cell carcinoma of the skin such as Marjolin's ulcer. If such treatment will clear the lesion, as happened in Case 1, the skin defect may be repaired. If the malignancy involves the underlying bone, the bone must be resected, but this can be done after much of the original tumor has been greatly decreased in size. Regional lymph node dissection is performed only when clinically positive lymph nodes are present. As stated previously,[26] we believe that 5-FU causes some type of immune reaction or sensitization of the tumor, and should be used before surgery.

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Discussion

Dr. John C. McDonald (Shreveport, Louisiana): Dr. Ryan and his colleagues suggest that the success of this program depends upon the unique characteristics of the tumor. The hypothesis suggests that the burn scar, due to its paucity of lymphatic channels, represents an immunologically privileged site, and when low-grade malignant transformation occurs within this site, the host is unaware of its presence until it attains too large a bulk for autogenous control, or it metastasizes to regional nodes at a time when the host has not developed an immune state.

Indeed, there is evidence to support such a hypothesis, the best of which was performed in a laboratory model by Dr. William Futrell, whose work is referenced in the manuscript. A correlate of this hypothesis is that local 5-FU either combines with the tumor, or induces the tumor, to produce more antigenic material, which creates a state of immunity to aid in the control of the lesion.

The experience of others suggests that scar cancers which engender round cell infiltrates have a better prognosis than those which do not, and this current experience supports this general hypothesis.

Drs. Ryan, Litwin, and Krementz have diligently studied the value of topically applied 5-fluorouracil in the treatment of integument tumors for numbers of years. This body of work is scholarly, and among the best in the field, and I recommend it to you.

I should point out that the evidence supporting this hypothesis is circumstantial, and the phenomenon can be explained by a number of alternative mechanisms, one of which might be that the burn scar simply acts as a mechanical barrier, allowing the tumor to grow to substantial size without metastasizing. Nevertheless, the paper is important, in that it proposes a hypothesis which can be tested, and it offers an additional example of the successful treatment of a malignancy with a multimodal approach, thus supporting the thesis that some tumors can be treated from a biologic point of view, rather than in a purely anatomic way.

Dr. James D. Hardy (Jackson, Mississippi): I'm somewhat apprehensive about discussing this paper, on two counts. First, Dr. Ryan and his colleagues have given us such a comprehensive survey of this problem that my one case may seem a little thin. Second, I fear I may be accused of attempted one-upmanship in relating the following experiences.

But when I arrived in Philadelphia from the Army in 1946, all set to begin surgical training and do hernias, Dr. I. S. Ravdin looked

me in the eye and, instead of telling me what service I was to start on, he asked, "Doctor, what do you plan to investigate?"

I replied, "Malignant cachexia, sir."

And he looked at me with that curious, quizzical glance that all of us came to know so well and said, "But, Doctor, that's a blank wall. What, exactly, do you intend to do?"

I said, "Well, sir, I'm going to put a tube down and force feed these patients dying of cancer and, using metabolic and isotopic body composition studies, see whether they can fabricate tissue." And these studies led to a lot of other things.

But in 1959, 13 years later, (slide) so many things had come out about how cancer patients died that I decided to review the literature and publish an editorial entitled "Why do cancer patients die?" It started out: "It is useful to re-examine from time to time the status of our knowledge of a disease. It will be the purpose here to examine the mechanism of death from cancer."

I began by summarizing current knowledge regarding systemic biochemical changes and tumor markers, but then went on to the recent interest in immunology: "More and more the concept of individual host immunity to cancer has come to be accepted. All of us can recall patients whose tumor had grown slowly for months or years, only to metastasize widely shortly following surgery at which the primary neoplasm was incompletely excised. A patient with a malignant ulcer in a burn scar, present for years, suddenly exhibits widespread metastases a few weeks following local excision."

(slide) This was an elderly woman who had an old, childhood burn scar, and had a Marjolin's ulcer in the center of it, present for years. She was reluctant to have it excised, but then in 1958 she accepted wide local excision with immediate skin grafting, as you see in the photograph. To our dismay, this woman rapidly developed widespread metastases and was dead in two months. She almost certainly had dormant distant cancer foci which were somehow activated by the operative experience. This case made a lasting impression on me.

DR. M. J. JURKIEWICZ (Atlanta, Georgia): I think it's perfectly evident to everybody in the audience, highlighted by the single case report discussed by Dr. Hardy, that there are two generic problems with any meaningful study of Marjolin's ulcer.

First it is obviously a disease where each of us has a very limited experience; thus each of us may be seeing only a portion of the truth.

It is obviously a protean disease as well. Marjolin did not actually describe a malignant ulcer arising in burn scar. He described malignant transformation in other chronic scars and, actually, it was Hawkins in 1833 that gave the notion of the malignant potential of burn scar. Marjolin's ulcer has been described therefore in the scar of burns, sinus tracts, avulsion wounds, stasis ulcers, chronic fistulae and the like.

To our patient cohort that was mentioned by Dr. Ryan we have added four patients. The clinical course of one is pertinent to this discussion and lends support to the idea that this may well be a mechanical phenomenon; *i.e.*, tumor trapping, rather than the tenuous hypothesis that scar behaves in some way as an immunologically privileged site. It may, but the evidence for immunologic privilege is all inferential.

This particular patient is alive and well at the moment, but he has had two recurrences. He had scar cancer arising in a traumatic ulcer of the great toe. The latter was amputated. In the 20-year interval after he had sustained the trauma to the toe he had developed a typical postphlebitic leg. He had, therefore, a circumferential scar around the distal third of the leg.

One year after therapeutic amputation of the great toe he then developed subcutaneous nodules that were trapped in the postphlebitic scar. These were excised and the area grafted. On a second occasion another tumor nodule developed in the postphlebitic scar. Excision and grafting again was carried out.

All the four patients that we have added to this cohort have been studied. Their immunologic profile indicates general systemic relative anergy. Their T-rossette, for example, is abnormally low, which suggests that these patients have both an efferent and an afferent limb abnormality if the Ryan hypothesis is correct.

I have two questions. What is the immunologic profile of these patients before and after treatment? It is very clear to me that what you're doing is to some extent cytoreductive. Is there any direct evidence that those lymphocytes that are being recruited have any specificity, or are they merely responding to nonspecific inflammation?

DR. ROBERT F. RYAN (Closing discussion): One of the things that we really hoped that we would do by this paper is to stimulate more of you to become involved with the use of 5-FU, and I think that thus far we have raised more questions than we have provided answers; and I hope that surgeons will become involved in it, and not forfeit to somebody else the work in this field.

In answer to the questions that Dr. Jurkiewicz asked, only in the last patient did we have any type of an immunologic profile. This man had a battery of skin tests done before we started our treatment. He was negative to all the skin tests. After we completed the treatment, and six months later, when he had no evidence of any tumor, all six skin tests became positive except for mumps, and he had never had mumps. So he did change somewhat his immunologic profile.

We have not done the studies on the lymphocytes that you suggest, but this is an area that must be done.

The late Oscar Creech said that surgeons will often make things work, but it may take years to explain why. I think we are in this situation here.