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Research Article

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STUDIES ON DELAYED HYPERSENSITIVITY IN HODGKIN'S DISEASE *

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The susceptibility of patients with Hodgkin's disease to mycotic and viral infections has long directed attention to an immunological defect in that condition (1). The early finding of tuberculin negativity in these patients (2, 3), even in the presence of active tuberculous infection, has been confirmed repeatedly. Subsequent investigations have indicated that this cutaneous anergy extends to many other allergens mediated by the delayed or cellular type of hypersensitivity mechanism (4–11). Recently, the demonstration of tolerance to skin homografts in some patients with Hodgkin's disease (12) has further emphasized the extent of the immunological defect.

The purpose of the present communication is to inquire how intimately, and with what consistency, loss of the delayed type of hypersensitivity is associated with Hodgkin's disease and to pose certain questions regarding the causal relationships. Dinitrochlorobenzene (13, 14), a compound which uniformly induces hypersensitivity in normal individuals, has been used in the present investigation to study cutaneous anergy in 37 patients with Hodgkin's disease. Unlike the earlier methods of study, the use of dinitrochlorobenzene permits the evaluation of the state of the delayed sensitivity mechanism in the individual Hodgkin's patient. Several previous investigators (15–17) have studied small groups of patients with Hodgkin's disease and other lymphomas by this method; the present study is the first extensive study of this disease with a technique of active sensitization and the first in which the results have been correlated with the activity of the disease. In the present experiments, active Hodgkin's disease was always found to be associated with a loss of delayed hypersensitivity, whereas normal cutaneous sensitivity was found in all patients whose disease had been inactive for more than two years.

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MATERIALS AND METHODS

Selection and classification of patients. Only patients with histologically verified Hodgkin's disease were studied. In most instances the histologic material for the present study was reviewed by a member of the Pathology Department of the Massachusetts General Hospital and was classified as Hodgkin's granuloma except for three cases of Hodgkin's paragranuloma (Cases 2, 3, and 15). Patients with no evidence of active disease and with all stages of active disease were investigated. The 37 patients of Table I represent the entire Hodgkin's disease patient population seen by the author over a one-year period. Patients in the series received conventional treatment, radiation for localized disease and alklyating agents for generalized or systemic manifestations, or both. Treatment was not delayed for skin testing. No patients were studied while on prednisone, and of the 13 who had prior alkylating agents (Cases 4, 5, 13, 20, 21, 23, 28, 29, 31, 33, 34, 35, and 37), in only four (Cases 21, 29, 34, and 35) did the alkylating agent precede sensitization by less than 4 weeks. Six patients (Cases 7, 20, 21, 23, 28, and 33) were studied while receiving local radiation therapy, but three of these were retested with consistent results after completion of treatment. Otherwise, at least 3 weeks were allowed to elapse from the time of completion of local radiation to the onset of skin testing.

For the purposes of the present investigation patients with Hodgkin's disease were classified as either inactive or active with respect to their clinical state at the time of skin testing. A patient was considered inactive if there was no evidence of Hodgkin's disease at the time of testing or during the prior month (as determined on at least two clinic visits). The following criteria were used in establishing inactive disease: no peripheral adenopathy, splenomegaly or retroperitoneal adenopathy by physical examination, no mediastinal adenopathy or parenchymal changes on chest X-ray examination, no weight loss or fever, no anemia (hemoglobin of 12.0 g or above), no leukocytosis (leukocyte count of 9,000 per mm^3 or less), and no pruritis, sweats or chills, or other signs or symptoms which could be ascribed to Hodgkin's disease involvement of other organ systems. Exceptions to these criteria were two patients classified as inactive who each had a single one-centimeter cervical node which had been

TABLE I

Dinitrochlorobenzene testing in Hodgkin's disease *

Case	Sex	Age	Onset	Clinical state when tested			Results of DNCB testing	
				Active	General condition	Inactive†	Date	Result (No. of tests)
1.	FR ♂	57	1952	sp, 1	E		3/61	0 (2)
2.	CH‡ ♀	36	1936		E	c (1936)	3/61	+
3.	KD‡ ♀	39	1932		E	c (1932)	4/61	+
4.	RL ♂	23	1958	c, a, m, r, i; f, an, p, w, b, pul; died (10/61)	P		4/61–6/61	0 (3)
5.	IP ♀	35	1956	c, m, r; f, an, p, w, pul; died 7/61	P		4/61–6/61	0 (3)
6.	CB ♀	65	1950		E	c (1950)	4/61	+
7.	WD ♂	28	1961	c, m	E		5/61	0
					E	c, m; f (7/61)	11/61	0
					E		1/62	0
					E	i (1/62)	4/62	0
				b	E		5/62	0
8.	PM ♂	46	1961	c	E		5/61	0
					E	c (7/61)	8/61; 1/62	0 (2)
					E	c (7/61)	2/62	+
				c	E		5/62	0
9.	MC ♀	43	1951		E	m, c (5/55)	5/61	+
10.	AD ♂	73	1957	c	E		5/61	0
					E	c (5/61)	6/61	±
					E	c (5/61)	9/61	+
11.	FB ♀	60	1952		E	r (1952)	5/61	+
12.	JC ♂	80	1944		E	c (1954)	6/61	+
13.	MG§ ♀	34	1956	c, a, m, r, i; an, w	F		6/61–10/61	0 (3
14.	EG§ ♀	50	1958	c a, m, r; f, an, w; died (6/61)	P		6/61	0
15.	RM‡ ♀	70	1955		E	c (1955)	7/61	+
16.	RB ♀	23	1961	c, m	E		7/61	0
17.	MP ♂	50	1947		E	c, a, m, i; sp, an (1952)	7/61	+
18.	JP ♂	30	1961	r; an, w	G		8/61	0
19.	ML ♀	35	1955		E	c, m; pul (1959)	8/61	+
20.	EW ♀	25	1959	m; pul, an, w	F		9/61; 10/61	0 (2)
21.	ML ♀	68	1961	a; b, f, w; died (9/61)	P		9/61	0
22.	SP ♀	40	1958	r	E		9/61; 12/61	0 (2)
23.	EM ♀	32	1958	c, a, m; l	G		9/61; 12/61	0 (2)
24.	GW ♀	57	1937		E	c, m (5/60)	10/61	+
25.	SA ♀	35	1956		E	c (1956)	11/61	+ (2)
26.	RS ♂	23	1958	c, m, r; f an, l, w	G		12/61–1/62	0 (3)
27.	MD ♀	30	1958	c, a, m	G		12/61	0
28.	SM ♂	39	1947	c; b	F		12/61	0
29.	JP ♂	55	1961	c, a, m, i; f, b, l, w	F		12/61	0
30.	VV ♂	62	1961	c, a, m, i; l, w	F		12/61	0
31.	CD ♀	29	1961	c, a, m, i; l, w	F		1/62	0
32.	SR ♀	40	1960		E	c, m (5/60)	1/62	0
33.	CS ♀	24	1960	c, m; f, pul, an, w	F		1/62	0
34.	AL ♀	14	1958	c, m, f; pul, an, w	G		2/62	0
35.	MJ ♂	56	1958	c, a; f, an, l, w	G		2/62	0
36.	RS ♂	41	1959	c, a	E		3/62	0
37.	BK ♀	30	1957	c, a, m, r, f, an; w, sp	P		3/62	0

* Abbreviations: c = cervical; a = axillary; m = mediastinal; r = retroperitoneal; i = inguinal; sp = spleen; f = fever; an = anemia; l = leukocytosis; p = pruritis; w = weight loss; pul = pulmonary disease; b = osseous disease; E = excellent; G = food; F = fair; P = poor.
† Under this heading is given the manifestation of the disease and the date when it was active in patients with inactive disease when tested.
‡ Hodgkin's paragranuloma.
§ Negative to 1 mg of old tuberculin in the presence of active tuberculosis.

present and unchanged for 3 and 5 years, respectively. Patients classified as active had at least one of the manifestations listed in Table I at the time of testing, and all the items listed for the particular patient had been present in the prior month. Except for a single individual with splenomegaly, each of the active patients had significant adenopathy (2- to 3-cm nodes) at the time of testing. In the few instances where the clinical findings as to the state of activity of a patient's disease were ambiguous, testing was deferred until the clinical picture was clarified. We recognize the fact that the available clinical methods may not detect minor degrees of disease

and, therefore, that certain patients classified as inactive because of the absence of overt disease may have in reality active disease. It seems highly unlikely that any patient classified as active had inactive disease.

Dinitrochlorobenzene (DNCB) sensitization. The method used for sensitization was very similar to that described by Epstein and Kligman (13, 14). A ring of acetone 2.2 cm in diameter was applied to the volar surface of the forearm with a ring-shaped applicator. One-tenth ml of a 10 per cent acetone solution of recrystallized DNCB (2,4-dinitro-1-chlorobenzene obtained from Matheson, Coleman, and Bell) was then applied to the enclosed circular area of skin, and the solvent was evaporated with a stream of air. A Band-aid was applied, and the patch left in place for 10 days to 2 weeks.

The area of original application undergoes intense erythema and desquamates after several weeks, leaving a variable degree of pigmentation. In some instances there is bulla formation at the height of the reaction which usually is not symptomatic. Some individuals who become sensitized display a well-defined flare of the area of application at the end of 7 to 10 days which has all the characteristics of the delayed response described below.

The presence of sensitization to DNCB is evaluated after 3 weeks by the application of a 0.1 per cent acetone solution of DNCB to the volar surface of the opposite forearm in a manner completely identical to the primary application. The test is read at 2 days and, if necessary, again at 4 and 7 days. The eliciting concentration of DNCB (0.1 per cent) may give some erythema in the unsensitized individual due to its mild irritative action. In preliminary studies this erythema was evaluated in 10 unsensitized normal subjects. In the unsensitized, the redness is never more than moderately intense and does not occupy the entire area of application, rarely being more than an incomplete rim. Furthermore, the erythema of the unsensitized individual is well developed by 24 hours, no more intense at 2 days, has faded markedly by 4 days, and has disappeared by the end of a week. The reaction of the unsensitized individual never shows significant induration. The positive test in the sensitized individual is quite different. At 2 days there is usually marked erythema, which often has a salmon hue and usually occupies the entire area of DNCB application. An essential feature of the sensitive reaction is the marked induration of the skin in the area of reaction. The reaction usually itches intensely and may show vesicle formation. The response is usually more intense at 4 days than at 2 and is still very evident at a week. In short, the reaction has all the characteristics of a delayed or tuberculin type response. The differentiation between positive (+ in Table I) and negative (0 in Table I) responses is quite clear if the above criteria are used. Induration is always seen in the sensitive reaction and never in the insensitive (the same criterion that is used in tuberculin testing). Severe itching, usually present, and vesiculation, which is less common, both indicate sensitization, as does the occurrence of a flare 7 to 10 days after the primary application. Finally, the erythema of the insensitive reaction is gone by the end of a week, whereas that of the sensitive reaction is still quite intense at this time. Only two atypical tests were observed. One was an intermediate reaction in Case 10, whose previous test was negative and whose subsequent test was positive. This presumably represented a transition from an anergic state to one of normal skin sensitivity. A second patient, Case 25, had had active Hodgkin's disease 5 years before and showed a typical positive reaction, but one which was delayed, beginning a week after application of the eliciting DNCB.

We have retested only 10 normal controls, all of whom gave positive reactions. Because of the extent of the reaction to the primary DNCB application and the discomfort and persistence of the positive response to the eliciting application of the compound, we have felt that evaluation of a large group of controls was not justified. With the same method, Epstein and Kligman (13, 14) report that retesting elicits positive reactions in over 90 per cent of a large series of normal controls.

For retesting, only the eliciting concentration (0.1 per cent) is applied. This concentration will also sensitize over 60 per cent of normal individuals (13, 14).

RESULTS

The results of 60 tests of cutaneous sensitivity in 37 patients with Hodgkin's disease are presented in Table I. This table also contains selected clinical material in abbreviated form, particularly that regarding the state of activity of the disease at the time of DNCB testing. When the disease was active at the time of testing, the nature of the activity is noted, and when inactive, the time and nature of the last activity are indicated. In Table II the skin test results in the active and inactive patients are summarized.

Twenty-five patients had active disease when studied. All showed cutaneous anergy as judged by an inability to induce DNCB sensitization. The active group included a number of patients with

TABLE II

Summary of dinitrochlorobenzene testing

	Inactive*	Active
Number of patients†	15	25
Number of tests	20	40
Positive	14	0
Equivocal	1	0
Negative (anergic)	5	40

* Inactive disease denotes the absence of any manifestations of disease in the month prior to testing.

† Because the disease status of three patients changed during testing, there have been 40 patient entries in the table for the 37 patients.

advanced disease, including four who died within 6 months of testing. However, 14 of 25 anergic patients were in good to excellent general health and were able to lead normal lives. Eight patients in particular (Cases 7, 8, 10, 16, 22, 23, 27, and 36) had early and localized disease despite their anergic state.

Twelve patients were studied only when their disease was inactive and had been so for 1 to 29 years. All had normal skin sensitivity except one (Case 32), whose disease was inactive for 18 months. Three patients were studied when their disease was active (anergic) and again at subsequent periods of quiescence and activity (Cases 7, 8, and 10). One of these (Case 10) showed an equivocal reaction one month after his disease became inactive and had recovered his skin sensitivity when tested 4 months after control of his disease. Case 8 remained anergic for 8 months after treatment of his disease by radiation, developed a positive skin test at 9 months, but again became anergic 3 months later when his cervical adenopathy recurred. Case 7 had two remissions in disease activity lasting 3 and 4 months respectively, each terminated by return of active disease. The patient remained anergic throughout the period of observation.

DISCUSSION

Over the past three decades there have been many studies of the delayed type of hypersensitivity in patients with Hodgkin's disease. For the most part these studies have consisted of skin-testing patients with tuberculin and other allergens causing delayed reactions (extracts of trichophytin, histoplasmin, candida albicans, mumps, streptokinase-streptodornase, and diphtheria toxoid) and comparing the Hodgkin's group with a normal control group. Results of these studies have consistently revealed a much lower incidence of positive skin reactions in the Hodgkin's patients than in the normal controls (2–11). Studies of this type suffer from two serious limitations. The first is that rarely do more than 50 per cent of the normal controls react to a particular antigen, and frequently the percentage is much smaller. Thus, the results of such studies permit a conclusion to be drawn about individuals with Hodgkin's disease as a group, but allow no conclusion about the individual patient. A particular patient may not react either because he is anergic or because he has never been exposed to the antigen. The second shortcoming of this type of study is the failure to note the clinical state of the patient when tested. The course of Hodgkin's disease is extremely varied. The failure to distinguish a patient whose initial enlarged cervical lymph node has been followed by 30 years of complete health from a patient with florid generalized disease only obscures significant findings. Clearly, normal immune responses in the two patients have different implications about the importance of immune mechanisms in the disease process.

Several recent studies have been done which obviate, in part, the first of the above objections. Kelly, Good, Varco, and Levitt (7, 8) have reported their inability to induce hypersensitivity to diphtheria toxoid in nine patients with Hodgkin's disease. However, only nine of 13 normal controls became sensitized with the technique they employed. Kelly, Lamb, Varco, and Good (12) have also reported a delayed homograft rejection in 10 of 17 Hodgkin's patients, whereas the graft in three additional patients behaved like autografts. We feel that the complexity of the homograft reaction (18, 19) makes it a relatively unsatisfactory technique to use in the evaluation of the anergic state of the Hodgkin's patient. BCG vaccination (9) has been reported to induce tuberculin positivity in 10 of 12 tuberculin negative Hodgkin's patients without systemic manifestations, but in none of three patients with systemic manifestations.

The induction of skin sensitivity with a delayed contact allergen such as dinitrochlorobenzene would appear to be a very satisfactory way of studying the anergic state of the Hodgkin's patient. Epstein and Kligman (13, 14) report that a single application of dinitrochlorobenzene sensitizes over 90 per cent of a large series of normal controls. Our 10 normal controls were uniformly sensitized, and we therefore feel that this is indeed a valuable technique for studying delayed sensitivity. Furthermore, repeated testing with this technique is possible; the eliciting application itself serves to sensitize over 60 per cent of normal individuals. With this technique several previous groups of investigators, in prelimi-

nary reports, have studied small groups of patients with Hodgkin's disease and leukemia (15–17). In these studies, the number of patients with Hodgkin's disease has been small (4 to 5 cases), the results in Hodgkin's patients have not been separated from other lymphomas, and no clinical information has been given. No comprehensive investigations employing DNCB in Hodgkin's patients have been reported.

Using the technique of dinitrochlorobenzene sensitization, we have been impressed with the regularity of cutaneous anergy in patients with active Hodgkin's disease. In the present series all 25 patients with active disease were anergic. Nine patients whose disease was inactive for periods of more than 2 years displayed normal skin reactions, whereas in six whose disease was inactive for periods of less than 2 years, the reactions were either normal or anergic. Our data are not sufficient to permit us to be certain either that all our inactive patients were anergic when their disease was active, or that all patients with active Hodgkin's disease are anergic. In particular, our data are inadequate with regard to two variants of Hodgkin's disease, the paragranuloma type (no active and three inactive cases in our series) and disease localized to a single lymph node group (two active and seven inactive cases). We have observed, however, the transition from depressed to normal skin sensitivity, coincident with response of local disease to radiation, in two individuals and the opposite transition with activation of disease in one patient, indicating that these transitions do occur. [Sokal and Primikirios (9) have observed the recovery of tuberculin sensitivity with remission of Hodgkin's disease in two patients.] From our data, we can infer that it takes from several months to several years for the recovery of skin sensitivity after the disappearance of clinical activity. It appears likely that a number of our inactive patients with normal skin sensitivity were anergic when their disease was active. That this was true of the entire group is an attractive but unproven hypothesis.

It is well known that severely debilitating diseases (9) and the acute febrile stage of several infectious viral diseases (20) may be associated with a depression of delayed-type hypersensitivity. These mechanisms probably contribute to the anergy of nine of our Hodgkin's patients in fair to poor condition and may contribute to the anergy of several others with minor fever or weight loss. They probably do not account for the anergy of 10 patients in good to excellent condition with neither fever nor weight loss. It is also unlikely, on the basis of available data (21, 22), that local radiation or alkylating agent therapy given more than a month prior to sensitization could interfere with skin sensitivity. Therefore, it appears likely that the Hodgkin's disease process itself is associated with cutaneous anergy. It should be noted that sarcoidosis may also be accompanied by a loss of delayed sensitivity (10).

The reason for the association of cutaneous anergy with active Hodgkin's disease is not clear. The work of others (12, 23) and our own studies in the present group of patients, which will be reported later, indicate that the immediate immune response (antibody production) is relatively intact in Hodgkin's disease. In eight patients in the present series, the extent of disease was quite limited judged by clinical criteria, making it unlikely that the anergic state results from a generalized obliteration of the lymphoid system by the disease process. Although it is possible that the cutaneous anergy of Hodgkin's disease is due to a defect in the reactivity of the skin, the known susceptibility of these patients to viral and mycotic infections suggests that the anergic state is systemic rather than cutaneous. Because of the possible viral etiology of Hodgkin's disease, we have not tried the leukocyte transfer of DNCB sensitivity from anergic Hodgkin's patients, after their attempted DNCB sensitization, to normal controls. [The transfer of delayed sensitivity with leukocytes from sensitized normals to several anergic Hodgkin's patients has been attempted by Warwick, Archer, Kelly, and Page (17) with negative results.]

In our opinion, it seems most plausible to assume that the Hodgkin's disease process, even when clinically localized, can cause a suppression of delayed hypersensitivity. The recovery of skin sensitivity we and others (9) have observed after local radiation favors this sequence. Where in the complex and poorly understood process of delayed sensitivity this block takes place, and whether the block is mediated by a humoral agent

or cells, is speculative. Another possibility is that the immunologic defect results from disease involvement of some unknown site necessary for immune responsiveness. In this connection the accumulating evidence for an immunologic role of the thymus (24, 25) and the proposed (26) but disputed (27) thymic origin of Hodgkin's disease should be mentioned. Finally, the possibility should be considered that the immunologic defect is primary (perhaps a biochemical defect of a particular cell type), and glandular enlargement of the specific cellular pattern that characterizes Hodgkin's disease is a secondary reactive event (1).

Many serious students of the disease have not been convinced of the neoplastic nature of Hodgkin's granuloma (28). A viral etiology has been repeatedly proposed but never established (29), and an immunologic mechanism involving a graft-versus-host reaction has been recently suggested (30, 31). Although the significance of the cutaneous anergy of Hodgkin's disease remains to be established, it should be explained by a satisfactory disease mechanism.

SUMMARY

Delayed hypersensitivity has been studied in 37 patients with Hodgkin's disease by means of active sensitization with dinitrochlorobenzene. In the presence of active Hodgkin's disease, even when clinically localized, cutaneous anergy was consistently found, and in two patients anergy fluctuated with the activity of the disease. Patients whose Hodgkin's disease was inactive for two years or longer had normal skin reactivity, whereas those whose disease was inactive for less than two years showed either anergy or a normal reaction. A close association of active Hodgkin's granuloma and an immunologic defect characterized by cutaneous anergy is clear from these studies. The significance of this association remains to be established.

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