Urticarial Reactions*

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There can be little doubt that urticaria, as an abnormal reaction of the skin, was observed long before the time of Hippocrates, because of its appearance in response to a wide variety of injurious agents found throughout the plant and animal kingdom. It is mentioned by early medical writers under a number of different generic titles such as scarlatina, essera, erysipelas, purpura, erythema, and uredo; Hippocrates, Galen, and Aetius each noted its appearance with certain febrile illnesses. So far as British dermatology is concerned urticaria was very familiar to its acknowledged father and founder, Robert Willan, and to his pupil, Thomas Bateman. Willan (1808) said: "The disease thus continues with repeated eruptions, more or less continuous, for several months or even years. It occurs most frequently in persons of sanguine temperament, especially those who have a delicate stomach and an irritable skin. The occasional causes are heat, fatigue, watchy agitation of mind or anxiety and a too stimulating diet." His experience was gained as physician to the Public Dispensary in Carey Street, London, which drew its patients chiefly from the poor in "the vicinity of Clare-market, Drury-Lane, Chancery-Lane, Temple-Bar, Strand, Holborn, Fleet Street and market, Ludgate, Black and White Friars, etc.," as well as from "poor objects from any quarter, if properly recommended."

Willan (1808) wrote: "The urticaria or nettle rash is characterized by the round, oval or longitudinal elevations of the cuticle, usually denominated wheals, having a white top often surrounded by diffuse redness." He described six varieties—urticaria febrilis, evanida, perstans, conferta, subcutanea, and tuberosa—and his descriptions of these types are illustrated with vivid personal case reports, which would grace the pages of many modern textbooks.

In the nineteenth century dermatology was almost entirely concerned with morphology—the recording and classification of data obtained from the accurate and careful observation of skin diseases. But in the first few years of the present century a young and able physician, working in the infectious-disease section of the Allgemeine Krankenhaus in Vienna, kept careful case notes of his patients and propounded in a small book his own hypothesis to explain what he had observed. I refer, of course, to C. Frh. von Pirquet, whose volume *Die Serumkrankheit* was first published in 1905, and then translated by his co-author Bela Schick and republished in English 46 years later in 1951. Urticaria is part of the serum-sickness reaction which is produced by the acquired, specific, altered capacity to react, for which von Pirquet coined the word allergy in 1906. His somewhat lengthy and cumbersome definition is now usually abbreviated by adding "antibody-mediated" to the vital words "acquired, specific, altered capacity to react."

It is readily understandable that, in the years following, urticaria should have been regarded as an allergic, antibody-

dependent disorder. This supposition was strongly reinforced by the demonstration on 20 July 1920 of the passive transfer of antibody in serum, and its capacity to mediate an urticarial reaction, by Küstner and the late Carl Prausnitz-Giles (who died in April 1963 at the age of 87 at his home on the Isle of Wight). It will be recalled that Küstner found he developed urticaria from the striped muscle of bony fishes, but only after it had been heated. He could eat caviar or any raw fish. One must conclude that the antigen in his case was a denatured or altered protein, because many other patients find they are equally sensitive to raw fish. Hence the antigen may not be the same in every patient. Unfortunately, the use of the passive transfer or Prausnitz-Küstner (1921) test has serious limitations at the present time because of the ubiquity of the virus of homologous serum hepatitis which can be lethal (Ackroyd, 1958); and, as shown later, its value as evidence for the presence of antibody may be questionable.

Sir Henry Dale's identification of histamine in tissues and the demonstration that it had the capacity to replicate the urticarial reaction provided what appeared to be the final link in the chain: antigen-antibody-histamine-capillary dilatation-weal. Sir Thomas Lewis (1927) had for a decade been analysing urticarial and other responses of the small blood-vessels of the skin in man. He showed that his "triple response" from firm stroking was identical with the response to histamine.

The state of medical thought, then, in the years immediately preceding the second world war, was that urticaria is an allergic disorder produced by the interaction of an antigen and its antibody, which induces the activation of histamine in the vicinity of the small vessels of the skin, which are thereby dilated and leak serum to produce the characteristic erythema, weal, and flare. The rational therapeutic approach was thought to be the identification and elimination of the allergen.

The past two decades have witnessed an almost explosive scientific expansion, especially in the realm of biology in its widest sense. All branches of medicine have either experienced or been influenced by this expansion, and the spheres of dermatology and immunology are not exceptions. The inevitable result is that many disease processes have been subjected to a new look from different minds; and the approach of experimental biology has often served as a bridge between the clinician and the biochemist.

Our present-day understanding of urticaria and allied reactions has changed from that of twenty-five years ago because of the recent growth in our knowledge of the three tissue elements which are vitally concerned in the urticarial reaction. These are the mast cell, the eosinophil cell, and the endothelial cell of the capillary vessels in the skin.

The Mast Cell

When Paul Ehrlich was but a medical student at the University of Freiburg, he became familiar with the application

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to textiles of the new aniline dyes being synthesized by the German dye industry. He used several of these dyes to reinvestigate Waldayer's (1875) work on plasma cells (Ehrlich, 1877), and two years later presented his evidence to the Berlin Physiology Society for the distinction from plasma cells of a group of connective-tissue cells which stained specifically with dahlia (Ehrlich, 1879). He named them "Mastzellen" because he thought the granules represented the nutrient reserves of storage connective-tissue cells. Michels wrote a brilliant thesis on "The Mast Cells in the Lower Vertebrate" for his doctorate at Louvain University, and his monograph on the "Mast Cells" (Michels, 1938) remains the most complete account of the cytological aspects. Although he could not convince himself from his own work of any really important function of these cells in the animal kingdom, Michels has lived to see the discovery of the presence of heparin, histamine, and serotonin in these cells and their elevation to a major role as a result of the special properties of the three substances. Serotonin (5-hydroxytryptamine) is present in the mast cells of many animal species but is absent from those of man.

Considerable interest naturally followed Jorpes's (1936) finding that mast cells contain heparin, but it is now generally agreed that this heparin has no physiological function in maintaining the fluidity of circulating blood, although it does evoke such an action in certain cases of mastocytosis or mast-cell disease.

Riley and West (1953) are responsible for the finding that these cells also contain histamine. It was the evidence of the release of histamine and the incoagulable blood in the peptone-shocked dog, as well as a knowledge of mast-cell tumours, which suggested to Riley that histamine and heparin are located in the same cell—namely, the mast cell. He now believes that histamine has a physiological role in what he has called the "mast-cell cycle" of connective tissue, as well as a pharmacological and a pathological action (Riley, 1962). His thesis is that when mild injury ruptures a tissue mast cell a wave of histamine rapidly diffuses out and activates near-by phagocytic histiocytes. There follows a slower wave of heparin granules which are engulfed by, or simply transferred to, the phagocytes; the latter use the mucopolysaccharide for ground substance or other injury repair. The histamine wave additionally dilates the capillary and lymph vessels, which leak protein-rich fluid that may be necessary for, or an aid to, the phagocytic process. The rapid metabolic turnover of histamine in growing connective tissue supports such a thesis (Kahlson *et al.*, 1960).

The normal function of the basophil, or motile mast cell, in the circulating blood is uncertain, although some light may be thrown on this shortly as a result of recent studies of the cell in urticaria, anaphylaxis, and allied states (Rorsman, 1957, 1958; Shelley and Juhlin, 1962). Active urticaria is almost always associated with basopenia (Rorsman, 1962), while a number of hypersensitivity states induce basophilia (Shelley, 1963).

The normal distribution of histamine varies in different species and its concentration varies in different sites in the same tissue. The skin, lungs, and alimentary tract are the chief sites in man, but histamine is also present in platelets and leucocytes, especially the bland basophils. Most of it is found in tissue mast cells except for the stomach. The morphology of mast cells can be very varied, and it seems likely that the cell population is not homogeneous as regards their biological reactions any more than the lymphocyte population is. For example, not all mast cells can be ruptured by even the most potent histamine liberators such as 48/80, some being resistant to repeated injections.

The presence of histamine in mast cells and its release in the absence of severe cellular damage prompts an inquiry into the method of binding and the mechanism of release. On neither point is there an agreed explanation, yet it is clearly

of fundamental importance to problems of urticaria. Mast cells contain the enzyme histidine decarboxylase, which converts L-histidine to histamine, and this is presumably the normal process of synthesis, although another view is that it is produced by intestinal bacteria. Histamine, as a basic amine, can form a complex with the polysaccharide heparin via its acidic groups, and an ionic bond of this type offers the best explanation at the present time. The agents which can break the bond and release histamine, and so cause urticaria, are numerous and diverse. They may be grouped as follows (Paton, 1956): (1) the complex formed by the interaction of antigen and antibody; (2) certain toxins, venoms, and proteolytic enzymes found in a wide range of animal and plant tissues; (3) many substances of high molecular weight such as certain proteins, dextran, and polyvinylpyrrolidone; (4) surfactants such as bile salts, Tween 20, and lysolecithin; (5) monobasic amines such as octylamine; (6) certain drugs such as curare, polymyxin, propamidine, and compound 48/80. This last group of drugs is separated and designated histamine-liberators because their action is immediate, uniform, and solitary, and causes no other tissue damage.

The most useful experimental drug in man is compound 48/80, because it may be used to deplete an area of skin of virtually all its available histamine (although more than one injection may be required). If a reaction is produced in an area of skin treated in this way, one may conclude that histamine plays no part in it.

In spite of the wide range of agents capable of releasing histamine, their mode or modes of action are still in dispute. The main theories are: (a) enzymatic via protease, esterase, or lecithinase activity; (b) blocking of an inhibitor which is normally present to prevent lysis of the phospholipid membrane of the granule and/or cell; and (c) competitive displacement of histamine from its link with heparin or a peptide.

All of these suggestions and others have evidence for and against them. One of the difficulties is to explain how histamine is released without any apparent cell damage, as well as after granule discharge and cell disruption. But knowledge of histamine release must be preceded by knowledge of the state in which the amine is held in the mast-cell granule, bearing in mind that there may be more than one. And until the mechanisms of histamine release are better understood the full details of an urticarial reaction will remain speculative, and rational therapy cannot be devised.

The Eosinophil Leucocyte

Although certain blood and tissue cells containing especially large granules in their cytoplasm were previously recognized and described by Wharton-Jones to the Royal Society in 1846, it was again Paul Ehrlich's use of aniline dyes which enabled him to define and name them as eosinophils. The great size of the granules in the eosinophil leucocyte of the horse makes it ideal for the study of these cells, and hence it is not surprising that they have been subjected to special investigation by a veterinary scientist, Dr. R. K. Archer, at the Equine Research Station of the Animal Health Trust at Newmarket. After surmounting numerous difficulties he has devised a method for separating and concentrating eosinophils from whole blood of both man and animals (Archer, 1963). Special centrifuge tubes are required, but with them the cells can be obtained in a state of about 80% purity. Isolated eosinophils can then be ruptured and fractionated. There are about 85 granules per cell. Each granule is believed to consist of a central core of arginine-rich protein surrounded by a phospholipid cortical layer (which stains with eosin), and then covered with an outer layer of phospholipoprotein containing sphingosine (Vercauteren, 1953). Several enzymes are present in the granule, including a peroxidase which differs from that of other leuco-

cytes (Archer and Broome, 1963), lactic dehydrogenase, phosphoglucanase and glucose-6-phosphate dehydrogenase, and adenosine triphosphate diphosphorylase. The hexosemonophosphate shunt and not the Krebs cycle provides aerobic respiration.

In contrast to the relatively fixed nature of tissue mast cells, eosinophils are motile like other leucocytes. Most of them normally reside in the bone-marrow, the concentration there being about three hundred times that of the blood. Their distribution in tissues throughout the body is quite different from mast cells, and hence it might be thought that they have little relation to one another. In fact, they show a remarkable interrelationship, for degranulated mast cells attract eosinophils in a most striking way. This is readily seen in a section of a lesion of urticaria pigmentosa of the skin after it has been urticated by rubbing. Welsh and Greer (1959) have watched and recorded the phagocytosis by eosinophils of mast-cell granules after their release by 48/80 in the peritoneum of the rat.

An intravenous injection of heparin will produce a rise in the blood eosinophil count, while corticosteroids will suppress it (Godlowski, 1951). Adrenaline also suppresses the level, but presumably exerts this action via the corticosteroid pathway. Steroids have no effect on eosinophils *in vitro*. The eosinopenia induced by A.C.T.H. relates to the circulating blood only, since the cells in the marrow are not depressed, and hence it is likely to be secondary to a reduction in circulating histamine.

An injection of histamine into the skin results in a local tissue eosinophilia. Archer (1960) examined injection sites at intervals of one, three, and twenty-four hours and showed that graded doses of histamine produced a graded eosinophilic response with a maximal effect from 100 μ g. The tissue eosinophilia falls off over about five days. The cellular response appears to be as standardized as the weal from histamine, and it can likewise be inhibited by mepyramine. It is not, however, inhibited by corticosteroids, which suggests that the mode of action of therapeutically administered corticosteroids in urticaria differs from that of antihistamine drugs.

Histamine is normally removed from the circulation very rapidly via the lung and the gut, both tissues being rich in deamination enzymes, as well as being normal sites for eosinophils. It is excreted in the urine as 4-imidazole acetic acid.

The repeated daily injection of histamine into skin at the same site does not result in a weal after the first occasion. As has been mentioned, a tissue eosinophilia results and lasts for several days. The cells act as inhibitors of further weals, and hence may be regarded as antihistaminic. Both in the horse and in man (Bruce and Archer, 1962) it has been shown that prior injection of eosinophils into the skin will completely prevent the oedema-producing effect of both histamine and serotonin. The latter substance does not play any part in this eosinophil-histamine reaction since it is not affected by BOL 148 (dibromolysergic acid diethylamide), which is a specific antagonist of serotonin (West, 1957).

The precise way in which eosinophils (and freeze-dried extracts are just as effective) exert their antihistamine effect is uncertain. Drugs like adrenaline are physiological histamine antagonists, while synthetic antihistamine drugs like mepyramine compete for histamine receptor sites in tissues. The eosinophils are probably not competitors in the same way but are more likely to "detoxicate" histamine directly, for Archer (1963) had produced evidence that the cells will do this *in vitro*. Since small quantities of hydrogen peroxide are necessary for the reaction it is likely that the potent peroxidase enzyme systems in these cells are vitally concerned in it.

The eosinophil cell can inhibit two of the effects of histamine—the tissue oedema or weal and the smooth-muscle contraction. It can probably detoxicate or alter histamine by a direct action. Histamine is chemotactic to eosinophil cells. The

local release of histamine in a tissue results in tissue eosinophilia, while the general release of histamine into the circulation results in an eosinopenia. The disappearance of cells in the latter case is only apparent, however, because the cell count in the marrow and in the tissues is high. It is evident that the cell count in the peripheral blood is not an accurate index of eosinophil activity and can appear quite paradoxical. The circulating blood merely acts as a "throughway" from the large stores of the marrow to the sites of action in the tissues, where again the concentration may be large. The cells appear to be disposed of in lymph nodes and the reticulo-endothelial system.

The Blood-vessel

The pathological change which is reflected to the clinical observer as urticaria is the leakage of protein from capillary vessels over a more or less circumscribed area. The walls of capillaries are normally freely permeable to water and electrolytes, but not to protein or cells. The means by which capillaries can allow blood proteins to leak is clearly important. The rate of leakage is at times so rapid that it almost certainly takes place via intercellular channels rather than across the cell membranes. The channels between the endothelial cells of a capillary are estimated to be about 30–60 Å in diameter (quite wide enough for the passage of protein molecules), but they do not total more than about 0.2% of the capillary length (Spector, 1958). This being so, there must be some normal inhibitory device to prevent the passage of proteins outside the vessel. At present it is uncertain whether the control operates by varying the size of the pores or by some alteration in electrical charges around them. A most sensitive way to observe and record the process is by labelling serum albumin with intravenous trypan blue or pontamine blue dye and watching the dye leak out.

In recent years it has been found that a number of other substances, unrelated to histamine but occurring in tissues, can increase capillary permeability to protein. These substances include serotonin, plasmin, a serum-globulin permeability factor, slow-reacting substances, adenosine triphosphate, leucotaxine, bradykinin, kallikrein, the products of proteolysis, and extracts of lymph-node cells (Willoughby *et al.*, 1963). Their actions are mostly independent of histamine, although they may act conjointly with it. How they produce their effect on the capillary wall is not known. Do they play any part in the pathogenesis of normal urticarial reactions? Urticaria and oedema are not features of the carcinoid syndrome, in which large amounts of serotonin are circulating and the latter substance is not present in human-tissue mast cells. Hence, it is unlikely to be a mediator of urticaria. An important substance to be considered, however, is acetylcholine, because of its undoubted involvement in the so-called cholinergic urticarias induced by heat, exercise, and emotion. Most, but not all, investigators have felt that its action is mediated via histamine release (Grant *et al.*, 1936; Perry *et al.*, 1951; Moynahan, 1952; Morgan, 1953).

The principal need for an additional mediator is to explain the continuation of the wealing response in many urticarial reactions after the histamine effect should have passed. Vasoactive peptides are normally thought to be responsible for sustaining inflammatory responses. Some support for the claim of kallidin in this role is supplied by the evidence of an inhibitor of kallidin or the serum globulin factor in cases of congenital angioneurotic oedema (Landerman *et al.*, 1962). In general, however, Sir Thomas Lewis's (1927) contention remains correct, that all urticarial reactions in the skin—the physiology of which he so meticulously worked out—are ultimately mediated by the action of histamine (his H-substance) on the vessel wall, although it is likely that this is not the whole truth of the matter.

One should perhaps also remind oneself that most of Sir Thomas Lewis's studies were concerned with factitious urticaria or dermatographism, presumably because it was so readily reproducible for experimental purposes, and one cannot necessarily extrapolate his findings to all cases of urticaria.

Clinical Approach

When the clinician looks at patients with lesions of urticaria he will discern four main groups which appear to be more or less distinct. There are no agreed labels or definitions for these groups, but they are readily recognized as follows: (1) dermatographism, or hypersensitivity to trauma; (2) urticaria from physical agents; (3) cholinergic urticaria; and (4) "ordinary" urticaria.

Dermatographism

Urticarial dermatographism, or factitious urticaria, is self-explanatory. Violent mechanical stimuli to the skin, such as physical and chemical burns or the lash of a whip, will produce an erythema and an urticarial weal in a normal individual. The abnormal individual produces this response from relatively weak stimulation, such as firm stroking of the skin with a blunt instrument. Lewis (1927) found that 5% of the population showed this feature. But, without wishing to be pedantic, it all depends on what one means by "firm stroking" or "light pressure," or whatever term is used to describe the mechanical force required to elicit it. If the pressure is measured by attaching a weight, it is found that 200 g. or less

FIG. 1.—Relation of weight of stimulus to factitious urticaria.

is effective in dermatographic persons but not in control subjects (Walzer, 1928; Lorincz, 1956). When the weight is increased to 1,000 g. about 20% of control subjects produce the reaction. The response is also to some extent quantitative, a larger weal being produced by the greater stimulus. Hence, there appears to be a gradation from a normal physiological to an abnormal pathological response to this type of mechanical stimulus (Fig. 1).

Two other points are relevant. First, is there any aetiological relation between dermatographism and clinical urticaria? The lack of standardization of the eliciting stimulus probably accounts for the varied answers to this question (from 6% to 100%), but I believe the correct answer is "no." I agree with Fisher and Schwartz (1953), who found that 6 out of 100 patients with urticaria were dermatographic, compared with 5 out of 100 patients with other cutaneous disease. Dermatographic patients rarely show lesions of ordinary urticaria.

The second question is whether or not dermatographism is allergic—that is, antibody-mediated. Passive transfer tests with serum are usually thought to be the most effective way of answering this. In more than half the cases in which it has been attempted the result was unequivocally positive (Walzer, 1928; Lorincz, 1956; Rothman, 1956). And Shelley (1963) obtained a positive basophil degranulation test in four cases.

The production or activation of antigens in the skin by physical stimuli has been strongly argued to explain hypersensitivity to physical agents, but it has not yet been effectively proved that the transferred material in these examples of positive Prausnitz-Küstner tests is antibody and not some other mediator of histamine release.

Physical Urticaria

In the group of physical urticarias are included those due to the direct local action of light, heat, cold, and pressure. Urbach (1946) found 88 such cases out of 500 urticaria patients. Each of these physical agencies may produce wealing by more than one mechanism, which can often be recognized by the clinician. The methodology of testing is important, however, to ensure accurate diagnosis.

Urticarial hypersensitivity to heat may be a purely local (non-cholinergic) response and is readily elicited at will by application of a test-tube containing hot water. The generalized response to heat is the separate type described as cholinergic urticaria.

Urticarial hypersensitivity to light or solar urticaria may have its action spectrum in one of four spectral ranges—namely, 3,100, 3,700, 4,000, and 6,000—or rarely show no specific wavelength sensitivity. In a minority of cases a chemical substance such as a porphyrin can be shown to be responsible for inducing it. Whether the reaction has an immunological, photodynamic, phototoxic, or other basis remains unproved, although it is likely that more than one mechanism can be responsible.

Urticarial sensitivity to cold, like that due to heat, may be local or general, although the pathogenesis is usually quite different. A wide range of systemic disorders can be found responsible for the generalized type as a result of the presence of cryoglobulins in the serum (Gilliland, 1949), but other clinical features, such as Raynaud's phenomenon, purpura, and ulceration, are usually associated. Urticaria also occurs with syphilitic paroxysmal cold haemoglobinuria, but it is not related to the presence of cold agglutinins in the blood.

Idiopathic, or so-called essential, cold urticaria may be congenital or acquired. The congenital form is often familial and is inherited as a non-sex-linked Mendelian dominant. The acquired form may begin at any age. A wide variety of triggering "events" have been reported to precede it—such as infections, pregnancy, serum injections, and so on. In most cases the reaction is limited to the area of skin exposed to the cold air, water, ice, or other agent, but in severer cases it may be generalized. As in heat urticaria, the afferent stimulus travels in the blood-stream from the cooled skin, and the reaction may be associated with the signs of general histamine release, anaphylactic shock and death being a rare but well-documented event.

Pressure urticaria from a mild or moderate stimulus is the phenomenon of dermatographism. In certain individuals, however, localized wealing follows heavy or prolonged pressure. The pressure required is at least 14 lb./sq. in. (1 kg./sq. cm.). The stimulus may be short, such as hand-clapping, or prolonged as in sitting on a hard chair. A feature which separates it from all other types is the long latent period, which is four to six or even 24 hours. A patient with pressure urticaria (kindly referred to me by Dr. F. F. Hellier, of Leeds) told me that it could be induced by running, clapping, sitting, leaning over a rail, or kissing.

All these types of physical hypersensitivity have some features in common. They are mediated via histamine and show a local refractory state. They are not infrequently associated with other physical or non-physically induced urticarias. Although passive transfer tests may be positive in more than half of some types (cold), this cannot be taken as certain proof of the presence of antibody. None of them can therefore be regarded as

unequivocally allergic in the strict immunological sense. It is salutary to note that little or nothing has been added to our knowledge of these physical phenomena since the work of Duke in 1924 and Grant *et al.* in 1936 (Kierland, 1953).

Cholinergic Urticaria

Some 30 years ago the late Dr. H. W. Barber, of Guy's Hospital, was impressed by three patients whose urticaria could be produced at will by heat, exercise, or emotion. He referred them for investigation to his colleagues, Grant, Pearson, and Comeau, who published their classic paper in 1936, although a number of similar cases had been recorded previously. The clinical appearance of this type of urticaria is recognizable in that it consists of small even-sized weals (a few millimetres in diameter) and a large flare. It may be elicited by raising the body temperature by 0.2 to 1° F. (0.1 to 0.6° C.), by physical exercise, hot food or drink, alcohol, or emotional "heat." It is commoner in men than in women, and the peak incidence is in adolescence and young adults. A small number of the patients are dermatographic and may react to cold, pressure, or direct heat, or have ordinary chronic urticaria. The usual duration is a few years, but it may be two decades or more. Severe attacks can be accompanied by faintness, dizziness, palpitation, cramps, and vomiting.

Grant *et al.* (1936) showed that the afferent stimulus travels in the blood-stream to some centre in the brain, but in emotional cases the stimulus evidently originates in the cerebral cortex. The response is mediated from the central nervous system via the efferent cholinergic nerves. Herxheimer (personal communication, 1963) believes that the pathway is via the sympathetic nerves. The lesions can be induced by choline esters and pilocarpine and inhibited by atropine. Positive passive transfer and direct skin tests to lactic acid (0.1 ml. of 1% aqueous solution) have been recorded in cases of this type of urticaria from exercise; it is suggested that the patients are hypersensitive to the lactic acid produced by muscle activity (Herlitz, 1949).

Cholinergic itching and erythema without weals are variants of the syndrome. When this is appreciated it is found that the condition is by no means rare. In a survey of 1,083 university students, Herxheimer (personal communication, 1963) found an incidence of about 20%. There is evidence that its onset is associated with a change in the thermo-regulatory mechanism either as a result of the transition from childhood to adolescence at puberty, or in climatic conditions as in the transfer from a tropical to a temperate climate (Sigel, 1948). Perhaps the best way to regard it is as an exaggeration of the normal physiological response to these stimuli.

Ordinary Urticaria

This group essentially comprises all the cases which do not fit into the other three groups. As such it is something of a rag-bag and is by far the largest group; but, as with other medical and cutaneous disorders, small well-defined subgroups are from time to time separated off. The clinician separates these patients into acute and chronic, the distinction being made arbitrarily by the duration period, varying from one to six months or more according to choice.

Patients with acute or short-duration urticaria may at once be divided into (a) those in whom the reaction occurs within seconds or minutes of exposure to the supposed cause, and (b) those in whom the reaction occurs hours or days after such exposure.

The reaction in the first group is almost certainly antibody-mediated, and skin tests, passive transfer, and re-exposure tests are normally positive. Most, if not all, of the patients who

show this are atopics—that is, those special genetically susceptible persons who produce reagin-type antibody.

Evidence for antibody in the second group is hard to come by. Skin tests and passive transfer tests are negative. Re-exposure tests also are frequently unsuccessful. Wide variation in clinical responses is characteristic of this group, for which several explanations have been offered (Paulsen, 1961): (a) only large quantities of the foodstuff may contain an eliciting dose of allergen; (b) the mode of cooking may inactivate the allergen; (c) repeated meals of the foodstuff may be necessary to accumulate enough of the allergen; (d) one attack may induce a long refractory period in which the same allergen is ineffective; (e) the addition of multiple subclinical sensitivities may be necessary to evoke a response; and (f) the vasodilator effect of alcohol may be necessary to facilitate absorption of the allergen.

Although patients' histories may be quoted to support these plausible suggestions, none of them is very convincing when viewed against our knowledge of reagin-sensitivity. The more likely interpretation is that none of the cases of "delayed" acute urticaria are allergic in the strict sense, but are examples of direct histamine release. A number of foodstuffs have been shown to produce, after enzymatic digestion, polypeptides which are potent histamine liberators (Paton, 1956; Schacter, 1956). Not infrequently the particular foodstuff has been eaten to excess, or its "freshness" or mode of cooking has been questionable. Such a thesis would explain the variability of clinical response.

These considerations are pertinent also to some instances of urticaria following drugs, especially aspirin, as I shall mention later.

Chronic Urticaria

Chronic urticaria is not to be regarded as a disease *sui generis* but as a symptom-complex. The large number of patients in this group comprise the hard core of the urticaria problem. One may say at once that in almost all of them a cause remains undiscovered or not proved. Hence it is not surprising that almost every pathogenetic mechanism has been invoked by clinicians, including infection, physical and psychic trauma, metabolic and endocrine disorder, allergy, and autoimmunity. The evidence is rarely more than circumstantial, although this is not to imply that each of these mechanisms may not at times be responsible in any individual case. It is to be noted that allergists no longer emphasize the allergic nature and many do not even bother to skin-test these patients (Frankland, 1963). All that can be said is that the urticarial syndrome is likely to be the result of histamine release from mast cells. It is seen in association with a wide range of disease states, ranging from infections to metabolic disorders, inflammatory damage to tissues, neoplasia, and autoimmunity as in systemic lupus erythematosus. But in the majority of patients no close association with another disease state is recordable. Its natural history is variable and cannot accurately be prophesied. Its duration may be some months or more than 20 years. Its course may be continuous or intermittent, with remissions lasting a few weeks, months, or many years. The disorder is susceptible to aggravation by a number of non-specific stimuli such as heat, the menses, and certain drugs, the most striking of which is aspirin (Calnan, 1957; Warin, 1960).

Allison (unpublished) found that one-third of a series of chronic urticaria patients were aspirin-"sensitive" in this way. More interesting was his finding that when the urticaria ceased the patient was no longer aspirin-sensitive. The effect is quantitative rather than qualitative and may be induced in a number of patients with a large dose of the drug. Aspirin is rarely the sole cause of urticaria, just as it is rarely the sole cause of asthma or hay-fever, in which the same phenomenon is encountered. I have noted a similar effect produced by penicillin in cases of

chronic urticaria, and this also is seen in asthma.¹ Skin tests with aspirin are virtually always negative (positive skin and passive transfer tests have been recorded), and the sensitivity is curiously specific in that it does not extend to sodium salicylate, salicylic acid, acetamide, or para-aminosalicylate. A dramatic effect of this type from aspirin was recorded by Hamrin (1957) in a patient with extensive mast-cell disease (urticaria pigmentosa) who developed severe flushing, vomiting, and collapse after aspirin. It is likely that aspirin is acting non-specifically as a histamine liberator in a particularly vulnerable person, although evidence has not been produced to show that these patients are more sensitive to all histamine liberators (their skin is not more sensitive to histamine itself), although the threshold for 48/80 is lowered in acute urticaria (Juhlin and Rune, 1962). This does not, however, invalidate the thesis.

Salicylate has an exceptionally wide range of effects on enzyme systems. It has been shown to interfere with many dehydrogenases and transaminases as well as the synthesis of glutamine, oxidative phosphorylation, and the supply of phosphate compounds. In addition it will block the action of Trafuril, bradykinin, and nicotine. These effects, however, are non-specific and may be revealed only under conditions of abnormal cell-metabolism.

Interpretation

How, then, is one to interpret the disease state or syndrome of urticaria? When Sir George Pickering (1950) was analysing the causes of disease in considering the influence of Hench's discovery of cortisone in relation to rheumatoid arthritis, he said that "the state in which the animal finds itself at any time is determined by two prime factors—its inherited constitution and the effects of its environment, past and present." The common causes of disease thus include (1) in-born or inherited abnormalities; (2) the effects of excess of a chemical agent in the environment; (3) the effects of a deficiency of a chemical substance; (4) infection or infestation by viruses, bacteria, fungi, or animal parasites; and (5) physical trauma. Examples may be quoted of urticaria being caused by each one of these agencies and many more that are not so caused. Pickering commented that an appreciable number of disease states could not at present be fitted into any of these categories. Dowling (1958) has emphasized that a large number of dermatological maladies are equally unclassifiable on these grounds; and it is particularly these disorders for which the concepts of focal sepsis, intestinal stasis, the seborrhoeic state, the psychosomatic origin, the general adaptation syndrome, and autoimmunity have been put forward to explain. Pickering and Dowling are equally sceptical of such approaches, and there is no doubt that one would be wise to view them with caution rather than with enthusiasm.

There are some functional deviations from normal health which can be readily induced in virtually any normal individual. No special genetic predisposition appears to be manda-

tory for their induction, although (as George Orwell might have said) in some individuals the induction is more easily achieved than in others. The deviation from health may also be either short-lived or temporary, and capable of complete reversion unless some secondary damage takes place. Examples of such disorders are bronchial spasm (asthma), epilepsy, stammering, eczema, urticaria, and perhaps acne. These functional deviations also tend to show the phenomenon of self-perpetuation. After one or more attacks the patient's condition no longer reverts to normal when the evident cause is removed. The abnormality of function appears to become a habit—a chronic state (Fig. 2). This event occurred in 10 of Warin's (1960) 70 patients with urticaria. Such a state may last for months or years, but eventually tends to revert to normal. It can be inhibited by corticosteroids or specific blocking agents.

FIG. 2.—Cycle of events going on to chronicity (see Text).

In a number of instances there is no perceptible transition from the normal or physiological adaptation state to the abnormal or pathological response. For example, some degree of seborrhoea and comedones may be considered as much a physiological response to the normal androgenic stimulus of puberty as the growth of sexual hair or an alteration in a boy's frontal hair line. As I have mentioned already, the most logical interpretation of cholinergic itching and urticaria is to regard it as an exaggeration of the physiological reaction of the cutaneous vascular system to thermo-regulatory mechanisms, some such manifestation of it being found to occur in about a quarter of normal people after puberty.

It is now widely acknowledged that similar or identical disease states may be the consequence of more than one of the causes listed by Pickering (1950), and this has given rise to the concept of reaction-pattern disease which is particularly frequent in the skin—for example, erythema nodosum, erythema multiforme, acne, and urticaria—although it undoubtedly occurs in other tissues—for example, asthma, epilepsy, lupus erythematosus syndrome, and hepatic cirrhosis. The disease state is, as it were, the observed end-result of a number of agents which exert their effect along a common pathway, either in different patients or in the same patient at different times. The "common path" leading to urticaria is the release of histamine from mast cells and its action on the small blood-vessels in the skin.

Urticaria is a very common disorder. It has been estimated that more than one in five of the population will manifest it at some time in their lives (Swinney, 1941). Women are more likely to be affected than men in the ratio of three to two; which is what one might expect in view of their greater cutaneous vascular lability, especially during the reproductive years. The age incidence is greatest in the third and fourth decades of life (Table I).

TABLE I.—Age Incidence in 500 Cases of Urticaria (After Urbach, 1946)

Age	0-11	11-20	21-30	31-40	41-50	51-60	Over 60
Incidence ..	Rare	8%	33%	25%	14%	8%	Rare

On the arbitrary basis of dividing cases into acute and chronic at three months' duration, there are equal numbers of each (Table II).

Many cases persist for several years. A family history of eczema, asthma, hay-fever, or urticaria is not frequent, Urbach

¹ Other explanations also merit attention. De Weck and Eisen (1960) stated that the antigen in penicillin-sensitivity must be a stable hapten-protein conjugate. They found that derivatives of penicillin such as penicillenic and penicilloic acids could form such conjugates, whereas the parent drug could not, and believed that these were the antigenic determinants. Cronin and I have so far had no success with their penicilloyl-polylysine conjugate as a test antigen, and it has fallen short of our expectations.

In a most interesting clinical study of immediate-type sensitivity to amidopyrine, Halpern (1958) demonstrated reagin-type antibodies by skin test and passive transfer. The drug apparently reacted direct with the antibody without prior conjugation with a protein, but it could be dissociated from it by a simple dialysis. This is reminiscent of the Sedormid (apronal)-platelet association producing thrombocytopenic purpura, and indicates that dissociable unstable linkages between low-molecular-weight chemicals and proteins may cause immunological reactions. The formation of this type of loose chemical bonding may also be a less-permanent facility and account for the loss of sensitivity, which is said to be so frequent with penicillin, and may be the reason for the easier desensitization after a lapse of a year in Borrie's (Borrie and Barrett, 1961; Borrie, 1963) patients with extreme sensitivity to the drug.

(1946) finding it only in 15%, although some striking pedigrees have been described.

TABLE II.—Duration of Urticaria in 500 Cases (After Urbach, 1946)

Duration Incidence	1-12 weeks 50%	3-12 months 19%	1-5 years 20%	6-10 years 4%	11-20 years 1.5%

There is a disparity between the views of allergists and dermatologists regarding identifiable causes. Urbach (1946) states that the cause was found in 88% of his 500 cases, 117 of which were allergic. On the other hand, Hopkins and Kesten (1934) could total certain and probable causes in only 21 (10%) out of 214 cases of chronic urticaria. Many dermatologists to-day might well regard even this as an optimistic estimate, and will freely admit that they rarely find a precise cause for almost any case of chronic urticaria. Nevertheless, a persevering search for such a cause can be fruitful, as illustrated by Shelley and Florence's (1961) patient with chronic urticaria and mycotic infection associated with extreme sensitivity to trichophyton and mould allergens.

Conclusions

In my own mind I regard urticaria as the analogue of eczema or dermatitis. It is a valuable principle to regard eczema as a manifestation of delayed-type hypersensitivity until proved otherwise, even though one is well aware that there will be no supportive evidence in many instances. In the same way, each case of urticaria should be regarded as a manifestation of immediate-type hypersensitivity until proved otherwise, although we may now believe that the majority are not allergic. These two types of reaction in the skin—eczema and urticaria—are probably more often produced by non-immunological mechanisms. All individuals can manifest them. They are non-specific reactions. The allergic and non-allergic variants can be histologically indistinguishable. They may wax and wane and show remissions and relapses. They are capable of complete reversibility, but they may show self-perpetuation into a kind of habituated state. In such a state the threshold of response to many stimuli is lowered—the so-called status eczematicus in the case of eczema and status urticatus in urticaria. Both reactions may reflect metabolic disorders—phenylketonuria, intestinal malabsorption, Aldrich's syndrome, and acrodermatitis enteropathica in the case of eczema; and in urticaria the enzyme deficiencies of congenital cold urticaria and familial angioneurotic oedema.

At the present time our state of knowledge in regard to both eczema and urticaria is at about the same stage. A great deal has been learnt in the past two decades about the mechanisms involved in the production of the reaction at the cellular level, both by immunological and by non-immunological pathways. Clinical study has classified the patients largely on morphological and supposedly aetiological grounds. But the gulf to be spanned between the two areas of knowledge—namely, relating the cellular mechanisms to the clinical state of the patient—seems as wide as ever for both eczema and urticaria. Perhaps more new thoughts and ideas will evolve to bridge the gap so far as urticaria is concerned in the next decade than in the 13 years since the death of Dr. Watson Smith.

Summary

Because of its association with serum sickness, urticaria has been regarded as a primarily allergic reaction since von Pirquet's original work. Although the urticarial lesion could be replicated with histamine, the Prausnitz-Küstner reaction appeared to confirm the role of antibody.

Current knowledge of the physiology and pharmacology of the mast cells, the eosinophil leucocyte, and the small cutaneous

blood-vessels has shown that the urticarial response is the consequence of histamine release from mast cells, and that serum-type antibody is only one of the many agents which can effect this release.

Patients with urticarial reactions may be divided on clinical grounds into four groups: (1) dermatographism, (2) physical, (3) cholinergic, and (4) "ordinary." They are all dependent and histamine-released from mast cells, though the mechanisms of inducing this process in response to stimuli are different. Chronic "ordinary"-type urticaria may depend on a varying susceptibility of the mast cell to histamine-releasing agents, rather than on the presence or absence of specific inducing substance.

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