PATHOGENESIS OF SKIN DISEASE

Edited by

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PREFACE

Mankind has always sought an explanation for illness and other natural phenomena. Divine intervention gave way to the four humors of the ancient Greeks and Romans, only to be replaced at the dawn of medicine by the germ theory and later by the focus of infection school of thought. World War II saw the rise of psychosomatics, and nowadays genetic and immunologic mechanisms dominate etiologic considerations.

In clinical practice we are continually impressed by the extent to which old and even ancient etiologic concepts dominate our patients' (and sometimes even our own) appreciation of their illness. The teenager's wish to have his face "cleaned" implies a belief that acne is the result of divine retribution for sins, either real or imagined. The patient with atopic dermatitis who attributes the problem to "acid in my blood" illustrates that the humoral theory has not been abandoned. The focus of infection theory endures in patients with "id" reactions. A willingness to accept "nerves" as a cause of anything that cannot otherwise be explained is a source of comfort to both them and us.

Despite great strides in recent decades in our knowledge of molecular and even submolecular function in biologic systems, we still understand very little about what causes disease; however, significant progress has been made in appreciating disease pathogenesis. We are particularly grateful that much of the discussion in this volume will be out-of-date at the time of publication or shortly thereafter. This is evidence of the rapid progress being made in our basic comprehension of skin disorders and will inevitably lead to improved therapy for our patients.

Bruce H. Thiers, M.D.
Richard L. Dobson, M.D.

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SECTION I

Allergic and Eczematous Disorders

1

Allergic Contact Dermatitis

Daniel N. Sauder

Allergic contact dermatitis can be defined as inflammation of the skin characterized clinically by erythematous papules and vesicles and histologically, in the acute stage, by spongiosis, dermal edema, and a perivascular lymphohistiocytic infiltrate; the process is induced by a delayed-type hypersensitivity (DTH) reaction to epicutaneously applied agents.

Contact dermatitis was first recognized as an immunologic disease by Jadassohn[25] in 1895, eight years before von Pirquet introduced the term "allergy." Jadassohn established that what is now called allergic contact dermatitis is caused by increased sensitivity to a chemical applied to the skin, and not by toxic properties. He noted that the application of iodoform to normal skin of sensitized subjects reproduced their dermatitis. The present diagnosis of allergic contact dermatitis is still based on this method of testing.

HISTORICAL PERSPECTIVE

The use of animal models has greatly facilitated our understanding of mechanisms involved in allergic contact dermatitis. Bloch and Steiner-Wourlisch[13] and W. Jadassohn[26] showed that extracts of *Primula* could induce allergic contact sensitization in guinea pigs. In this model, Landsteiner and Jacobs[29] established that low molecular weight substances called haptens become immunogenic only after conjugation with carrier proteins. In these studies, dinitrochlorobenzene and trinitrochlorobenzene (picryl chloride) were used as haptens. These chemicals remain the major sensitizers used in experimental models of allergic contact sensitization, which has been induced in several animal species. In the late 1960s Asherson and Ptak[4] developed a quantitative model of allergic contact sensitization by measuring ear swelling in mice.

The finding that the skin plays an important role in allergic contact sensitization was firmly established by the elegant work of Macher and Chase[31] who demonstrated that for the induction of allergic contact sensitization to occur following skin painting with a hapten, an initial phase must occur in which the hapten interacts with constituents of the skin. By using dinitrochlorobenzene injected intradermally into the ears of guinea pigs, these investigators established that the site of application of hapten had to remain intact during the first 24 hours after application. Excision of the ear before the end of the first 24-hour interval failed to induce sensitization.

DELAYED-TYPE HYPERSENSITIVITY SKIN REACTIONS

The concept of delayed-type hypersensitivity was originally based on the tuberculin-type skin reaction, which develops in sensitized guinea pigs within 4 to 6 hours after antigenic challenge and becomes fully manifest within 18 to 24 hours. Delayed-type hypersensitivity is now defined as an immunologically specific inflammatory reaction, maximal at 24 to 48 hours after challenge, with a characteristic histologic appearance consisting of infiltration with mononuclear cells. This reaction differs from antibody-mediated allergic reactions in several ways. In delayed-type hypersensitivity reactions, the time between the initial sensitization and the first manifestation of hypersensitivity is 5 to 7 days, whereas antibodies usually are not demonstrable before 14 days. In a sensitized person, the delayed-type hypersensitivity skin reaction to challenge with the specific antigen or hapten requires 24 to 48 hours to reach peak intensity, whereas antibody-mediated reactions may be observed within hours (Arthus phenomenon) or minutes (anaphylaxis). In delayed-type hypersensitivity reactions like contact sensitization, proliferation and differentation of stimulated lymphocytes occurs in the thymus-dependent (paracortical) areas of the lymph node, whereas in antibody-mediated reactions, proliferation takes place in the germinal centers and at the corticomedullary junction (B cell zones). In delayed-type hypersensitivity the sensitivity is not mediated by antibody and cannot be transferred passively to nonsensitized recipients by serum from sensitized donors. Delayed-type hypersensitivity is transferable by T lymphocytes whose activities are

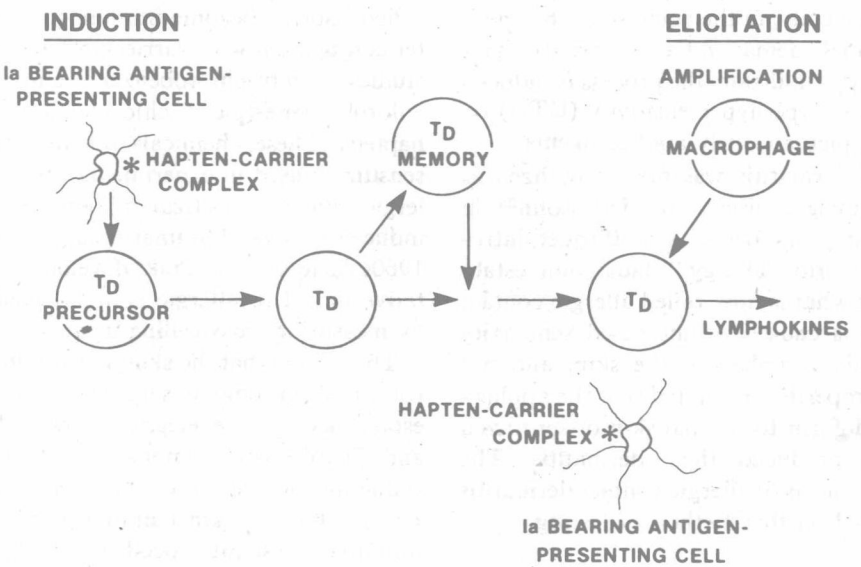

Fig.1.1 Mechanisms in delayed-type hypersensitivity reactions. After the hapten combines with the carrier protein, the hapten-carrier complex is processed by Langerhans cells or other antigen-presenting cells. This triggers precursor delayed-type hypersensitivity T lymphocytes (T_D precursor cells) to become sensitized T lymphocytes (T_D cells). These cells enter the regional lymph node where they undergo blastogenesis. A subset of these cells differentiates to become memory cells, while others become effector T cells. These cells leave the lymph node via the efferent lymphatics and return to the antigenic site in the skin. Upon contact with antigen, a variety of amplification steps may occur, including release of cytokines. This leads to a local inflammatory response.