IMMUNOLOGIC ASPECTS OF HODGKIN'S DISEASE*

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1. Introduction

This presentation is concerned with the immunological deficiency of Hodgkin's disease, a deficiency which contributes to the infectious complications seen so frequently in this disorder. The defect also raises important questions about the pathogenesis of Hodgkin's disease.

A high incidence of tuberculosis in patients with Hodgkin's disease led Ewing (19) to comment that "...tuberculosis follows Hodgkin's disease like a shadow." Jackson and Parker (34) reported coexistent tuberculosis in 20 per cent of their cases and more recently, it has been noted that Hodgkin's patients have a proclivity to a variety of fungal infections as well, particularly cryptococcosis. Although this predisposition to certain infectious complications, of itself, raised the question of an immunological deficiency in Hodgkin's disease (18), it was through tuberculin testing of Hodgkin's patients that the immune defect was demonstrated.

In the 1930's several investigators (Steiner (68) and Parker **et al.** (53)) noted that the percentage of positive tuberculin reactions obtained in Hodgkin's disease patient was much lower than that found in a comparable control population. Most remarkable, however, was the observation that in Hodgkin's disease the tuberculin reaction frequently remained positive in the face of overt tuberculosis. Finally, in the 1950's, with the increased understanding of cellular immunity then available, Schier and his colleagues (61, 62) were able to show that the depressed reactivity of the Hodgkin's patient to tuberculin was but one manifestation of impaired delayed hypersensitivity.

2. Depressed Delayed Hypersensitivity — Loss of Preexisting Allergy

Immunological reactivity can be divided into the immediate type mediated by antibody and the delayed type mediated by cells. Delayed hypersensitivity is best studied by skin testing, and the slow evolution of the skin reaction over 48 hours and longer after application of the allergen differentiates this type of immunity from the immediate Arthus skin reaction. Tuberculin hypersensitivity and contact allergy are two classical examples of delayed hypersensitivity. Depression of this form of immunolo-

* The author's work is supported by Research Grant No. CA-07179 of the National Cancer Institute, United States Public Health Service.

gical response is called "anergy" and is the predominant immune deficiency of early, active Hodgkin's disease.

Schier **et al.** (61, 62) tested a group of Hodgkin's patients and normal controls with four delayed-type allergens (mumps skin test antigen, **Candida albicans, Trichophyton gypseum** and purified tuberculoprotein) and found that 68 to 92 per cent of the controls reacted to the various antigens but only 14 to 23 per cent of the Hodgkin's group responded (Table I). This unreactivity to delayed allergens has been amply confirmed (38, 68).

It is important to point out that the anergy of Hodgkin's disease differs significantly from the anergy which may accompany advanced cancer and other debilitating illnesses. This is illustrated in Table II from the work of Lamb **et al.** (38) in which anergy is defined as unreactivity to all six of the following allergens: mumps skin test antigen, diptheria toxoid, **Candida albicans, Trichophyton gypseum,** streptokinase-streptodornase, and purified tuberculoprotein. This table clearly indicates that while cancer, leukemia and non-Hodgkin's lymphoma patients are frequently anergic when in poor clinical condition, only Hodgkin's patients are anergic when their clinical status is **good.**

3. Depressed Delayed Hypersensitivity — Active Sensitization

Determination of anergy by testing for previously acquired sensitivity has the disadvantage that the anergic patient cannot be distinguished from the individual never exposed to the allergen. This difficulty can be overcome by assessing the ability of the individual to acquire sensitivity to a material of such unusual character that absence of exposure can be assumed, or to a material to which preexisting sensitivity can be ruled out by skin test. It should be pointed out that the ability to acquire sensitivity is probably a more demanding criterion of normal cellular immune function than the ability to maintain preexisting hypersensitivity.

The technique which has been used most extensively to assess delayed hypersensitivity in Hodgkin's disease is sensitization to the contact allergen dinitrochlorobenzene (37). Two to four weeks after the application of a concentrated (usually 10 per cent) acetone solution of dinitrochlorobenzene, the subject is tested by the application of a dilute solution (0.1 per cent), a concentration to which an unsensitized individual will not respond. The initial application sensitizes at least 95 per cent of young, healthy controls (31, 37), but none of a group of 25 individuals with active Hodgkin's disease (1) could be sensitized (Table III). However, some Hodgkin's patients with inactive disease, including all those whose disease was inactive for periods greater than two years, could acquire dinitrochlorobenzene sensitivity. In this study two patients were of particular interest; anergic with active disease when first studied, these individuals recovered normal skin reactivity after a prolonged irradiation-induced remission. It should be emphasized that a number of the anergic Hodgkin's individuals in this study had early disease which by clinical criteria was quite localized. A second group of workers has confirmed the inability of the Hodgkin's patient to develop contact sensitivity, but the less uniform sensitization of normal controls observed may have been the result of differences in the technique of sensitization (41). Depression of the delayed hypersensitivity response to dinitrochlorobenzene has also been observed in patients with chronic lymphatic leukemia (16), malignant epithelial neoplasms and chronic non-neoplastic disease (31).

Kelly **et al.** have attempted to induce delayed hypersensitivity in Hodgkin's patients with diptheria toxoid (36). Whereas 9 of 14 controls were sensitized by the procedure they employed, the 9 Hodgkin's patients could not be sensitized. Sokal and Primikirios, however, were able to convert 10 of 12 patients whose Hodgkin's disease was free of systemic manifestations to tuberculin positive status with BCG, but could not convert 3 individuals with such manifestations (66). It is possible that the discrepant results with contact sensitization and with BCG reflect differing strengths of the antigenic stimulus, or that BCG may be actually functioning as a secondary antigenic stimulus in some Hodgkin's patients. It should be noted that two patients were

observed to recover tuberculin sensitivity following the remission of their disease, while two additional patients became tuberculin negative when the conditions exacerbated (66). Recovery of tuberculin sensitivity associated with the remission of Hodgkin's disease has been commented upon in the past (14, 18).

4. Antibody Formation

The adequacy of antibody formation in Hodgkin's disease has been the subject of some debate. While certain investigators have reported depressed antibody response to pneumococcal polysaccharide (21, 39), brucella (18) and primary immunization with tetanus toxoid (9), essentially normal antibody response to typhoid-paratyphoid (33, 36), mumps (62), tularemia (60) and secondary tetanus immunization (9) have been observed by others. Normal levels of isohemagglutinins (20) and complement-fixing antibodies to a variety of common viruses (51) have also been noted. Despite these discordant findings there can be little doubt that the anergic Hodgkin's patient is able to form normal amounts of antibody in response to some antigenic stimuli. Thus, it was recently observed that normal amounts of antibody to both Types II and VII VII pneumococcal polysaccharide were produced in 13 of 19 individuals with this disorder (6). Four of the six who failed to produce normal amounts of the two antibodies were in very poor general condition and died within 6 months of completion of the immunological studies.

Thus antibody formation appears to be largely intact except in the final months of Hodgkin's disease, though there are suggestions that a subtle deficiency in this function may exist. For example, antibody synthesis may not be sustained in the normal manner in Hodgkin's disease (4, 33), and there may be depression of the primary as opposed to the secondary antibody response (9). These matters require further investigation, particularly with respect to the transition from macroglobulin to 7S-antibody synthesis.

Immunoglobulin levels (IgG, IgM, and IgA) are within normal limits in Hodgkin's disease (8, 46), a finding consistent with the preservation of antibody function. However, it is generally conceded that gamma globulin levels may decline in the terminal stage (70).

5. Homograft Reaction

The homograft reaction is probably a more complex immunological function than either delayed hypersensitivity or antibody formation (12). At present, it is believed that homografts are rejected in most instances by a cellular mechanism similar to the one involved in delayed hypersensitivity but that exceptionally, rejection may be mediated by antibody. In Hodgkin's patients, 17 (59 per cent) of 29 experimental skin grafts persisted for 30 days or longer)30, 36, 48). However, such abnormal survivals were also observed in 10 of 23 individuals with chronic lymphatic leukemia and multiple myeloma, two diseases in which humoral rather than cellular immunity is depressed (26, 47, 71). The protracted graft survivals in these latter diseases make it difficult to use homograft survival in Hodgkin's patients to incriminate a cellular immune defect. A single Hodgkin's individual has been reported in whom there was protracted survival of a bone marrow graft resulting in a chimeric state (10).

6. The Lymphocyte in Hodgkin's Disease

During the past two decades experimental evidence coming from a variety of sources has made it clear that lymphoid cells are important mediators of immunological reactivity, particularly cellular immunity (28, 42). Thus the depression of cell-mediated, delayed hypersensitivity in Hodgkin's disease calls attention to the lymphocyte in this disorder.

The medical literature prior to the Second World War is replete with observations of lymphocytopenia in Hodgkin's disease. Wiseman (74), for example, reported that 27 of 31 individuals with this disorder had depressed lymphocyte counts, and Rosenthal in 1936 (58) stressed the importance of tissue lymphocyte depletion in prognosis. When this problem was reinvestigated recently, it was readily confirmed that profound lymphocytopenia was a regular feature of advanced Hodgkin's disease (4). At the onset of the disease, however, at a time when the patient may be anergic,

blood lymphocyte counts were only slightly depressed or in the low normal range. It is thus hard to account for the anergy of early Hodgkin's disease in terms of lymphocytopenia.

Since lymphocytes may not be lacking in number in early Hodgkin's disease, is is reasonable to inquire into their function. Unfortunately, at the present time techniques for the study of human lymphocytes are just being developed, and the following conclusions must be considered tentative. Two such techniques have been employed, the measurement of lymphocyte reactivity **in vitro** and the lymphocyte transfer reaction.

Several reports suggest impaired response of cultured Hodgkin's lymphocytes. In an early study (5), 6 of 10 Hodgkin's lymphocyte samples displayed impaired response to the mitogen phytohemagglutinin and to mixed-cell culture, two conditions which regularly stimulate normal lymphocytes. In a later report, Hersh and Oppenheim (32) observed that 87 per cent of the 23 Hodgkin's patients studied showed diminution in their lymphocyte response to **in vitro** stimulation with phytohemagglutinin and vaccinia. The phytohemagglutinin-stimulated Hodgkin's cultures contained a median of 11 per cent transformed cells as compared to 70 per cent in stimulated cultures of normal controls, and vaccinia-stimulated Hodgkin's cultures showed 0 per cent transformation as compared to 8 per cent in controls. It also has been observed that the phytohemagglutinin-induced cytotoxicity of Hodgkin's lymphocytes against cultured human liver target cells is impaired (33a).

A second approach to the Hodgkin's lymphocyte is the study of the skin reaction which follows transfer of purified lymphocytes from patients with this disorder to the skin of another individual. The reaction is a complex one into which histocompatibility difference of graft and host, immunological competence and non-immunological factors may enter (29). Transferred Hodgkin's lymphocytes displayed several abnormalities which can be appreciated in Table IV; that thought to correlate best with the anergy of the lymphocyte donor was the absence of reaction of Hodgkin's lymphocytes 7 days after their transfer, a time when most normal lymphocytes still displayed a reaction. A second abnormality was seen in the Hodgkin's patients in poor condition who served as lymphocyte recipients and who were unable to support the initial reaction (48 hours) of cells transferred from normal controls. Finally, an abnormally protracted reaction (beyond 14 days) or normal lymphocytes seen in some debilitated Hodgkin's recipients was attributed to delayed rejection of the lymphocyte graft. The lymphocyte transfer reaction is of sufficient complexity that these interpretations will remain in doubt for some time to come, but the data is consistent with a functional defect of the Hodgkin's lymphocyte.

7. The Eosinophil

While the eosinophil is believed to participate in allergic reactions, particularly those mediated by reaginic antibody, the precise function of the cell remains unclear (59). It appears either to be linked to the antigen-antibody interaction, perhaps via a soluble intermediate, or to be involved in the processing of antigen or the synthesis of antibody. The presence of the eosinophil in the lesion of Hodgkin's granuloma has been repeatedly commented upon (34, 74), and eosinophilia is seen in a fraction of cases (32 per cent of Wiseman's series (74)). In view of the present uncertainty about eosinophil function, it is difficult to speculate profitably about the significance of this cell in Hodgkin's disease.

8. Infectious Complications

Tuberculosis was the first infectious complication noted in Hodgkin's patients, but with the control of the infection in the general population this complication is seen much less frequently. In its place a striking association of Hodgkin's disease with cryptococcosis and other uncommon fungus diseases has emerged. Thus 8 per cent (22), 18 per cent (15) and 5 per cent (75) of reported cases of cryptococcosis occur in Hodgkin's patients, and a similar disproportionate incidence of infection with **Nocardia, Candida, Histoplasma, Aspergillus and Actinomycetes** is seen in this condition (13). The high incidence of herpes zoster in Hodg-

kin's disease is well known (57, 73), but only recently cytomegalovirus infection has been recognized (13). It has also become clear that the incidence of **Toxoplasma** and **Pneumocystis** infection is unusually high in Hodgkin's disease (13). The observation has been made that the course of cryptococcal infection is particularly virulent in the lymphoma patient (13).

While fungi, and certain viruses and protozoa are the **characteristic** microbial agents in the Hodgkin's patient, bacterial infections remain the most **common** infectious complications of the disorder. The spectrum of such complications in a carefully studied group of 51 Hodgkin's patients was presented is presented in Table V (13). Of 86 episodes **cles to the Control of Hodgkin's Disease,** and cent Rye, New York **Conference on Obsta**by Casazza, Duvall and Carbone at the reof infection, 56 were of bacterial etiology either alone or in combination with other agents. The bacterial invaders are those which are prominent in hospital medicine: **Staphylococcus aureus, Pseudomonas,** and **E. coli.**

It hardly requires reiteration that resistance to infection is a complex phenomenon dependent on the integrity of the skin and mucous membranes, phagocytosis by granulocytes and the reticuloendothelial system, non-specific humoral factors including interferon (virus infection), and finally the specific cellular and humoral immunologic mechanisms. Since the importance of each component is different for each microbial agent, it is unlikely that a single explanation will account for the varied infectious complications of Hodgkin's disease. Howver, it does contributes significantly to the susceptibility of these individuals to fungal and other infections, particularly when it is noted that delayed hypersensitivity has always been considered critical in resistance to tuberculosis and fungal infections. It appears that a high degree of anergy is needed, since clinical infection is ordinarily seen only late in Hodgkin's disease (13, 65). Presumably, the susceptibility to bacterial infection reflects depression of both cellular and humoral immunity in the far advanced Hodgkin's patient, as well as loss of continuity of the skin or mucous membranes due to local factors. The part played by corticosteroids and chemotherapeutic agents (known to be immunosuppressive) in all these infections is difficult to assess.

9. Comparison of the Immune Defects of Hodgkin's Disease and Lymphatic Leukemia and Myeloma

In considering the immunological deficiency of Hodgkin's disease it is important to separate this disease from other lymphoid disorders, particularly chronic lymphatic leukemia and multiple myeloma. The deficiency of these other lymphoid disorders differs from that under consideration in this chapter. Indeed, the defect of lymphatic leukemia and myeloma is quite similar to that of the more common, congenital, sex-linked form of agammaglobulinemia (24, 26), being characterized by hypogammaglobulinemia, poor antibody formation in the face of relatively intact delayed hypersensitivity (dinitrofluorobenzene sensitization is impaired in chronic lymphatic leukemia (16), and frequent bacterial but **not** fungal infections (47, 71). Furthermore, infections tend to punctuate the entire clinical course of these hypogammaglobulinemic states, but in Hodgkin's disease occur predominantly in the far-advanced and terminal patient (13). In addition, the pneumococcus which is such a common offender in lymphatic leukemia and myeloma only rarely attacks the Hodgkin's patient (13).

10. Progression of the Immunologic Defect in Hodgkin's Disease

It should be pointed out that Hodgkin's disease is a clinical condition with varying involvement of the reticuloendothelial system rather than an immunological entity. Presumably, the immunological defect alters and progresses with the advancing disease process. Thus, Table VI attempts to define the immunological deficiency in relation to the disease involvement. In this table, Hodgkin's disease has been divided arbitrarily into 4 divisions: 1) healed localized disease, 2) active localized disease (Stage I and II of Peters and Middlemess (56) and 3) generalized disease, progressing to 4) the terminal condition.

The immunological deficiency of early, active (localized) disease is characterized by

Hodgkin's disease lead to a similar end stage of lymphoid and immunological exhaustion, but of different causation. (In this connection the parallel between the Swiss form of agammaglobulinemia (23, 27), a condition characterized by lymphocytopenia, thymic hypoplasia, frequent bacterial and **fungal** infections and early death, and the immunological state of the patient with advanced Hodgkin's disease should be recalled). Certainly it is unlikely, at least in the majority of Hodgkin's patients, that the thymus is the primary seat of the disease process (55) as Thomson has suggested (69), nor would this explain the defect. The little available direct evidence has failed to substantiate frequent thymus involvement early in Hodgkin's disease (43), and thymectomy beyond the neonatal period does not lead to early or severe immunologic impairment without an additional manipulation to deplete lymphoid tissue drastically (7, 50, 76). However, it is perhaps that immunological function which the thymus subserves which is impaired in Hodgkin's disease. As more is learned of the mechanism of thymic function (17) and delayed hypersensitivity, this idea may be formulated with more precision.

TABLE I
CUTANEOUS RESPONSE TO DELAYED ALLERGENS
(Modified from Schier *et al., Am. J. Med. 20*: 94, 1956)

Group	No.	Mumps	Candida albicans	Trichophyton gypseum	P.P.D.
Controls	79	90%	92%	68%	71%
Hodgkin's disease	43	14%	19%	16%	23%

TABLE II
COMPARISON OF THE INCIDENCE OF ANERGY AMONG PATIENTS IN GOOD OR POOR CONDITION
(Modified from Lamb *et al., J. Immunol. 89*: 555, 1962)

Group	Good Condition			Poor condition		
	No. Tested	No. Anergic	Per cent Anergic	No. Tested	No. Anergic	Per cent Anergic
Control	208	3	1.4			
Hodgkin's	49	26	53	8	7	88
Carcinoma	27	0	0	32	12	38
Leukemia	25	3	12	10	5	50
Non-Hodgkin's Lymphoma	20	1	5	21	13	62

TABLE III
SUMMARY OF DINITROCHLOROBENZENE TESTING IN HODGKIN'S DISEASE (1)

	Inactive disease	Active disease
No. of patients	15	25
No. of tests	20	40
Positive	14	0
Equivocal	1	0
Negative (Anergic)	5	40

TABLE IV

LYMPHOCYTE TRANSFER REACTION IN HODGKIN'S RECIPIENTS (3)

Recipient (Condition)	Donor	Millimeters of induration		
		48 hours	7 days	11-14 days
HD-1 (Good)	N-1	7	14	
	N-2	5	10	
	HD-2	7	0	
HD-2 (Good)	N-1	6	8	6
	N-3	5	5	?4
	HD-3	8	0	0
	HD-4	4	0	0
HD-4 (Good)	N-1	8	9	9
	N-2	5	8	6
	HD-3	3	0	0
	HD-5	3	0	0
HD-6 (Poor)	N-1	0	4	
	N-2	2	8	
	HD-1	2	0	
	HD-3	0	0	
HD-7 (Poor)	N-1	2	0	8*
	HD-8	4	2	0

Abbreviations: N = normal, HD = Hodgkin's disease

* Induration undiminished at 21 days

TABLE V

INFECTIOUS COMPLICATIONS IN HODGKIN'S DISEASE

(Modified from Casazza, Duvall, and Carbone,

Cancer Research 26: 1290, 1966)

Type of infection		No. of episodes in 51 patients
I	Bacterial	56
	A. Septicemia (from lung, skin and G.I. tract)	10
	1. *H. Staphylococcus aureus*	
	2. *Pseudomonas sp.*	5
	3. *E. coli sp.*	5
	4. *Streptococcus sp.*	2
	5. *Klebsiella sp.*	1
	6. *Proteus sp.*	1
	7. Paracolon bacillus	1
	8. Mixed gram-negative	3
	9. *H. Staph.* and gram-negative	1
	B. Pneumonia (*H. Staph.*, gram-negative and one pneumococcus)	14
	C. Enteritis (*Salmonella*)	4
	D. Urinary tract	4
	E. Skin abcesses	4
	F. Miscellaneous	1
II.	Viral infection	17
	A. Herpes zoster	8
	B. Varicella	1
	C. Cytomegalovirus	5
	D. Herpes simplex	3
III.	Fungal infections	10
	A. Disseminated	4
	1. *Cryptococcus*	
	2. *Histoplasma*	1
	3. Nocardia	1
	B. Localized	
	1. Pulmonary (*Nocardia* and *Candida*)	2
	2. Gastrointestinal (*Candida*)	2
IV.	Miscellaneous infections	3
	A. *Mycobacterium*	1
	B. *Toxoplasma*	1
	C. *Pneumocystis c.*	1
	TOTAL	86

TABLE VI

IMMUNOLOGICAL UNRESPONSIVENESS AND DISEASE STATUS

IN HODGKIN'S DISEASE

Disease status	Delayed hypersensitivity							
	Delayed allergens	Active sensitization (DNCB)	Antibody	Gamma globulin	Lymphocyte count	Lymphocyte transfer reaction	Lymphocyte function *in vitro*	Resistance to fungal, viral and bacterial agents
Localized (Inactive or healed)	N	N	N	N	N	N	N	N
Localized (Active)	↓	↓	N?	N	N or ↓	↓	?	N?
Generalized	↓ or ↓↓	↓	N?	N	↓ or ↓↓	↓	↓	↓
Terminal	↓↓	↓	↓	↓	↓↓	↓↓	↓	↓↓

Abbreviations: DNCB = dinitrochlorobenzene, N = normal, ↓ = depressed, and ↓↓ = markedly depressed.

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