

INDUCTION OF IMMEDIATE CUTANEOUS REACTIVITY TO AN ANTIGEN (ASCARIS) IN CANCEROUS AND NONCANCEROUS INDIVIDUALS

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THE IMPORTANCE of host resistance to the development and spread of cancer^{1, 2, 3} has focused attention on the immunologic responsiveness of cancer patients. Moreover, methods that would seek to utilize active immunization procedures for the treatment or containment of cancer must, of necessity, be based on a knowledge that such patients have a capability of adequately responding to a primary or first antigenic exposure. Evidence for impaired capacity for the development of sensitivity of the classical delayed or tuberculin variety has already been noted in an allied neoplastic condition, Hodgkin's disease.^{4, 5} The present study was undertaken to test the ability of a diverse group of cancer patients to develop the immediate type of hypersensitivity to an almost universal skin sensitizer, ascaris.

METHOD OF STUDY

Twenty-one cancer patients* were given weekly intradermal injections of 0.1 c.c. of an aqueous ascaris extract (1 mg. of protein nitrogen per cubic centimeter), utilizing a method similar to that described by Davidson, Baron and Walzer,⁶ Kailin, Davidson and Walzer,^{7, 8} and Kailin, Rossbach, and Walzer.⁹ The degree of skin sensitivity induced was estimated quantitatively by titrating simultaneously with 0.02 c.c. intradermally of solutions of 0.01 mg., 0.1 mg., and 1 mg. strengths of ascaris protein nitrogen per cubic centimeter. A scratch test with a glycerinated saline extract of dried ascaris powder (1:10 by volume and containing 30 mg. protein nitrogen per cubic centimeter) preceded the intradermal tests and immunization by 20 minutes. If positive, only the 0.01 mg. per cubic centimeter strength of ascaris was then tested. Control sites for both the intradermal and scratch tests were included.

The end point was arbitrarily selected as the development of a positive scratch test as well as a gradation of positive intradermal tests to the 0.01, 0.1,

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*Adenocarcinoma of stomach, colon, breast, cervix, tongue, larynx, metastatic carcinoma of liver, and one with lymphosarcoma of the stomach.

and 1 mg. strengths. Results within each dilution were graded from 1+ to 4+. One plus consisted of an area of erythema and edema at least three times that of the control, with each succeeding plus being two or three times larger than the preceding strength. When the end point was achieved, the titration was repeated on a following week to further confirm the results.

The development of skin reactivity in these cancer patients was compared with that of atopic, nonatopic noncancerous, and noncancerous aspirin-sensitive patients.

RESULTS

Immediate cutaneous hypersensitivity developed rapidly and to a high degree in 2 to 4 weeks of immunization in a group of 10 atopic patients (Fig. 1). None manifested evidence of delayed onset of reactivity following an immunizing or testing injection.

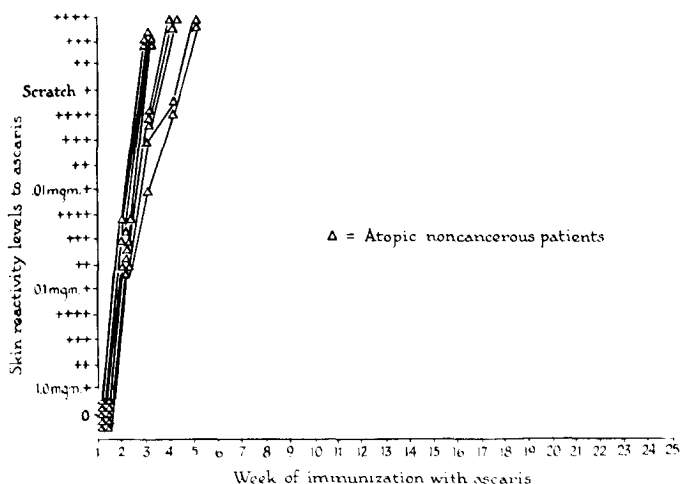


Fig. 1.

A group of 7 noncancerous, nonatopic patients, as well as 3 aspirin-sensitive asthmatic, nonatopic, noncancerous patients, required 4 to 7 weeks to attain a similar level of immediate reactivity (Fig. 2). Seven manifested a stage of delayed onset of reactivity to an immunizing injection in the weeks before the onset of a high level of immediate cutaneous response. This delayed reactivity appeared in some initially as late as 48 to 96 hours after injections, with time of onset decreasing from 3 days to 4 hours in the ensuing weeks. Thereafter immediate skin reactivity appeared on testing. The delayed reactivity consisted of the delayed appearance of a pruritic, erythematous, and edematous area at the site of testing, and was similar to the delayed reactivity to be described in many of the patients of the cancer group. This reactivity was difficult to classify as being definitely either of the classical delayed or immediate variety, and may be of a category not yet classified of an atypical immediate or para-delayed type of reaction.

The response of the 21 cancer patients can be divided into 2 distinct groups. The first consists of 5 patients who demonstrated minimal to moderate pre-existing sensitivity to ascaris as evidenced by at least a 2+ to 4+ immediate reaction to the initial immunizing dose. These patients with presumptive evidence of previous sensitivity rapidly recalled high levels of skin reactivity

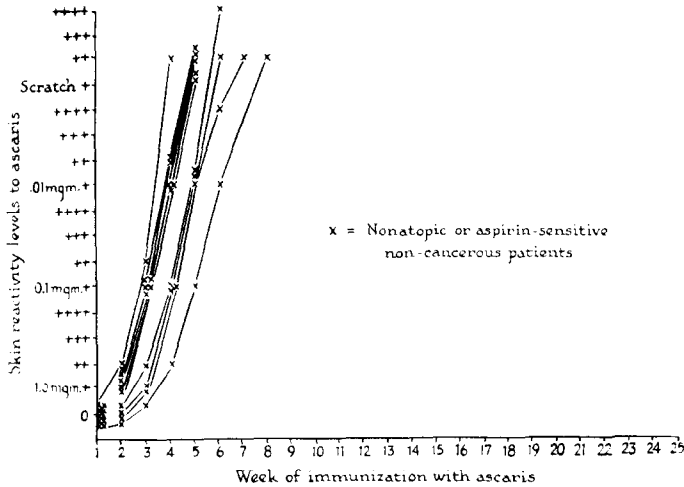


Fig. 2.

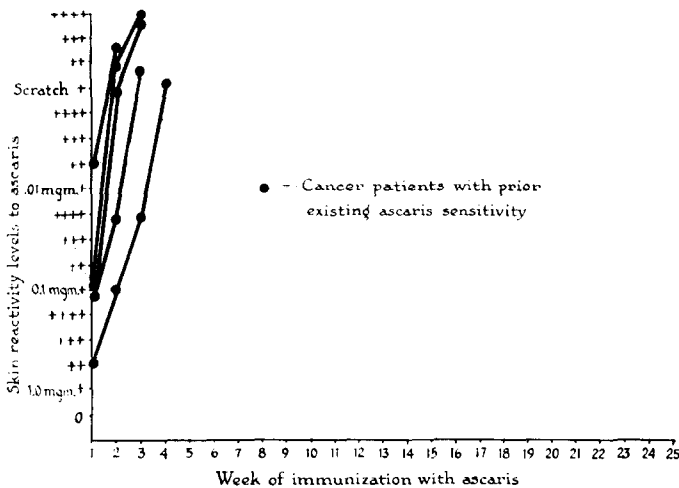


Fig. 3.

within 1 to 2 weeks (Fig. 3). The other group of 16 cancer patients, being immunized on a primary basis, required 8 to 24 weeks to develop similar reactivity (Fig. 4).

Twelve of these cancer patients required stimulation with emulsified antigen in addition to their continuing weekly immunizations and titrations. This was given usually after 8 weeks of aqueous antigen alone had not materially stimulated a response. The emulsion consisted of 1.3 mg. of ascaris protein nitrogen

in 1 c.c. of a 2:1 incomplete adjuvant* and was given deep into the subcutaneous tissues or superficial muscle layers of the deltoid region. Although slow in appearing, the ultimate level of sensitivity achieved in these cancer patients was only somewhat less in degree in most instances than in noncancerous patients.

DISCUSSION

Although the various groups tested were not matched, the atopic patients were sensitized to high levels of immediate reactivity after only 2 to 4 weeks of immunization. Unlike the other groups primarily sensitized, no evidence of delayed onset of reactivity was noted, possibly because of the protective effect of the rapidly achieved high levels of skin sensitizing antibody associated with the immediate cutaneous reactivity. In this regard it is interesting to note that, early in the study, 2 cancer patients who had been given emulsified ascaris antigen deep in the deltoid region, without prior aqueous immunization, developed, 16 days later, a marked firm area of induration and tumescence at the

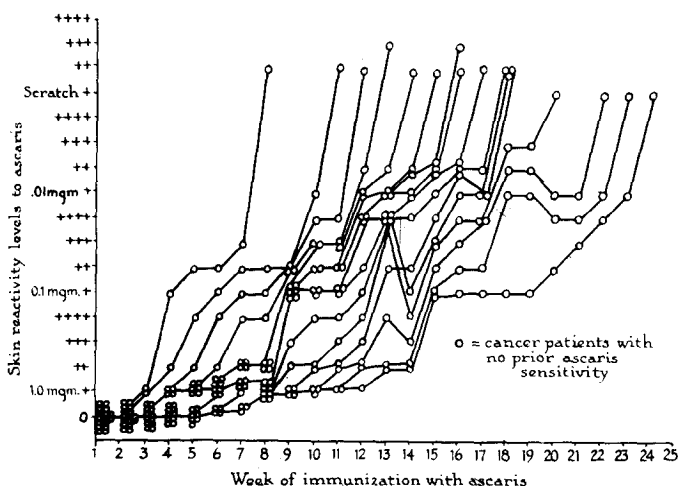


Fig. 4.

site of the injection that was warm to the touch and continued to enlarge in the ensuing weeks. It was associated with a discrete but firm axillary adenopathy on the side of the injection. No fluctuation or suppuration occurred and the process resolved slowly without need for antibiotics or surgical drainage. It maintained its firmness to palpation throughout the 2 or 3 months it required to resolve. No difficulty of this type was noted in any of the patients receiving emulsified antigen who had received, during the preceding weeks, aqueous immunizations.

The delayed reactivity, in terms of time of onset that had been noted in many of the patients in both the nonatopic, noncancer group and the aspirin-sensitive, asthmatic intrinsic group, disappeared after 4 to 7 weeks when these patients had developed high levels of immediate cutaneous reactivity.

*One part aqueous phase. 2 parts oil phase (oil phase consists of Arlacel-A, 1 part; Drakeol, 9 parts).

Marked delay in onset of reactivity, initially beginning as long as 4 to 5 days after an immunization, was noted in most of the cancer patients not initially sensitive to ascaris. However, the time of onset became shorter with each immunization until, with the establishment of high levels of immediate cutaneous reactivity, they disappeared. These cancer patients required 8 to 24 weeks to reach relatively high levels of immediate reactivity. It should be pointed out further that the delayed reactivity noted was not associated with either necrosis, suppuration, or vesiculation but rather with marked pruritic, erythematous, and edematous lesions at the test sites, whose size and intensity of reaction varied directly with the strength of the test solution. These reactions, although difficult to categorize, seemed most probably due to the delayed appearance of the immediate type of hypersensitivity rather than the classical delayed hypersensitivity. However, an alternative exists that this represents a stage of delayed or para-delayed hypersensitivity. Serial testing of sera obtained from the cancer patients during both the phases of delayed and later immediate reactivity failed to reveal precipitins, either by the classical ring test or by gel diffusion studies, although passive transfer of 3 of such sera tried was successful.

The observation that the group of cancer patients who exhibited pre-existing ascaris sensitivity were able to rapidly recall high levels of cutaneous reactivity with 1 or 2 weeks compared to the slow response in those primarily immunized, raises the speculation that response to a primary immunization or new antigen is impaired or slow in cancer patients, whereas secondary recall of sensitivity is not apparently impaired.

SUMMARY

1. Rapid cutaneous reactivity to ascaris can be induced in atopic patients (2 to 4 weeks) and in a somewhat longer time in noneancerous, nonatopic and, also, aspirin-sensitive patients (4 to 7 weeks).
2. The capacity of non-ascaris sensitive cancer patients to develop immediate cutaneous reactivity to ascaris is impaired or slow in appearing, although this can be induced after 8 to 24 weeks of immunization.
3. Cancer patients with presumptive evidence of existing, though weak, ascaris sensitivity rapidly recalled in 1 or 2 weeks high levels of cutaneous reactivity, suggesting that, in this group, recall or secondary immunization is apparently unimpaired.
4. A stage of delayed reactivity, in terms of time of onset after test injection, frequently preceded the onset of immediate cutaneous reactivity in many of the cancer patients being primarily immunized and also in the nonatopic, noneancerous, and aspirin-sensitive group of patients.
5. The observations noted do not permit a decision as to whether they point to a pre-existing immunologic defect in the pre-cancerous patient or an alteration in the immunologic response because of the establishment of the cancerous state.

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