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Discussion

DR. JOHN A. SCHILLING (Seattle, Washington): This is a splendid paper of Dr. Levenson's, another interesting step in a tortuous route to controlled wound healing, common to all of surgery.

As I listened to the paper, I could not help but think back 20 or 25 years ago when DeDuve described lysosomes. Vitamin A was one of the labilizing drugs, whereas cortisone was a stabilizer.

And then Tom Hunt, of this Association, some years ago described a salutary influence of vitamin A in a chronic leg ulcer.

And now this sophisticated continuation of original observations by Dr. Levenson is important. We have so many patients that we must operate on with immune suppressive drugs and irradiation therapy.

Finally, I would like to ask Dr. Levenson if he now recommends giving vitamin A to his patients in these categories? And if so, how much?

DR. CHARLES E. LUCAS (Detroit, Michigan): Did you monitor the breaking strength of the uncut skin? And if so, was the uncut skin altered by the radiation, and was that alteration ameliorated by the vitamin A?

DR. RICHARD E. WILSON (Boston, Massachusetts): I rise to ask Dr. Levenson if he can discuss for a moment the use of vitamin A in patients who are receiving radiation therapy.

When radiation therapy is given, it has a biologic effect; we try to destroy certain populations of cells in a progressive way. I would like to know what the vitamin A's effect is on cell populations of tumors that are radiated, and whether or not it would, in fact, be possible to use this, or would it interfere with the known biologic effects for cell destruction by radiation?

DR. STANLEY M. LEVENSON (Closing discussion): As many of you know, John Schilling has been an innovative investigator in the wound healing field for many years and published an excellent paper with the effect of whole-body radiation on the healing of open wounds almost 30 years ago. I had read the paper when it first appeared and I reread it when we planned our current experiments, John, you will be glad to know. We do give supplemental vitamin A to certain groups of patients, but I will come back to that question when I reply to Dr. Wilson.

In regard to Dr. Lucas' question, we did not monitor the breaking strength of the unwounded skin. I think that is a good suggestion and one we will follow in some future experiments, but I do not think we will find much of a change in the breaking strength of unwounded skin in the time periods following acute whole-body radiation, which we have been following in the most of the experiments reported today, namely, 5, 7, 10, and 14 days postradiation and postoperation. Certainly, the changes in body weight *per se* would not suggest that the skin weight (thickness) would have changed enough to lead to a substantial decrease in body weight, nor do I believe the character of the dermis would have been altered by the levels of whole-body radiation we employed to result in decreased breaking strength. I do not believe that changes in unwounded skin *per se* would account for the decrease in breaking strengths of the skin incisions following acute whole-body radiation we observed and, of course, such postulated changes would not explain the decrease in accumulation of reparative collagen in the implanted sponges we observed in the rats following the acute whole-body radiation.

In regard to Dr. Wilson's question about the effect of supplemental vitamin A on radiation therapy of patients with malignant tumors, animal experiments in our laboratory have shown that supplemental vitamin A, which itself has antineoplastic action, increases significantly the therapeutic efficacy of tumor radiotherapy. Specifically, when CBA/J mice with C3HBA tumors in an extremity are treated with 3000 rad local x-irradiation alone (single dose), there is temporary regression of the tumor for about 3 weeks, but then tumor regrowth begins and all mice die in about 3 to 3.5 months on the average (2 experiments), a survival time double that of untreated tumor bearing mice (Seifter E, Rettura G, Padawer J, et al. Regression of C3HBA mouse tumor due to x-ray therapy combined with supplemental beta carotene or vitamin A. J National Cancer Institute, 1983; 71(2): 409–417. Supplemental vitamin A by itself slowed tumor growth but did not lead to tumor regression, and all mice died in about 9 weeks. When supplemental vitamin A and local x-irradiation [3000 rad (single dose)] were both given, "complete" tumor regression occurred and, so long as the supplemental vitamin A was continued for a year, there was no gross evidence of tumor recurrence in 22 of 24 mice. At the end of the year, 10 of the vitamin A-supplemented mice remained on the vitamin A supplement, while it was discontinued in the other 12. Within the next year, no gross evidence of tumor appeared in the vitamin A-supplemented rats, while tumor grew in eight of 12 mice in whom the vitamin A supplement was discontinued. These findings indicate that the initial single-dose, whole-body, local x-irradiation and continuing vitamin A during the next 2 years suppressed but did not eliminate the tumor (as judged by tumor recurrence when the supplemental vitamin A was discontinued at the end of the first year).

In other experiments, we have found that supplemental vitamin A (which, as mentioned, has antitumor action itself) will not interfere with the antitumor action of cyclophosphamide, but in fact will enhance it (Rettura G, Levenson SM, Seifter E. Improvement of cyclophosphamide's therapeutic activity by supplemental vitamin A or beta carotene (Abstract #181). Proceedings 13th International Cancer Congress, International Union Against Cancer, Seattle, Washington, September 8–15, 1982; 34.

Based on these experimental data, my colleagues and I think that a prospective study of supplemental vitamin A and radiotherapy and chemotherapy should be carried out in patients with malignant tumors, and we hope to be able to do that at our school and hospitals.

Now, in regard to the use of supplemental vitamin A for other types of patients, it is our practice to give supplemental vitamin A to patients with serious injury and/or infection. The amounts of vitamin A we give vary depending on the severity of the injury and/or the severity of the infection. If the gastrointestinal tract is functioning, for extensively injured or septic patients (adults) we give 50,000 IU vit. A a day for several days. For the less severely injured or infected patients we give 25,000 IU vit. A a day. We do not think there is any concern about vitamin A toxicity at these levels, for the periods of time for which we use it. If the gastrointestinal tract is not functioning, we are limited by available IV vitamin A preparations and we give 10,000 IU per day. We have done this for many years and have never seen any evidence of vitamin A toxicity.

I would like, if I may, Mr. President, to show two slides quickly. I ended up my talk by saying that our observation that supplemental vitamin A ameliorates the wound healing, thymic involution, adrenal enlargement, gastric ulceration, and thrombocytopenia following whole-body radiation, not only when given before radiation but also when given hours, 1, 2, or 4 days after radiation has clinical implications. In related studies, we investigated the effect of supplemental vitamin A on the mortality of burns in mice exposed to acute whole-body radiation 13 days prior to the burn.

(Slide) This slide shows that when a hot water burn, which itself is minimally lethal for unirradiated mice, is produced in mice previously exposed to a level of acute whole-body radiation, which in and of itself is nonlethal or carries a very low mortality ($LD_{5/30}$), the mortality of the burn is increased very substantially and signficantly.

(Slide) This next slide shows that when the irradiated burned animals are given supplemental vitamin A starting at the time of burning, the enhanced mortality induced by the radiation is obviated.