that were undisturbed by operative trauma.

REFERENCES

An Experimental Study of the Lateral Spread of Epidermoid (Squamous Cell) Carcinoma in Man, and the Reaction of Such a Lesion to the Wound-Healing Stimulus

Alexander Brunschwig and Thomas F. Thornton, Jr.

*Cancer Res* 1944;4:515-518.