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Edited by
E. Rajka and S. Korossy

Volume 7

ALLERGIC DISEASES OF THE SKIN

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CHAPTER 63

ALLERGIC DISEASES OF THE SKIN. ALLERGODERMATOSES

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INTRODUCTION

Classification of allergodermatoses was in the past generally based on pathological criteria (urticaria, erythema, eczema, etc.) which although failing to fulfill the requirements of theoretical allergology, is often indispensable for the practi-

tioner. An aetiological classification would be more correct, but would result in confusion because a correlation of most diseases with most aetiological factors can easily be found. Classification according to localization of the target tissue (epidermis, stratum papillare, middle and deepest third of the dermis, subcutaneous tissue, etc.) is not convenient either, because only few lesions involve a single skin layer (e.g. urticaria). Evidence is lacking that inflammatory processes, including allergic ones, could develop without the participation of vascular elements. Even if it were supposed that in certain cases of contact dermatitis sensitization is limited to the epidermis, the role of the small vessels of the stratum papillare and dermis in the process could not be excluded.

At the present state of allergological and immunological knowledge a pathogenetical classification seems to be the best choice. In terms of pathogenesis two main groups of allergodermatoses can be distinguished, viz. immediate-type and delayed-type (tuberculin-type) processes. The number of mixed-type cases is, however, high. Nevertheless, this classification can be most easily adapted to the schemes proposed for the classification of hypersensitivity reactions by Gell and Coombs [100], Steffen [249] and Rajka [209*d*] (see Chapter 2 in Volume 1). Four or five types of reactions are distinguished; type I allergic response with antibody mediation, anaphylactic type; type II allergic response with skin-sensitizing (reagin)-type antibodies; type III cytolytic-cytotoxic response in which the antibody reacts with the antigenic components of cells, or with antigens or haptens attached to the cell surface; type IV Arthus phenomenon and systemic serum sickness, mediated by soluble antigen–antibody complexes formed in moderate antigen excess and having a C binding ability. These reaction types come primarily under the heading of immediate-type sensitization; type V delayed, i.e. tuberculin-type and contact eczematous type hypersensitivity.

In this chapter the allergic skin diseases are classified as follows:

1. Skin processes due to immediate hypersensitivity reactions including
   - urticaria, Quincke's angioedema
   - atopic dermatitis (Besnier's prurigo, Gottron's endogenous eczema, neurodermatitis constitutionalis, etc.)
   - infantile eczema
2. Skin processes due to delayed hypersensitivity reactions including
   - allergic contact dermatitis (eczema)
   - microbial (bacterial) eczema } These may also occur as a result of
   - mycotic eczema } mixed-type hypersensitivity
3. Processes referred to the category of mixed-type hypersensitivity reactions including
   - physical allergy
   - serum sickness and serum allergy
   - allergy to drugs
   - microbial (bacterial) allergy
   - mycotic allergy
   - viral allergy
4. Allergic itching

The sequence of diseases listed in group 3 indicates the relative importance of immediate and delayed hypersensitivity in their pathogenesis: descending order showing the importance of the immediate type and *vice versa* [209*d*]. Accordingly, urticarial and erythematous lesions appear in the immediate-type, papulous, infiltrative inflammatory exanthemas, eczemas, dyshidroses, etc. in the delayed type, and transitional forms in the mixed type of hypersensitivity. This applies above all to allergic processes, which can imitate practically all skin diseases from acute urticarial, erythematous, oedematous, haemorrhagic or vesicular inflammatory lesions to chronic, infiltrative, nodular, granulomatous, necrotic inflammations and circumscribed or extensive cutaneous degenerative processes.

Pure forms of hypersensitivity, i.e. the conditions classified as conditions belonging to group 1 and 2, are those in which the other reaction type plays no role, or at least not a primary one. There is generally no immediate-type reaction in contact eczema, whereas in immediate-type urticarial processes the delayed reaction is lacking. If it occurs at all, e.g. in atopic dermatitis, it can well be regarded as a secondary phenomenon. The matter is, however, as a rule not so simple as that. The delayed reaction may be positive in most cases of urticaria (mainly in drug-induced forms), despite the exclusively immediate-type cutaneous manifestation. Also, epicutaneous reactions may be occasionally—above all in penicillin urticarias—elicited by the Fernström technique [189*b*]. In certain cases of hay fever, however, the delayed-type reaction was still demonstrable after the suppression of the immediate-type reaction by antihistamines [37, 38]. On the other hand, an immediate-type reaction may occur in contact eczema: in certain cases the absorbed material (mercury, also via inhalation) elicited an urticarial eruption with positive immediate-type reaction apart from the positive epicutaneous test [209*d*]. It was reported that among others in ambrosia caused pollinosis, the intracutaneously administered water-soluble pollen extract elicited an immediate-type reaction, whereas the lipid-soluble fraction a delayed-type contact dermatitis in the same patient [54]. The simultaneous occurrence of urticarial and contact sensitivity was observed in the course of benzophenone therapy [212*d*]. In the case of broad-spectrum light sensitivity to 2-hydroxy-4-methoxybenzophenone-5-sulphuric acid (Sulisobenzone) both the benzophenone and sulphonic acid parts of the molecule were needed to elicit the contact reaction, while benzophenone was in itself sufficient to elicit the urticarial reaction. The quantitative relations and the site of entry presumably also play a role. Patients with previous contact eczema to nickel developed during or shortly after i.v. infusion of blood, plasma or saline, clinical evidence of immediate and Arthus-type reactions (anaphylactoid reactions, intense erythema, generalized urticaria and/or angioedema) [133*a*, 249*b*]. The infusion cannulae having a nickel-plated shaft and nickel-plated brass hub with a roughly finished internal surface were left for 48h in distilled water at 37 °C. Up to 20 mg of nickel were recovered from the eluate. All patients had in addition to positive delayed-type hypersensitivity epicutaneous test to 1 per cent $NiSO_4$, weal and flare reactions to intracutaneous and prick tests with this solution. They also developed at the test sites weals with pseudopodia 3–4 h later. These subsided within 18 h. Passive transfer reaction was positive in the majority of cases. The patients' skin lesions showed the histological features of allergic vasculitis, but not any eczema.

Atopy, a constitutional or hereditary background of predisposition to develop

an immediate hypersensitivity state. Urticaria and angioedema may occur in patients with seasonal allergic rhinitis or allergic bronchial asthma during the appropriate season of the year [235]. Localized urtication occurring in such sensitized individuals may follow upon contact with fur or saliva of the animals to which the patient is sensitive [235]. Inhalants such as mould spores, pollens, feathers, animal dander, flour and dust, as well as various ingestants, are recognized precipitants of generalized urticaria in sensitized individuals [74]. Formerly only the intracutaneous and prick tests or, depending on the nature of the antigen, the exposure test had been available for demonstration of the skin-sensitizing antibody; recently the demonstration of specific IgE may be additionally attempted.

The classification of mixed types is in fact based on aetiology, while those of the clear forms on morphology which may be subject to diverse influences. In this way, contact eczema is the best defined condition. For the time being we have to put up with this non-uniform classification. Lesions of the internal organs may be present in the majority of allergic skin diseases and may become predominant (e.g. in drug and microbial allergy).

As a matter of fact, other operational classifications based on different criteria may also be conceived as will be illustrated by some examples. All have advantages and disadvantages and none is devoid of a compromise.

Sheffer and Austen [235] divided skin diseases of altered reactivity with vascular responses into two main groups, viz. (I) anaphylactic syndrome and (II) urticaria and angioedema. Type II is subdivided into four subgroups: (1) immunological, comprising (*a*) anaphylaxis, (*b*) serum sickness and (*c*) atopy; (2) anaphylactoid (as hereditary angioedema); (3) presumptive immunological, comprising (*a*) cold urticaria, (*b*) light urticaria (*c*) secondary urticaria (as infectious, parasitic processes; SLE); (4) idiopathic, comprising (*a*) cholinergic urticaria, (*b*) dermographism, (*c*) miscellaneous (as neoplasms, psychogenic, endocrine) conditions of urticaria and angioedema.

Bendixen [18] proposed the following classification of clinical hypersensitivity disorders, using in part a new nomenclature: the 'humoral hypersensitivity' state including three types: (1) precipitinogen type (with antigen–antibody complexes) with serum sickness and SLE as the main sub-types; (2) cytotropic type having urticaria and anaphylactic shock as major representatives; (3) cytolytic type with various haemolytic forms and the 'cellular hypersensitivity' state including four types: (1) microbial type; (2) haptenic type, with allergic contact dermatitis and exanthematic reactions to drug hypersensitivity as major types; (3) transplantation type and (4) organ-specific type.

Parish [200c] characterized the types of allergic reactions with some of the skin or vascular changes caused, or presumably caused, by them as follows: (1) anaphylaxis type, as urticaria, angioedema; (2) Arthus-type reaction as allergic nodular vasculitis, ? purpura, ? polyarteritis, ? erythema multiforme, ? erythema nodosum; (3) cytotoxic reaction type as purpura, ? SLE; (4) delayed-type reaction as contact dermatitis (? = allergic origin and type of response unknown but suspected). Parish remarks that this classification serves only as a guide; not all conditions named result from allergic reactions and others are found in circumstances that are assumed, though not proved, to have an allergic origin. Thus urticaria is not exclusively allergic and angioedema may seldom be so. Polyarteritis is presumed to be allergic in origin by analogy with experimental disease

in animals. However, there are not even experimental analogies to support the presumption that systemic or discoid lupus erythematosus is allergic in nature.

The following classification of Rook and Wilkinson includes the principal forms of eczema, and also, by convention, certain conditions, which do not necessarily show the histological changes of eczema at all stages [218]. (I) Exogenous eczemas: (1) irritant dermatitis, as a response of the skin to direct physical or chemical injury; (2) allergic contact dermatitis, as a response of the skin to contact with substances to which it is allergically sensitive; (3) infective dermatitis, as a response to contact with certain microorganisms or their products. (II) Endogenous eczemas: (1) atopic dermatitis, with genetically determined constitutional factors of primary importance; (2) seborrhoeic dermatitis, with constitutional factors, probably genetically determined, of primary importance; (3) nummular eczema with constitutional factors of primary importance, but genetic predisposition seldom demonstrable; (4) dyshidrosis (pompholyx) with an acute vesicular or bullous pattern of response induced by many different factors; (5) pityriasis alba, with a common pattern of superficial eczema of unknown origin; (6) other patterns. A variety of other patterns of eczema occur rarely, or only in special environments, or exclusively in certain racial groups, like senile or asteatotic eczema, exudative discoid lichenoid dermatitis, eczema of dermatitis herpetiformis pattern, 'tropical' eczemas, juvenile papular dermatitis, eczema in relation to intestinal malabsorption.

With regard to optimal therapeutic approach, prevention and also to training, Skripkin et al. [246] have advocated the differentiation of five main types of eczema, such as (1) genuine eczema (including dyshidrosis and hyperkeratotic eczema); (2) microbial (including nummular, paratraumatic and 'sykosiform' eczema); (3) seborrhoeic eczema; (4) occupational and (5) infantile eczema.

'Eczematous dermatitis' commonly termed in Europe as eczema was subdivided by Soter and Fitzpatrick [247*b*] as follows: (I) eczema associated with exogenous agents; clinical types: (1) allergic contact eczema with exogenous chemical allergens; (2) photo-allergic contact eczema (Epstein, Wuepper, Maibach) with UV radiation plus topical chemicals (in soaps, perfumes, citrus fruits, etc.) which then become allergens; (3) polymorphous light-induced eruption-eczematous type (Epstein) with UV radiation as aetiological agent. (II) Eczema associated with endogenous agents; clinical types: (1) eczematous drug-induced eruption with drugs as aetiological agents; (2) dermatophytid with fungal products; (3) autosensitization or autoeczematization with altered epidermal products from site of eczema. (III) Eczema of unknown aetiology; clinical types: (1) atopic eczematous dermatitis (Peterson) with hereditary predisposition plus precipitating factors; (2) lichen simplex chronicus (Cleveland, Shaffer, Beerman) — one or more lichenified plaques, especially on the neck, with hereditary predisposition plus repeated local trauma; (3) prurigo nodularis (Shaffer, Beerman) one or more nodules, especially on extremities, repeated local trauma as suspected aetiological factors; (4) neurodermatitis (Shaffer, Beerman) generalized, or localized eczematous eruption at sites of repeated trauma with hereditary predisposition plus repeated scratching; (5) stasis dermatitis (Faber, Batts, Haeger, Bergman) with signs of chronic venous insufficiency; (6) nummular eczema with various precipitating factors; (7) seborrhoeic dermatitis (Pinkus, Mehregan) with constitutional diathesis; (8) hand eczema (Bettley) with four types of eczema that may be exclusively

localized to the hands (atopic eczematous dermatitis, allergic contact eczema, nummular eczema, 'dyshidrotic' eczema). Possibly, contact irritants to which the hands are frequently exposed may precipitate or aggravate one of the aforementioned basic types of eczema. (IV) Eczema-like eruptions with systemic disease (Rostenberg, Solomon) with metabolic and immunological disorders as Wiskott–Aldrich syndrome, X-linked agammaglobulinaemia, phenylketonuria (Fleisher, Zeligman), ahistidinaemia (Synderman et al.), Hurler's syndrome, Hartnup disease and acrodermatitis enteropathica.

According to Miescher [183*a*], eczema is a polyaetiological event with a uniform pathogenesis, taking place on the basis of the eczematous-allergic form of reaction. There are various types of eczema, all belonging to the same complex of phenomena. In the German literature [119, 147, 183*c*] three forms of eczema have been clearly defined: (1) eczema vulgare, (2) eczema endogenes (Gottron) and (3) eczema seborrhoeicum (Unna). Eczema vulgare is subdivided into four major types [147]: (*a*) allergic contact eczema; (*b*) clearly non-allergic contact eczema (irritant dermatitis, wear and tear dermatosis, 'degenerative' dermatitis, traumiterative eczema), (*c*) poorly defineable forms (nummular eczema, dermoepidermitis and stasis erythema types of leg eczema); (*d*) microbial eczema. Seborrhoeic eczema (Unna's disease) may appear in seborrhoeic regions of seborrhoeic persons as a follicular, figural, pityriasiform, exudative, papulovesicular, and pustular process [147]. Endogenous eczema or neurodermatitis constitutionalis corresponds to the condition termed atopic dermatitis in the Anglo-Saxon literature.

Steigleder [249*a*] differentiates two types of eczema, namely contact eczemas and atopic dermatitis. Of the former two major forms, viz. toxic and allergic can be distinguished. As toxic factors direct toxic stimuli, high-dose X-ray, UV or infrared irradiation may play a role. The clinical picture depends on the dose and, to a lesser extent, on individual factors. Several varieties of the toxic form can be differentiated. Among these that called wear and tear dermatosis or degenerative-itinerative eczema occurs most frequently. In these cases a single large dose of a toxic agent, or small doses acting for a long time may cause eczema without any demonstrable sensitization. The terms 'exsiccation eczematoid' and 'eczema craquelé' refer to eczema-like alterations caused by exsiccation of the skin of mainly old subjects. The phototoxic eczema is classified in the same form by Steigleder. A combined toxic-allergic form has also been observed.

In cases of contact eczema of allergic origin (allergic eczematous dermatitis) sensitization can be proved in clinical practice by positive epicutaneous, sometimes also intracutaneous, test. Essentially this is a delayed-type hypersensitivity mediated by sensitized T lymphocytes. Long-lasting or repeated exposure of the skin to an exogenous allergen may lead to an ever increasing allergization and consequent dissemination on the trunk of exanthema-like foci. The morphological picture is variable, resembling the morpheas of nummular, microbial or seborrhoeic eczema. Haematogenous eczema [22*a*], i.e. secondary eczematous skin phenomena due to an allergen active within the organism, as well as photoallergy, the pustular forms of eczema and the eczema developing on patients suffering from psoriasis have been classified in the same group by Steigleder.

The morphology, gross appearance and clinical course of cutaneous allergic manifestations differ scarcely, if at all, from those of a 'normergic' inflammation.

The lesions are not characteristic of the pathogenic agent, nor of the manner in which it enters the body or makes contact with the skin or mucous membranes. The same type of inflammatory lesions may be of external or internal (haematogenic or flare-up) [22*a*] origin; the same agent may induce different pathological processes; and the same change may be brought about by different agents and have different pathomechanisms. The allergic nature of an inflammatory lesion only signifies—regardless of its degree, extent, duration and localization—that the skin has been the target organ of the allergic response. Accordingly, neither the gross appearance of the lesions nor the clinical picture can be regarded as conclusive of the allergic or non-allergic origin of a disease. Correct diagnosis needs the identification of the causative agent and of the pathogenesis; otherwise the usual terms as urticaria, erythema, eczema, if applied without further specification only describe the clinical symptoms [263].

Immediate-type allergy is characterized by positive cutaneous and intracutaneous tests, negative epicutaneous test, often positive Prausnitz–Küstner (P–K) reaction or Layton transfer in monkeys; occasionally a positive basophil degranulation test or lymphocyte transformation test are also conclusive. Circulating antibodies may also appear mainly in IgE globulins and specific desensitization may be successful as well.

As to the mediators of the immediate-type reactions a decisive role is played by histamine. It is released in allergic weal and flare reactions from preformed stores located in skin mast cells. This release is basically a secretory process in which the stimulus to secretion is a combination of antigen with IgE antibody. This activates a multistep stimulus secretion coupling mechanism in the form of an enzyme cascade which leads to release of histamine from intracytoplasmic storage granules. Histamine release is inhibited by β-adrenergic agents such as isoprenaline and adrenaline, which increase formation of cellular cyclic 3′, 5′ adenosine monophosphate (AMP), and by theophylline which inhibits degradation of cyclic AMP. The reaction can also be divided into two steps depending upon calcium requirements—an initial calcium-independent step involving antigen-IgE antibody combination and mast cell activation and a final histamine release step which requires Ca^{2+}. This last step being reversibly inhibited by cytochalasin B is probably mediated by contraction of cytoplasmic microfilaments.

The delayed contact eczematous-type epidermal, dermoepidermal or vasculoepithelial allergies are characterized by a positive epicutaneous test and also the intracutaneous reaction is positive with high dilutions of certain contact materials, above all metals. The P–K transfer with the serum is, however, negative, while transfer with lymphocytes collected from peripheral blood or with their extract is positive. Occasionally, the lymphocyte transformation and the leukocyte migration tests may also be used for demonstration of the corresponding allergen. In tuberculin-type allergies, the sensitization of epidermis and corium may be of equal intensity, but the sensitivity of the epidermis persists longer. Thus both the intracutaneous and epicutaneous tests may be positive, but the positivity of one or another may be weak or absent. Antibody-mediated cytotoxic reactions in eczema are probably rare. C-fixing IgE antibodies cytotoxic for outer epidermal cells were found in only four out of 81 patients with generalized eczema [200*d*].

In response to specific antigenic challenge *in vitro*, appropriately sensitized lymphocytes elaborate a number of soluble non-antibody factors termed lympho-

kines. These putative mediators of cellular immunity express their activities in a variety of *in vitro* and *in vivo* systems, being important in delayed-type hypersensitivity reactions, lymphocyte transformation and macrophage migration inhibition. Contact eczematous and tuberculin-type hypersensitivity may differ in morphology and localization, but their pathogenesis is nevertheless identical and their aetiology is mixed.

IMMEDIATE-TYPE ALLERGIC DISEASES IN WHICH THE UNDERLYING MECHANISMS ARE KNOWN TO BE, OR LIKELY TO BE, OF IMMUNOLOGICAL NATURE

ANAPHYLACTIC SYNDROME

The clinical response of man begins within a few minutes after the antigen combines with the antibody on the surface of cells, but the clinical syndromes include a variety of reactions with widely different basic mechanisms, and seemingly identical clinical responses may arise by different immunological mechanisms, or by the release of histamine or various other chemical mediators, or both.

Responsible antigens in man may be divided into [6]: (*i*) proteins (antisera; hormones: relaxin, insulin, ACTH; enzymes: chymotrypsin, trypsin, penicillinase; Hymenoptera sting; pollen: Bermuda grass, ragweed; food: buck wheat, egg white; typhoid vaccine; cotton seed; glue; haemoglobin); (*ii*) polysaccharides (acacia, dextrane, iron-dextran); (*iii*) haptens (diagnostic agents: sodium dehydrocholate, sulphobromophthalein, iodinated organic contrast media; vitamins: thiamine, folic acid; analgesics: salicylates, aminopyrine; antibiotics: penicillin, tetracycline derivatives, streptomycin; nitrofurantoin; procaine; tripelennamine; pyribenzamine; 2-methyl-2-n-propyl-1,3-propanediol dicarbamate as Meprobamate, Miltown). The role of allergy in hypotensive states produced by local anaesthetic agents and organic iodides is less clear.

The route of administration responsible for severe or even fatal reactions ranges from oral or injected to percutaneous or mucosal exposure. Subclinical sensitization may result from a previous uneventful clinical exposure, from the presence of the material in food or from contact with a cross-reacting antigen.

Only immune reactions in which reagin-type or skin sensitizing antibodies participate are accepted as anaphylactic. These are characterized by a rapid onset after antigen exposure and association with vascular and respiratory phenomena. An accelerated and late urticarial reaction might be attributed to modification of the antigen by antibody and/or to requirement for decomposition of the eliciting determinant [6]. In addition, the late urticarial reaction probably reflects immunization and induction by the same course of treatment [6].

The i.c. injection of protein antigen has consistently produced immediate-type reactions. Similar tests with polysaccharide-type antigens are generally lacking. A number of haptens have also elicited positive skin test reactions. In other instances, the positive skin test reaction occurred only when the hapten was injected i.c. in a conjugated form or when a degradation product was carrying the new haptenic determinant [6]. The presence of antibody to a number of materials was confirmed by passive P–K transfer. Although the responsibility

of an antigen is proved by an immediate-type response to direct skin test, the same response is not conclusive of the responsibility of the skin sensitizing antibody for the systemic reaction in the given case. Allergic reactions to a given antigen fall into a number of categories, defined by the nature and specificity of the antibody, each carrying a different risk. Non-fatal anaphylactic reactions can appear after skin test without positive local immediate-type reaction, e.g. with iodinated contrast media [6]. The cause of such a phenomenon may be either that the proper determinant was not present at the skin site, or that some other immunoglobulin class of antibody was involved. Unfortunately, a negative history of a previous untoward reaction is no guarantee that administration of a pharmaceutical agent will not produce anaphylaxis.

The cutaneous symptoms appearing in clinical manifestations of the anaphylactic syndrome show the following reaction patterns, especially in cases of penicillin allergy: (*i*) immediate reaction (onset of a generalized pruritic urticaria associated with hypotension and bronchial spasms within minutes of exposure); (*ii*) accelerated urticaria (2 to 36 h after administration); (*iii*) serum sickness-like syndrome (8 to 21 days after exposure and disappearing within hours or days on termination of antigen contact); (*iv*) recurrent urticaria (occasional angioedema and arthralgia with fever or lymphadenopathy, beginning 2 to 15 weeks after the contact and subsiding either spontaneously or only on elimination of hidden contact); (*v*) heterogeneous cutaneous reaction (maculopapular or diffuse erythema occurring without any urticarial component).

Any life-threatening respiratory or vascular reaction pattern can appear either alone or along with a cutaneous manifestation or gastrointestinal involvement. Tightness in the throat and in the chest indicate laryngeal oedema and an intractable bronchial spasm, respectively. Both can proceed to cyanosis, increasing respiratory distress, secondary hypotension and death by suffocation. The so-called light-headedness involves chest discomfort or pressure, hypotension, and loss of consciousness. Cyanosis and persistent vascular collapse can proceed to cardiac arrest. The symptoms of gastrointestinal reactions are nausea, vomiting, abdominal cramps and diarrhoea.

The pathological findings associated with fatal systemic anaphylaxis in man fall into three patterns [6]: (*i*) Often acute pulmonary emphysema, with some secretion in the bronchial lumina, occasionally with submucous oedema, peribronchial vascular congestion and eosinophil infiltration of bronchial walls. (*ii*) Oedema of the upper respiratory tract (hypopharynx, epiglottis, larynx) is a contributing factor rather than an obstruction sufficient to be the cause of death. (*iii*) Vascular collapse without a preceding respiratory distress may be a characteristic finding.

Three factors determine the severity of the anaphylactic syndrome in man: (*i*) the sensitivity of the patient; (*ii*) the dose of antigen and (*iii*) the rate of its absorption. When only portions of the reaction syndrome are present, such as urticaria alone, or sudden bronchospasm in an asthmatic or vascular collapse following intravenous administration of some agent, it is more difficult to exclude some direct, non-immunological cause.

SERUM SICKNESS SYNDROME

This is a hypersensitivity reaction the symptoms of which appear a few days after a single large dose of antigen (usually after passive immunization with antiserum) and consist of local swelling at the injection site, generalized urticaria, enlargement of lymph nodes, fever, joint swellings and, less often, renal lesions [130]. The symptoms are due to the presence in the tissue of soluble antigen–antibody complexes formed between the antibody produced during the immune response and the large quantities of antigen still present. The symptoms therefore become expressed in the form of a generalized type III reaction. (For details about serum sickness see Chapter 68.)

URTICARIA AND QUINCKE'S ANGIOEDEMA

Urtica, the primary morphological sign of urticaria, is a well-circumscribed intensely itching inflammatory reaction, a white, compressible, usually evanescent, area of dermal or dermal plus subcutaneous oedema [263]. The local hyperaemic spot arising in consequence of capillary dilatation and subsequent oedema are directly induced by the endogenous or exogenous urticariogenic stimulus acting on the stratum papillare. The central nervous system may not participate in the development of the symptoms, but the hyperaemic flare surrounding the weal is due to an axon reflex dilatation of arterioles and does not develop in areas with paralysed sensory nerves. The lesions may be sparsely scattered over the entire body, may be few or numerous and vary in size from 1 to more than 10 cm in diameter. Annular and serpiginous lesions may occur; these are characteristically itchy at onset. The mucous membrane, e.g. of the mouth or gastrointestinal tract may participate in the process [50]. Urticaria preferably appears in irritated skin regions. Individual lesions rarely last longer than 24–28 h; however, new eruptions may continue to recur for indefinite periods.

If the inflammatory exudate develops with or without urticaria in the subcutaneous connective tissue rather than in the deep cutis or if it involves the submucosa, the demarcated swelling is termed urticaria gigantea, angioedema, or Quincke's oedema. These lesions evoke a burning or stinging sensation, not itching in most cases unless the stratum papillare participates in the process or the affected individual is atopic. The change subsides without leaving a trace, but sometimes only after a few days. The lesions develop above all in skin regions with a loose connective tissue (palpebra, lips, genitals) and often also in mucous membranes (upper respiratory and gastrointestinal tracts). Angioedema has been regarded as the subcutaneous, or submucosal equivalent of urticaria.

Clinical course

Urticaria and angioedema occur probably more frequently than generally believed, for the symptoms often subside in a few days and no recurrence occurs, thus many patients are not seen by the doctor [275]. On the basis of estimations and survey by questionnaire in a group of college students, its incidence in the normal population has been assessed as 10–22 per cent [176, 238, 257, 267],

infrequently as 32 per cent [134, 139, 264]. Women apparently are more liable (58–75 per cent) to urtication than men [156, 202, 231, 235]. The occurrence of urticaria is most frequent during the first decade of life [190] and a second peak was found to occur in the third, fourth or fifth decade [202, 231, 235, 267], depending on the country. Familial incidence [134] and association with allergic disease above all allergic rhinitis is possible [190, 233]. Acute urticaria may be accompanied by fever, indisposition, depression, headache, nausea and vomiting, which appear either along with the exanthem or precede it [70]. The syndrome corresponds to a minor or more severe systemic reaction (minor or major shock) and is partly the subjective concomitant phenomenon of the colloidoclastic crisis. The crisis is not a consequence of urticaria, but a co-ordinated phenomenon and a sequel to the release of tissue mediators. Angioedema of the larynx may be fatal in outcome [25*a*]. In severe cases ECG changes can also occur during the symptomatic phase of urticaria [201, 241]: low $ST_{2,3}$, flat T_2 wave or non-specific primary changes in T waves may be found. No similar ECG changes could be produced by histamine iontophoresis, but there was a great resemblance to the effect of intravenously administered serotonin. Exceptionally a rise in CSF pressure was found [92].

The urticaria is regarded as chronic, if the eruptions continue to appear longer than 4 [209*d*], 6 [48*a*, 235, 267], or 8 [95] weeks, during which symptomatic and symptom-free periods may alternate. Chronic recurrent eruptions have been observed in one-fifth of the patients with urticaria for as long as 20 to 30 years, despite the most judicious management [267]. The distinction between acute and chronic urticaria has some value, yet it is entirely arbitrary and there is much overlap [49*a*]. Just as urticaria may develop without any demonstrable reason ('intrinsic urticaria'), spontaneous improvement may also occur.

Histological studies

The histological picture of urticaria is characterized by a circumscribed oedema, loosening of connective tissue, dilatation of blood and lymph vessels (the oedematous area may also contain compressed vessels) and a low degree of perivascular infiltration, consisting chiefly of eosinophilic leukocytes in allergic urticaria [152]. An ultrastructural study of mast cells in urticaria both spontaneous and induced comparing them in skin and in nasal and bronchiolar tissue [264*a*] has shown that skin mast cells tend to have longer villous extensions of plasma membranes, and that granules have very frequent crystalline inclusions. Degranulation of mast cells has been observed similar to that seen in other tissues. Basophilic leukocytopenia in urticaria is caused by degranulation and destruction of basophils in blood and urticarial lesion [219*b*]. The basophil decrease is a counterpart of decreased blood histamine [219*a*].

Aetiology

The aetiology of urticaria is very variable, almost any substance or endogenous or exogenous influence may occasionally cause urticaria. This has many reasons, some of them related to the patient itself. In some cases of acute urticaria, a single exogenous cause may be found.

It has been generally accepted that gastrointestinal diseases interfering with digestion and absorption promote the increase of permeability in intestinal mucosa so that not fully degraded large molecules, above all proteins (α-lactalbumin, β-lactoglobulin, casein, bovine serum albumin and bovine γ-globulin have been studied in detail) become absorbed and thus act as sensitizing agents. According to the literary data, food hypersensitivity has been identified as one of the pathogenetic factors in 1–6 per cent of acute urticaria cases affecting young children and in 10–56 per cent of chronic urticaria cases in adults [47, 112, 134, 185*b*, 190, 195, 233]. Food allergy has been demonstrated in 5–26 per cent of angioedema cases [190, 195]. The target organ of food allergy is the intestinal mucosa: the related morphological and ultrastructural changes are described in Chapters 52 (Vol. 5) and 61 (Vol. 6). It is a characteristic feature of food allergy that symptoms of antigen–antibody reaction mostly fail to appear at the site of the interaction (in the gastrointestinal tract); they often have a more distant localization on the skin. According to Mosonyi [187*b*] this is due to the altered autonomic nervous tone of the organs reacting to vasoactive substances. Another possibility is that the patient suffers from an allergic condition which is not alimentary in origin, and this condition may at least be aggravated by the diet [46]. This problem will be discussed in more detail in connection with urticaria arising from non-immunological causes.

The gastrointestinal tract plays an important role in the immune defence against foreign proteins and autoantigens due to its lymphoid tissue [14, 67*a*, *b*, 68, 129]. Gastrointestinal disturbances have been demonstrated in about one half of acute urticaria cases and in nearly three-quarters of patients with chronic urticaria [156, 167, 185*a*, 202, 230]. Determinations of gastric acidity with Heidelberg's capsule and histological studies of gastric mucosa in urticaria patients showed that [287] (*i*) the hypo- or anacidity found correlated well with a state of gastritis; (*ii*) normoacidity and intact mucous membrane were simultaneously present in the overwhelming majority of the cases; (*iii*) atrophic gastritis, however, occurring in autoimmune diseases, was associated with anacidity in each case. On the basis of electrogastrographic examinations [285*b*] it cannot be excluded that acid irregularities, their causes or their functional consequences frequently present in certain skin diseases, may favour the appearance of these diseases. It is known that the incidence of hypo- or anacidity tends to increase with progressing age (25.5 per cent between 50 and 59 years and 33.3 per cent above 60 years) without a simultaneous rise in the frequency of allergic skin disease. Although hypo- or anacidity are more often associated with urticaria [156, 167, 230, 260, 278] than hyperacidity, a predominance of the latter has also been reported [185*a*, 202]. Gastroduodenal ulceration has been found in 17 per cent of urticaria cases, gastro-duodenitis has been much less frequent [202]. Parallel with an increase in serum pepsinogen level a quantitative increase of gastrogenic pepsin can well take place without the presence of hyperhistaminaemia [52, 202]. The serum α-1-antitrypsin level, being related to acid secretion and digestion, may act as a predisposing factor, even if not as a major one [135]. Activation of the proteolytic enzymes may give rise to the formation of uncommon breakdown products [127]. The IgA present in mucous membrane secretions protects the