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Urticaria

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by

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PREFACE

The purpose of this paper is to acquaint the student with the disease known as urticaria. It is written from the point of view of one who is relatively unfamiliar with the phenomon and it will therefore, be elementary.

Through the reading of the literature necessary to prepare this article the student hopes to gain a foundation for further study and understanding of allergical manifestations in general, and of urticaria in particular. There is no thought of writing a paper which will be of any benefit to the physician experienced in this field.

The thesis will deal with urticaria in general, except in rare instances when it is necessary to refer to a specific type of that condition. Discussing each variety in detail would lead to a lengthy article that would require experience and more time.

Angioneurtic edema will be included as an urticarial phenomen and not as a separate allergical manifestation.

Material for this work has been gathered exclusively from literature written in the English language and appearing in the University of Nebraska Medical College Library. Some abstracted translations of foreign

authors have been included. It is to be regretted that much of the early work in urticaria was carried out by foreign authors and their original articles could not be utilized.

FOREWORD

When reading the literature on the subject of urticaria one is impressed with the amount of discussion of general allergy interspersed in it. The two are so closely related that it is impossible to discuss urticaria without a superficial preliminary review of allergy.

Allergy is a comparatively modern word introduced by von Pirquet in 1907.[6] Since then it has been popularized by such authors as Duke, Vaughan, Balyeat, Coca, Rowe, van Leeuwen, and others who have assumed leadership in this field.

Von Pirquet defined the term as the sensitization of an organism so that its cells are temporarily or permanently altered, in such a manner that they have become susceptible to formerly harmless proteins. This definition coincides with, or is similiar to, definitions of certain other words. Included in these are anaphylaxis, introduced by Richet; serum sickness ; protein sensitization, first used by Vaughan; specific hypersensibility; atopy, originated by Coca; and hypersusceptibilty. Undoubtably, several of these headings have been used by different men in discussing the same phenomenon and different phenomena may have been classified under the same heading.

Doerr, Coca, Wells, and Zinsser insist that the terms anaphylaxis and allergy should not be interchangeable. They define anaphylaxis as an antigen-antibody reaction, while allergy is a broader term including anaphylaxis and also reactions of altered reactivity in which no antigen-antibody reaction is demonstrable. Most authors agree that this conception is correct, as will be shown in later statements.

Hekoten amplifies the variation in the words that allergy is a peculiar toxic reaction depending on the uniformity of the offending protein; in anaphylaxis there are constant symptons regardless of the proteins used.[98] Storm van Leeuwen points out further differences in the two phenomena; allergy is familial while anaphylaxis is not; allergy is introduced in experimental animals with difficulty and anaphylaxis occurs readily; patients may show symptons of allergy the first time they contact the offending substance but anaphylaxis is never present at the first contact.

We will accept the general opinion and use the two words discriminately. Allergy is derived from the Greek and means altered energy of altered reactivity. Anaphylaxis, as suggested by Richet, came from his animal experiments.[6] He found that antitoxin injections protected against death (prophylaxis), while some injections led to death (anaphylaxis).

The modern conception of allergy is a condition in which an individual is hypersensitive to foreign agents which are not in the least bothersome to normal individuals. Such a patient may react violently to any material which he is susceptible to, as foods, drugs, pollens, hair, feathers, smoke, vapor, volatile oils, sera, insect bites, bacteria, toxins, light, heat, cold, mental or physical exertion. Certain of these tend to produce specific symptons but may give rise to diversified syndromes which are indistinguishable from such pathology as peptic ulcer, gall bladder disease, chronic appendicitis, bladder irritation, kidney colic, epilepsy, sinusitis, chronic bronchitis, dysmenorrhea, arthritis, sour stomach, itching piles, canker sores, chronic hoarseness, skipping of the pulse, dizziness, and scaling ears.[6] It is generally accepted that allergy is the essential factor in urticaria, asthma, hay fever, angioneurotic edema, and many cases of migraine.

The variations in the symptons probably depends on the constitutional make-up of the individual (the hereditary factor), the qualities and characteristics of the alien body exciting the reaction, and its mode of entry. The definite factor in the constitutional make-up of an individual that causes him to be allergical is not known but most patients have a hyperirritability of the autonomic nervous system. The latter

supplies muscles of the eyes, glands, bronchi, and gastro-intestinal tract. It is opposed by the action of the sympathetic system. It is possible that the autonomic system is thrown into activity by the exciting agents, in allergic patients, and results in the symptons described. The relation of the autonomic system to urticaria will be discussed in some detail, later.

There are a few definitions that should be given to clarify succeeding discussion. It is desirable to compare allergical reactions to immunological phenomena as the two have many analagous points. In immunology we speak of an antigen and an antibody. In allergy we use the term allergen (comparable to antigen) to designate those substances which provoke the formation of reactive substances in the body tissues that will combine with said allergen upon its second administration to produce symptons of allergy.[6] However, a term analagous to antibody has not been successfully introduced into allergy. (Reagin, is used infrequently to designate the reacting substances).

A "sensitizing protein " and "atopen" are analagous with allergen. Hypoallergesis is the process of becoming less sensitive to allergens in general, usually as the result of treatment. A hypoallergesic is a medicianal agent which possesses the ability to pro-

duce hypoallergesis.

With these few facts concerning allergy in general we will attempt to discuss one of the specific phases of allergy, the phenomenon of urticaria.

HISTORY

The word urticaria has been used in English medical literature since the advent of periodicals, as far back as the early years of the nineteenth century. It was derived from the cognomen of the stinging nettle plant, urtica, which brushed against the skin produces raised, pale, itching blotches or hives. Skin reactions resembling this rash were designated as urticarias because of the similiarity.

Urticaria doubtlessly existed in the human race long before it was designated as such. Vaughan believes it has been a disease since the advent of man, basing his assumption on the fact that it can be produced in lower animals.[6]

The ancients seem to have classified all skin lesions under the headings of leprosy, scrofula and eczema; it is possible that urticarias were described under one of these terms. Storm van Leeuwen offers the interesting suggestion that the Hebrews may have omitted pork from their diet because it was quite often an exciting agent in urticaria, and the latter has never been a condition to cultivate.

Due to this lack of detailed description of skin conditions we cannot trace urticaria definitely to antiquity, but must begin where man first differentiated it from other cutaneous reactions. These earliest observations on urticaria were in no way

connected to the unheard of phenomenon of allergy. The authors spoke of lesions which resembled the urtica rash and suggested that they were due to contact with alien substances, especially foods.

In 1830, there appeared an article entitled, "Urticaria: Importance of Diet", in the London Medical Gazette. It was authored by F.Badgley and described how a case was cured by use of baths and cathartics.[126] Mac Farlane in 1833 published an account of the prevalence of urticaria as an epidemic in London. Gull, Purdon and others published cases of urticaria at about this time.

It was not until experimental work was started towards the close of the nineteenth century that the true nature of urticaria was suspected. The earliest works having a bearing on urticaria were primarily concerned with anaphylaxis.

That which we now designate as anaphylaxis was first observed by Jenner.[101] Majendie also noted this phenomenon at about the same time, 1839. In 1894, von Behring discovered diphtheria antitoxin and this led to investigations with guinea pigs. Strange results were obtained; some of the pigs survived the first tests but died in a few minutes after recieving the second injection. Koch's observation that

tuberculous guinea pigs were more susceptible to injections of tubercle bacilli than were normal animals was one of the first actual applications of this phenomenon of anaphylaxis.[101]

Richet, a Frenchman, was the first real student of anaphylaxis. At the beginning of the twentieth century he was working with poison of the sea anemone and found that a second injection of this toxin would kill a dog, although the first injection appeared to be harmless. He then tried egg albumen and found that the second injection of this was also fatal.[6] He then introduced the modern word of anaphylaxis to designate this reaction. The works mentioned of course do not deal directly with urticaria, but it was throuth these early efforts that urticaria was later linked to allergy.

Shick and von Pirquet were the men who brought anaphylaxis into relation with cutaneous medicine. The latter suggested allergy as a term analagous to anaphylaxis, and also substantiated Wolff-Eissner's belief that urticaria was to be included among the allergical manifestations.[98] His work with tuberculin suggested a method by which sensitization to various proteins could be clinically determined.

Smith and Schloss utilized this fact and started

using skin tests in diagnosis. Schloss, in 1912, recorded skin reactions to definite foods and later stated that urticaria and angioneurotic edema were the most frequent symptons of food allergy.

Later workers have definitely established the relationship of urticaria and allergy, and have thrown much light upon the etiology, symptons and treatment of that skin condition. Walker, Cooke, Rowe, van Leeuwen, Highman, Rackemann, Lewis, Walzer, Brown, Duke, Balyeat are only a few of the men who have contributed to this work. Lewis' efforts have been especially beneficial in studying the etiology. Duke has made contributions covering all phases of urticaria. A.andM. Walzer have worked on many experiments in attempting to explain urticaria.

Although the efforts of these men have been extensive the true nature of urticaria is still obscure and new chapters will be added to the history, year by year.

CLASSIFICATION.

The classifications offered for urticaria have been unsatisfactory due to the general confusion regarding etiology in this field.

Early authors evidently made little attempt to classify the condition, other than by its duration

(acute and chronic). Willan recognized six clinical forms. Two were acute, febrilis and conferta; four were chronic, evanida, perstans, subcutanea, and tuberosa. Crocker described three primary types, acuta, chronica and papulosa. Subvarieties were offered to describe the clinical picture, tuberosa, bullosa, hemorrhagica, factitia, and edematosa.[100]

In 1917, Sutton published a similiar classification with acute, chronic and pigmented forms. For the first time urticaria factitia was recognized and placed as a subvariety of the acute, along with papulosa, tuberosa, bullosa, hemorrhagica, gigans, and edematosa. The chronic urticarias were listed as recurrens and perstans. The pigmented forms were subdivided into mast-cell and mast-cell free types. Unna had demonstrated these mast-cells in many lesions while other authors showed that some pigmented forms did not have mast-cells. These arrangements were too detailed.

A few years later, G.L.Lambright decided that proteins were the etiological factor in most urticarias but that some of these reactions were occuring in non-protein sensitive patients. He formed a classification using that supposition as a basis. The non-sensitive to protein group included neuropathic,

chemical and constitutional factors as the etiological basis. The sensitive to protein group was subdivided into seasonal factors (pollens, bacteria, foods, animal proteins) and non-seasonal (foods, bacteria, animal proteins).[91] Here was an arrangement with etiology as the framework rather than the clinical pictures formed by the various lesions. However, his groups could allow the same lesion to be placed in either one or the other.

Stellwagon suggested the terms chronic, factitia, giant, papulosa(lichen), hemorrhagica, and bullosa to differentiate the various urticarias.[2]

Hallam, in 1928, published a simplified arrangement with all urticarias under four large groups, i.e. factitia, acute, chronic, and papular.[56]

At about the same time Duke propounded his theory of physical allergy, with "contact" and "reflex-like" reactions.[60] This phenomenon also causes a type of urticaria which should be definitely listed.

Another reaction which is not included in many lists is angioneurotic edema. Most authors agree that it is a form of urticaria or at least is due to identical or very similiar factors. This term has many synonyms that have been used at various times to describe the same condition; included in these are

giant, tuberosa, Quincke's edema, and wandering edema.

If we concede that all urticarias, or most all of them, are on an allergical basis, it is hardly necessary to attempt a classification according to their exciting factors, as Lambright did. Rather that they should be arranged according to the clinical pictures which they present. The following modified arrangement of Hallam's might be useful:

1. Urticaria acuta
2. Urticaria chronica
3. Urticaria hemorrhagica
4. Urticaria pigmentosa
5. Urticaria factitia
6. Angioneurotic edema
7. Lichen urticaria

The first two headings would include all of the more common forms of urticaria, regardless of their etiology, whether due to physical allergy, to proteins, to foods, to drugs, to animal danders, to pollens, or to any of the numerous alien substances mentioned as causes of urticaria. It would simply serve to differentiate the disease as to whether it was a long standing condition or a new and unusual affair in the patient's life.

If the rash possessed certain outstanding characteristics, regardless of its acuteness or chronicity, it would be placed in one of the other groups.

When hemorrhages into the skin accompanied a positively diagnosed urticarial rash the term hemorrhagica would be applied.

Urticaria pigmentosa would refer to the disease of children in which there was a pigmented condition of the skin that had been preceeded by a typical urticaria.

Lichen urticaria would designate the rather chronic papular urticaria which is likewise most common in children.

Urticaria factitia would apply to cases where the phenomenon of dermatographism was present.

Angioneurotic edema would represent the cases where massive edematous lesions appeared. At present there are to many terms used to describe this manifestation.

Such a classification would not clear up any confusion that now exists but it would give the student a working basis for recognizing the various types of urticarial lesions.

ETIOLOGY

When one attempts to write down the etiology of urticaria he realizes the confusion and complexities that have resulted from innumerable experimental and theoretical works, all of which have been authored by different men, each attacking the problem from a different angle.

One can find many specific substances which are definitely proved to have excited attacks of urticaria; and many conditions which have been shown to be present in patients at the same time they have the urticaria. He reads articles in which the author presents a single isolated case and attempts to show that the factor therein discussed is responsible for the urticaria. The diversity of the character of these alien substances suggests there are innumerable exciting agents and numerous predisposing conditions which will play a part in the causation.

But is there a single, fundamentally basic factor that can be found in the make-up of the hypersusceptible individuals which allows such substances to initiate an urticarial rash, although the same substance will not effect another person? Why do not the hypersensitive patients all respond to the same exciting factors if there is a basic reason for the reaction ? It is possible that the conditions

grouped under the title of urticaria, because of the resemblance of the clinical pictures and pathology, do not have directly related etiological factors.

The problems suggested will be discussed in the following paragraphs. The etiology will refer to urticarias in general except where it is necessary to discuss one of the specific varieties.

Figures regarding the incidence of urticaria are not numerous but we know that is very common , as evidenced by the many advertisements of patent medicines guaranteed to cure the hives. J.G.Tomkinson reported 14,370 skin cases of which two-hundred were urticarias. Of these, ninety were acute and chronic, one-hundred and two were lichen urticaria, six were angioneurotic edema, and two were urticaria pigmentosa.[75] Balyeat reported a series of one-hundred and eighty-eight cases.[1] Duke, Vaughan, Rowe, Rackemann, and others have reported rather large series.

From the work of these authors we find that age and sex play an important role in urticaria. In Tomkinson's series there were twice as many females suffering from acute and chronic forms, than there were males.[75] This preponderance was especially noticeable in the periods from twenty-one to forty years of age. The author attempts to blame this onto the men-

tal and nervous stress which the woman undergoes at this time. There was also a lesser preponderance after forty years of age which he claims was due to the after effects of these conditions. Menagh's series of two-hundred and sixty cases showed about the same results.[55]

Age plays an even more important role. In Balyeat's series, thirty-five percent of the cases occured before ten years of age, due to the high incidence of lichen urticaria. Fifteen percent occured in the second decade of life; twelve percent from twenty to thirty years of age; eighteen percent from thirty to fourty; twelve percent in the fifth decade and the rest in the waning years of life.

Tomkinson attempted to show a seasonal influence. He divided the year into a summer period, April to September inclusive, and a winter period, the first and last three months of the year. Sixty-seven percent of his cases occured in the summer period. Other authors have agreed that the condition is more prevalent during the warmer months. The type of foods eaten during that period may account for the higher incidence of urticaria.

Heredity as a factor in urticaria has caused much comment. Balyeat's series of one-hundred and

eighty-eight cases showed a positive family history of allergy in nearly seventy percent of the instances.[1] Goldsmith,[13] Hallam,[52] Duke,[78] and Mc Bride and Schorer[101] have published series of cases with a high incidence of positive family histories. Menagh had a group of two-hundred and sixty cases in which eighty-five persons had ancestors with allergical manifestations.[55]

We may conclude from such figures that urticaria is influenced by hereditary in almost one-half of the cases. (This does not mean that there is a positive family history of urticaria in that many instances, but of some allergical manifestation) .

McBride and Schorer, Hallam, and Others have tried to show that race plays a role in etiology. They find that the Jews are most susceptibile, while the North American Indians are among the most immune. This is interesting when one realizes that the former are among the oldest civilized peoples and that the Indians are a comparatively young race. This could be interpreted to mean that the urticarial tendency is a hereditary affair, which increases in virulence and prominence as it is passed from generation to generation; and that urticaria is an acquistion of civilization and its complexities, not a condition present since the advent of man .

Occupation, general hygiene and environment influence urticaria, insofar as they bring the individual into contact with the exciting factor of his particular case.

By exciting factors we mean those alien substances which have been definitely proved to have initiated an attack of urticaria in a patient when he has contacted them, providing he is sensitive to the particular substances. Authors disagree as to just how important a role such materials play in causing the reaction. Many claim there is a protein in the material which allows changes in the body tissues that result in a typical rash. This is especially true of ingested products where a toxic protein is supposed to be absorbed through the intestinal mucosa, enter the circulation and play a major role in the production of an urticaria. Roussel gives us the modern conception that the exciting factor is incidental rather than being the primary factor; that it acts as a catalytic agent in the production of a rash.[43]

Regardless of its importance it is the exciting factor which allows physicians to give relief to many patients by eliminating it from the environment. Stelwagon divides these factors into external and internal groups depending, of course, on their mode of entrance into the body.[2]

Goldsmith believes the factors may be conveniently placed in three groups; substances causing an antigen-antibody reaction, certain physical and mechanical agencies which do not cause this interaction (Duke's physical allergy), and, lastly, trauma.[13] Various other methods of classifying the exciting factors have also been utilized. This seems to be a rather useless and confusing proceedure so there will be no attempts at arranging the factors, in this paper.

Foods have long been associated with the etiology of urticaria. Badgley, in 1830, stressed the importance of diet in removing the causative material.[126] Most acute urticarias, especially in children, are found to have some food as the excitant.[4] They are proved to be exciting by such methods as elimination diets, positive skin reactions and by the history.

The following foodstuffs are most commonly found as irritating agents; sea foods, such as clams, lobsters, oysters, fish; meats, especially pork; egg albumin; fruits, especially strawberries and raspberries; vegetables of any description; nut meats, milk; and such cereals as wheat and rye. Generally speaking, the foods eaten most frequently, as wheat, eggs, milk, pork, e tc. are most likely to cause a rash; but almost any food that one can think of has been shown by some method to have been at fault in one or

more cases of urticaria.

Drugs often cause cutaneous reactions in certain individuals. Urticarial drug reactions most frequently result from the use of antipyrine, salicylic acid, verenal, quinine, luminal, salvarsan, boric acid, iodine, bromine, mercury salts, arsenic preparartions, and strychnine.[5] Formalin cases have beeen published quite often.[102-92] Phenolpthalein,[90] insulin,[27-22] cincophen,[23] and senna leaves[9] are some other preparations which are reported as being causative agents.

Animal proteins, other than the flesh, are sometimes responsible. Feathers, fur, wool, silk, and emanations may be exciting factors.

Pollens have recently become a source of study in regard to their association with urticaria. Lambright,[91] Brown,[26] Walker, and Taub and White have reported such cases, most of which have been found in association with hay fever and asthma.

Storm van Leeuwen has called attention to substances he designates as "miasms". These are colloidal materials of unknown composition whose prescene in the air is due to climatic influences.[5] He believes these materials are decided factors in urticaria.

The bites of many insects are known to produce local irritations in almost and person. In hypersusceptible

individuals these same insects may cause a generalized urticaria. Pediculi, fleas, mosquitoes, wasps, and bees are sometimes responsible for such attacks.[1] Churchhill is one of many who has pointed out the bedbug as an excitant in many cases.[33]

Duke listed certain substances which will initiate an urticarial attack.[78] These are purely physical agents and evidently do not involve an antigen-antibody reaction. For this reason the author has denoted them as physical allergens. The reactions produced are of two types. First the contact reactions in which the reaction is confined to the point of contact between a surface and the irritating agency; secondly, the reflex-like reactions which occur at the site of contact and in distant structures as well.[60] The former type may be due to light, cold, friction, and heat. The reflex-like reactions will result from cold and heat. (The latter may arise from physical or mental exertion).

Other authors have also published cases in which such a physical agent seemed to excite an attack of urticaria. Ward,[119] Beinhauer,[71] Pasteur-Vallery Radot,[64] and Weiss[16] have cases recorded in which the patients were hypersusceptible to sunlight. Wilson[21] and Alexander[25] demonstrated cases of heat sensitiveness, while Weiss[14] has recently shown a case due to hypersensibility to cold.

Bacteria and their products have been discussed a great deal in regard to their association with urticaria. The concensus of opinions seems to be that they will ex-

cite an urticarial attack, whether they come from a freshly introduced infection[88] or a chronic focus.[107] Many men agree with Barber that a great many chronic urticarias are due to bacterial sensitization.[81] Menagh and Goss[55-12] have numerous cases in which gall bladder disease was thought to be responsible for the urticaria; they believe that organ might be serving as a focus of infection.

Numerous isolated cases of urticaria have been attributed to other widely varying exciting factors. Pagniez and de Gennes had a patient who broke out in a rash whenever he ate rapidly but never when he ate slowly.[92] Flandin,[62] Dufke,[61] Golden,[30] and others have had patients who were thrown into an urticarial attack whenever they suffered a severe emotional disturbance, such as fear, anger, hate, etc. (Duke explains this type of phenomenon by his physical allergy, with the heat produced being the exciting factor). De Lavergne and Florentin published a case in which the urticaria was caused by white wine.[68]

Some of thesubstances mentioned are not exciting factors, pure and simple, but encompass certain elements of the predisposing factors. The two overlap to some extent. Predisposing factors may be defined as conditions in a patient's constitutional make-up which tend to make him hypersensitive, or are even instrumental in initiating the attack. The bacterial and nervous factors then are both exciting and predisposing.

Balyeat lists the following six conditions as constituting the predisposing factors of urticaria; physical fatigue(according to Duke this would be a physical allergen of the exciting variety); mental fatigue and depressed states (also listed as an exciting factor by Duke); thyroid dysfunction, especially hypothyroidism; toxic states; sudden changes in body surface temperature (likewise a physical allergen); and local irritation. If we accept Duke's work, three of these factors will be listed as exciting substances of the physical allergical type. Local irritation could be considered the same as trauma which most authors believe to be an exciting factor. This leaves only thyroid dysfunction and toxic states as predisposing to urticaria.

Ravitch,[111] Bolten,[99] and Roussel[43] are firm adherents of the thyroid insufficiency theory and present series of cases to back up their assertions. Ward states that twenty percent of his pneumonia cases were followed by an urticaria, resulting from the toxic state of the patient.[96] Froes,[93] Garin and Pasquier, Engman, Deuskar, Eyermann and Strauss[35] believe that malaria definitely predisposes to, or even excites attacks of urticaria.

Other authors have enumerated certain conditions which they believe predispose to urticaria. Menagh[55] and Goss[12] state that possibly gall bladder disease causes secondary liver changes which will result in urticaria. Hazen[105] and Hollander[97] are only two of many men who believe syphilis predisposes to urticaria. Lancash-

ire[79] and Harrison[8] published cases which are associated with menstrual disturbances.

Longcope and Rackemann[108] had a series or six cases in which they studied the renal function, and three showed funcional disturbances in the kidney activity, which the authors state may have been associated with the urticaria.

Hirshberg[117] and Pulay[80] believe that hyperacidity definitly predisposes to this disease, especially in the chronic forms. Criep has examined a series of cases with this in mind and found a hyperacidity in only a small percentage.[17]

Constipation has always been thought of in relation to urticaria, regardless of what might be the cause of the constipation. Eichenlaub found this to be the most common contributory cause of urticaria.[70] Marcovici found patients with atonia of the cecum and ptosis of the transverse colon in whom the resultant constipation was considered to be a factor.[56]

Atony of the stomach[20] and dilated stomach[120] have also been cited as predisposing factors of urticaria. Eichenlaub found several cases complicating pregnancy.[70] In general we may say that many gastro-intestinal disorders are found in association with urticaria and thought to be predisposing factors, with some of the other systems less frequently involved.

Having listed some of the varied exciting and predisposing factors of urticaria we will attempt to enumerate

some theories concerning a primary physiology-pathology in patients which must be present in order that so wide a range of substances will elicit practically the same symptons in different susceptible patients and still not efect the normal individual.

We shall start by saying that the urticarial lesion is a typical wheal formation arising probably from fluids which have passed out of the blood or lymph vessels into the surrounding tissues. It is this pathological structure which differentiates urticaria from other skin dyscrasias. The problem is to discover why this transudation, or exudation, occurs in sensitive individual when they came into contact with a specific alien product. Is it because of a change in the tissue where the whealing occurs, or because of the introduction of an alien protein or because of an interaction of the two?

Most authorities believe a foreign protein, or toxin, has something to do with exciting the reaction; the origin of this substance being disputed. Early authors thought this toxin initiated a simple inflammatory process; others stated it acted on the muscles of the vessels directly, causing a transudation of contents; some believed it acted on the nerves supplying the vessels. Numerous men have introduced the idea that the endocrine system is a large factor, probably through its control of the nervous system.

A few have attempted to explain the reaction purely by physical-chemical methods. Many consider the variations in the blood chemistry to be responsible. The acid-base equilibrium has served as a basis for much work. The latest research has centered around the experiments of Lewis and a histamine like substance.

A foreign protein, or toxin, is doubtlessly involved in most, if not all, cases of urticaria. Eichenlaub states specifically that the essential etiological factor is always a protein.[70] Peshkin tested one-hundred children asthma and found that some of them were sensitive to protein and others were not; further that urticaria occured in more of the non-protein sensitive cases than in the others.[58] Pulay attempts to group the essential factors into a toxic group, an albumin sensitized group (protein) and a group based on vagatonia (which may have a protein as the initiating force), believing that not all urticarias result from a protein reaction. Greenbaum,[54] Goldsmith[13] and others agree that there are some cases of urticaria not due to allergy or a foreign protein.

There is, then, a difference of opinions as the the prescence of a foreign protein in urticaria. However, this does not mean that there is not a true antigen-antibody reaction present in all cases, for even external trauma may stimulate the formation of an alien protein internally which would act as an antigen.

When considering the origin of the alien protein that acts as the fundamental excitant we find that Richet's conception is still considered to be logical. He thought the antigen-antibody interaction, caused by the entrance of or contact with the exciting factor, resulted in the fommation of a toxic entity, which was called an apotoxin. (It might be a protein or any split product of protein metabolism).

Micheal did not think the alien protein was the result of an antigen-antibldy reaction but was from direct absorption through the alimentary tract.[98] He found that only amino acids normally permeated the intestinal wall and these could not cause anaphylaxis, as peptones and proteoses do. In certain intestinal disorders the latter might be absorbed and anaphylactic phenomena result. Barnathon said these toxic substances were incompletely hydrolyzed proteins formed by some disturbance in the digestive juices.

Richet's theory fits the allergical conception of urticaria; Michael's and Barnathon's theories might imply that the protein they speak of could act primarily or cause the formation of an antibody and result in a true allergical reaction.

Even the earliest workers recognized the prescence of a foreign protein in urticaria but differed in regard to

its manner of action.

Jadassohn and Gilchrist advanced the theory that it excited an inflammatory process. The latter sectioned wheals and found edema of the connective tissue and fixed cells, emigration of polynuclear leucocytes and lymphocytes, pronounced fragmentation of the polynuclear leucocytes and fixed connective tissue cells, a few mast cells, swelling of the cells of the sweat glands, and fibrin scattered throught the corium.[101] He thought this signified an acute inflammatory change which had been caused by the toxin circulating in the blood and killing the tissue cells.

Unna another early worker, decided the wheal resulted from spasm of large veins of the skin which normally carried off the lymph, thus causing an accumulation of that substance. The spasm was said to be due to action of the alien protein. Mac Kenzie elaborated on this theory by explaining that there was a paralytic dilatation of the veins through a reflex action, caused by action of the alien protein of a dense plexus of fine nerve fibers in the superficial layer of the corium.

Hallopean, in 1902, stated that urticaria was an exaggeration of the vasomotor disturbances, of the skin tissues, that occured almost normally in some individuals after slight irritation; the irritation usually resulting from a toxin.[110] This idea of a nervous center being stimulated by an alien substance was not new at that time and has since recieved much favorable comment; especially in regard to chronic urticaria and angioneurotic edema.

The latter condition recieved its name because early observors were sure that it was caused by a disturbance in the innervation of the blood vessels. Quincke thougght the edema resulted from a vasomotor neuroses which allowed a sudden increase in the permeability of the vessels. Staffleri decided it was caused by an exaggerated excitability of certain nerves which controlled the lymph circulation.

Lancashire[79] and Klauder[69] are firm in the belief that the urticarial phenomenon is entirely angioneurotic and not anaphylactic in nature. Phillips, on the other hand, believes that allergy is more of a factor and angioneurosis is not so important.[133] Further discussion will show both factors enter into the etiology.

Rather recently, we find that authorities have attempted to associate the endocrine system with urticaria. In 1907, Ravitch decided that thyroid extract was a specific in many cases of chronic urticaria, due he thought, to its power of neutralizing poisons of auto-intoxication which might be in the blood stream.[111] Bolten, in 1919, presented cases in which he thought thyroid insufficiency was responsible, but differed from Ravitch in regard to the modus operandi.[99] He believed it induced a hypotony of the entire sympathetic system and not the vagus alone.

Samberger agreed with this explanation, explaining

further that the sympathetic paralysis caused blood to be squeezed out of the tissue locally and thus increase that tissue's demand for food and oxygen. This resulted in a hyperemia to satisfy the needs of the tissue with a resultant wheal.

Criep and Wechsler studied thirty-one patients with emphasis on thyroid activity.[20] The connection of this to urticaria was explained by the fact that thyroid extract is a stimulator of the vasodilators of blood vessels and this might cause a transudation of fluid to the tissues, by dilatation of blood vessels. However, these authors concluded that the relation of urticaria to thyroid insufficiency was not specific enough to warrant definite conclusions.

Roussel, on the other hand, is thoroughly convinced that the thyroid is absolutely a factor in urticaria. He believes the force and velocity of vasomotor impulses are controlled by the endocrine system, more especially the thyroid and supradrenals. (One is the dilator, the latter the constrictor). An imbalance between these two results in an urticaria.[43] He evens goes so far as to classify all urticarias as one of three types, depending on; first, a thyro-adrenal hyposecretory syndrome with the vasomotors in a state of constriction; second, a thyroid deficiency or adrenal hyperactivity; third, the opposite of the second type.

From this material we see that some men associate hypothyroidism and urticaria, others hyperthyroidism and urticaria, and finally one man who divides all urticaria into two types, one a hypothyroidism and the other a hyperthyroidism. We can draw no definite conclusions from such contradictory efforts. In fact they convince one that the endocrines alone cannot be responsible for urticaria but that some other factor must enter into the phenomenon. We might accept the conservative idea of Rowe and McCrudden that an endocrine imbalance may be responsible for some cases of urticaria.[70]

Some few authors have explained urticaria on a purely physical-chemical basis. Samberger advanced the original theory that cells in the involved area were asphyxiated and their consequent oxygen hunger called for an increased blood supply with hyperemia and capillary dilatation resulting. At the same time an increased number of leucocytes were needed to bring food to these cells and the circulation rate was decreased to allow this. This dilatation and lowered rate determined exudation, which in turn was influenced by a hypersecretion of the vascular endothelium, and not to angioneurosis. The lymphatics were thought to be especially active in this process and showed marked proliferation in an attempt to oxygenate and feed the asphyxiated cells.

Pulay explained the pruritus, edema and wheal formation by the disturbed and changed conditions in the chemical composition of the cell, in urticaria.[80] He believed there was a dislocation of the electrolytes or non-electrolytes, eventually causing a disturbance in the equilibrium of the balance of theions, which changed the osmotic pressure. This in turn led to a transudation, giving edema formation and whealing. He thought the alteration in ionization could be reversible or irreversible and in the latter case therapeusis would be of no value, but in the former the normal ion balance could be restored.

Paramore was one of the first men to experiment with urticaria patients in attempting to prove that the disease might be due to alterations in blood constituents, rather than acquired or inheirted alterations of cutaneous tissues or vessels. In 1906, he suggested that urticaria was of the nature of a serous hemorrhage associated with defective blood coagubility and due to a diminution of the calcium salts in the blood.[113] He concluded from his work that there were three basic types of urticaria; first, decalcification urticaria; second, urticaria due to alteration of salt content of the blood; third, inflammatory or toxic urticaria. He believed that secondary factors also entered into the production of wheals, as alterations in the skin and vessels.

Prior to this, in 1896, Wright had theorized that urticaria was due to a lowered blood serum calcium. Paramore's work substantited this as did that of White, Brown, Pulay, and others. However, some authors, including Pusey were opposed to the idea. Greenbaum agreed with Paramore that not all urticarias showed a calcium variation in the blood.[54] Criep believed calcium metabolism had a definite part in urticaria but could not determine exactly what it was.[17]

Warfield went a step further and correlated the calcium with other blood contents.[19] He found the calcium ion decreased permeability and contracted the capillaries while potassium and sodium had the opposite effects. Therefore, he reasoned there must be a definite balance of these opposed substances, and directed therapeusis towards maintaining such.

Some men have attempted to make detailed studies of the blood chemistry in urticaria. Criep found the blood sugar, non-protein nitrogen and urea were normal in a series of forty cases; the uric acid was slightly elevated and the chlorides diminished during an acute attack; the total blood calcium was normal, but the diffusible portion was slightly elevated.[17] Peterson and Levinson attempted experiments on a few cases and obtained varied results.[7] The work of these men is of little practical value because of the restricted

number of patients examined and the marked variations obtained.

The subject of acid-base balance in urticaria has created much discussion in regard to its etiological significance. The literature is divided with some insisting that the disease is associated with acidoses; others saying that alkalosis is present. Criep found that it was impossible to definitely associate the two, due to varied reults in laboratory experiments and to lack of therapeutic results from use of either alkali or acid.[17]

We now come to the more recent work of Lewis, Grant and others who believe there is a definite agent which initiates the urticarial reaction; and this substance is probably formed through the activity of the exciting factor the patient is susceptible to. Most of the experiments have concerned primarily a specific type of urticaria, i.e. urticaria factitia, but the results obtained show that the same reaction may occur in any of the forms of the disease.

Müller, Ebecke, Carrier, Lewis, and the Walzers have shown that wheals may be formed without the intervention of the autonomic nervous system. Mumford also demonstrated this by producing wheals on an anesthetized area of an advanced tabetic's leg.[76] Rulison and Lichenstein explain this by the action of contractile cells in the walls of the vessels which may be stimulated directly by certain substances.[44]

This stimulation leads to dilatation and increased permeability which in turn favors edema, and as the author's state, urticaria is determined by edema. They suggest that the etiology of urticaria may be discovered when such a stimulating substance has been unearthed.

Thomas Lewis and his fellow workers believe that they have found such a compound in histamine or a substance indistinguishable from histamine. Grant thinks this material is released whenever there is tissue damage from mechanical injuries, burning heat, cold, freezing, galvanic currents, ultra-violet light, many chemical compounds (including hydrochloric acid, lactic and formic acids, morphine, atropine, cocaine, etc.), and antigens in subjects susceptible to the protein concerned.[74] This substantiates the theory that sll types of urticaria are connected with this histamine like substance and not just the urticaria factitia with which early experiments were concerned.

Grant further states that the urticarial lesion is an expression of a general mechanism of defense in the skin against injuries of all kinds; it is the result of purely physiological processes and attracts special attention in susceptible patients because of the relatively mild grade of injury required to liberate the histamine. Other authors do not agree that it usually is some sort of a defense

of a purely physiological type but do agree with the idea that it is a defense mechanism of some sort.

These assumptions are based on the phenomenon resulting from stroking the skin. In patients with urticaria factitia, this results in the formation of a definite wheal of course resulting from the transudation of fluid into the tissues. Lewis explains this transudation by a "triple-response" initiated by release of a histamine like substance.

The "triple-response" is defined as a dilatation of capillaries from direct action of the histamine on the capillary walls, plus an increased permeability from direct toxic action of the histamine on the vessel walls, plus a widespread dilatation of surrounding arterioles from a local axon reflex stimulated by the histamine. Grant found this occured in normal individuals if the skin was stroked five of ten times roughly, rather than using only one light stroke; and so assumed that the phenomenon was physiological rather than pathological. Goldsmith thinks the response is physiological in normal people but becomes extensive enough in susceptible patients to be considered as pathological.[13]

We may assume, then, that urticarial lesions result from a local reaction (the triple-response) initiated by a histamine like substance which is released by any of the factors outlined by Grant, regardless of its pathological

status. This histamine must be present in the tissues at all times (Lewis states it is in normal skin in the dilution of 1:100,000 parts), especially if the process is sometimes physiological. But in what manner is it formed in the tissues ?

It probably is a product of protein metabolism. Eustis states it is formed in the intestinal tract by the action of putrefactive bacteria on the amino acid, histidine.[37] The latter is a composite of many protein foods and is released by pancreatic digestion of these foods. The histamine thus formed (chemically called beta-imid-azoloyl-ethylamin) is transported to the tissues, to be released by the exciting factor the patient is susceptible to.

The theory that histamine is the basic factor in urticaria, although rather new, has been experimented with and substantiated by many of the leading allergists including Lewis, Grant, Weiss, Harriss, Rackemann, Vaughan, Rulison, and Lichenstein, and Chen. We may conclude that a histamine like substance is responsible for urticaria but must not forget the other theories proposed, for there is a great possibility that other factors enter into the reaction and successful treatment would depend on the cognizance of such. Therefore, all the theories proposed should recieve some consideration and they have been recorded with that in mind.

PATHOLOGY

The typical lesion of urticaria is the wheal. In specific types this structure varies in appearance but in general it may be described as a firm, white or pinkish elevation, of a circumscribed collection of semi-fluid material, with a surrounding area of hyperemia and a tendency to acute onset and rapid subsidence.[41]

In angioneurotic edema the wheals are large, sometimes reaching three or four inches in diameter and tend to locate about the face, lips, eyes and extremities. Lichen urticaria has pin-head to pea-sized papular eruptions that are discrete and usually scattered upon the limbs. In hemorrhagic urticaria the wheals have hemorrhages into them with the hemorrhage being primary and the wheals secondary. In pigmentosa the wheals are usually papular and soon disappear leaving a pigmented area. In rare cases the wheals are displaced by vesicles and blebs.[2]

In all cases except angioneurotic edema the edema is restricted to the epidermis and, occasionally, the uppermost part of the dermis. In the one exception the edema may extend deep into the dermis.

Microscopically the wheal has been described by Gilchrist.[116] He excised wheals in three different patients fifteen minutes after the reaction was stimulated. His findings resembled an acute inflammatory process to such

an extent that he thought urticaria was just such a condition. The epidermis was unaltered but the whole dermis showed marked changes. The blood vessels, especially those to the sweat ducts, were enlarged and surrounded by polymorphonuclear leucocytes. The lymph vessels and spaces were dilated and contained granular material. There were large numbers of polymorphs throughout the dermis, and a few in the epidermis. Numerous mast-cells were found in the dermis which was swollen with the serous exudate.

Jarisch agreed that the wheal showed changes typical of inflammation. He found it consisted mainly of distention of lymph vessels and spaces of the coriom. The fluid was in these spaces and also in the tissue cells. Blood vessels of the lower cutis were dilated and those of the upper cutis compressed.

All later investigators have confirmed the findings of these two men as being that of the typical wheal.

SYMPTOMATOLOGY

In describing the symptomatology of urticaria many authors are prone to give minute details concerning the appearance of the rash as they have observed it. This is of relatively little practical value because of the wide variations which may be presented. The typical lesion, as discussed, may vary from a minute papular wheal to a very

large structure with all gradations between these extremes.

Stelwagon gives a general description which is useful in identifying the disease. The eruption appears suddenly and usually lasts only a few hours or days. It is an erythematous, scanty or profuse collection of pea to bean sized elevations, or linear streaks, or small or large irregular raised patches, or admixtures of these forms. The latter characteristic is most commonly associated with urticaria; gastric and febrile disturbances are rare.

Osler, in 1904, stressed the fact that visceral symptons might occur with urticaria, especially the acute forms, due probably to lesions in the peritoneum or gastro-intestinal tract. He had a series of twenty-nine cases with erythematous skin lesions, seventeen of which were urticaria. Twenty-five of the twenty-nine cases had abdominal colic. Fever, vomiting,diarrhea, evidences of nephritis, and joint pains occured in about half of them. This work is of benefit only if Osler eliminated other pathology in the patients which may have been responsible for the symptons and predisposed to the urticaria.

Hallopean has given a slightly different general description of urticaria.[110] It is an eruption composed of limited elevations of the cutaneous surfaces, always of irregular outline but distinctly circumscribed. These eruptive lesions are whitish or slightly pink in color.

They are of rather firm consistency and have something of an elastic feel, that is, they yield slightly to pressure but return to their former size at once. The separate lesions may be produced and disappear within a few minutes and it is somewhat of an exception for them to last many hours. The eruptions are usually accompanied by a special sensation of itching or burning, but may occur without any sensory symptons.

The efforts of Stelwagon and Hallopean serve to describe very well the acute and chronic forms of urticarial lesions. In the latter the symptons are the same as in the acute types but tend to remissions and exacerbations over a long period of time, with the general health of the patient suffering as a result of the worry and discomfort.

Lichen urticaria may be described more definitely. It is a disease of childhood, disappearing spontaneously at puberty in most cases.[38] It starts as an eruption of macules of one-fourth to one-half inch in diameter, each having a small papule in the center.[15] The child tends to scratch these and form a crust, sometimes bloody. The wheals disappear in one to two hours leaving a papular eruption. The papules soon assume the same color as the surrounding skin and become firm, dome shaped and appear to be lying on top of the skin. They are itchy and last for days. The rash usually occurs on covered portions of the body,

especially the limbs, and bothers the child most at nights. It runs a chronic course and persists, with intermissions, for months and years.

Osler, in 1888, gave the symptons of angioneurotic edema which are recognized today. He described the condition as local swellings in various parts of the body, face, hands, arms, legs, genitals, buttocks, and throat. These almost invariably were associated with gastro-intestinal disturbances as colic, nausea, vomiting, and sometimes diarrhea. Itching, heat and reddness often preceeded the outbreaks and smaller urticarial lesions occured simultaneously with the larger wheals. Some cases showed a marked regularity in the sequence of attacks, with occassional hemorrhages into the wheals and painful swellings of the joints.

Phillips added that the lesions were of a pale color and showed no signs of inflammation nor local pain.[133] He believed the edema might occur in mucous, synovial or skin membranes. Drysdale more definitely located the usual sight of the lesions in lips, eyelids, hands, and forearms; less frequently in tongue, pharynx, glottis, uvula, conjunctiva, gastro-intestinal tract, scrotum, and even the periosteum.[129]

He noticed the lack of febrile reactions in angioneurotic edema.

Urticaria pigmentosa is a rare condition occuring usually in children and occassionally carrying over into adult life.

The first lesions are urticarial wheals. These are replaced by macules or nodules, or both; sometimes papules are the secondary lesions. The eruptions are reddish-brown or walnut but change to bright red when irritated. They occur most often on the limbs and trunk, sometimes on the face. The lesions tend to spread over a period of time, without any remissions. Constitutional disturbances do not accompany this type.

Hemorrhagic urticaria is even a rarer form of the disease. It is characterized by wheals of various sizes and shapes which may have hemorrhages into them; there may be spots of hemorrhage where there are no wheals. There is usually much accompanying edema of the eyes and face. Gastro-intestinal disturbances often accompany the dyscrasia.

Urticaria factitia presents the most constant symptomatology, that is, formation of wheals when the skin is even slightly irritated. The lesions vary in color from pinkish to white and are surrounded by an area of hyperemia. They vary in size and shape being proportionate to the force and size of the irritant. The term dermatographism applies to this type of urticaria and implies that temporary outlines may be traced on the skin of susceptible patients by gentle pressure.

We find then that evanescent wheals of various sizes and shapes, varying in color from pink to white; itching;

and occassionally constitutional disturbances are the most constant signs and symptons of an urticaria. Hemorrhages and pigmentation occur only in rare forms.

DIAGNOSIS

The diagnosis of urticaria necessitates a complete history and physical examination as well as laboratory proceedures; not only to rule out possible sources of other pathology but also to find predisposing factors which may be present. Painstaking histories to indicate disease in any part of the body, as well as blood count, Wassermann and urinalysis should be routine with roentgen-ray studies whenever indicated. Gastric analysis, stool studies, blood chemistry, E.K.G., Kidney and gall-bladder function tests may prove of aid.

Duke suggests the following sources of information which may be used in diagnosis; family history, personal history, physical, laboratory and x-ray examinations, careful observations made by the patient, effect of adrenalin upon the symptons, specific tests (cutaneous, intracutaneous, opthalmic, nasal, subcutaneous, and clinical).

A careful history may reveal the prescence of allergy in the family, or of allergical disturbances in the past or present history of the patient, which would lend credence to a diagnosis of urticaria. Detailed questioning may be

necessary to bring out symptons of other types of allergy from which the patient could have suffered.

Observations by the patient as to substances which he believes he is sensitive to and his description of the condition, as it appears to him, are important.

Physical examination may reveal foci of infection, gastro-intestinal disturbances, menstrual or endocrine imbalances, etc. which predispose or excite the attacks. The type of eruption can be determined, if during the acute stage of attack, and the diagnosis correctly classified. Scratching the skin may bring out the cutaneous symptons previously discussed.

Roentgen studies will be useful in determining predisposing factors. Laboratory work may show an eosinophilia which is sometimes associated with urticaria. Rackemann believes a low white blood cell count will be found in many cases. Blood chemistry and alkaline-acid equilibrium have been studied but very little practical benefit derived from such.

In general, the personal and family history, the physical examination, roentgen studies, and the general laboratory work are necessary for two purposes. First, in determining that the rash is an urticaria and not due to some other source; second, in locating possible predisposing factors which are endogenous in nature.

Rowe proposes a detailed routine history form for all allergic patients which may be utilized in this work.[4] It would be more useful in patients suffering from urticaria plus some other allergical manifestation.

Probably the most useful proceedure in diagnosis of urticaria is skin testing, which has been a distinct development in the field of allergy. It, also, has two purposes; it shows that the patient is susceptible to some foreign substance, therefore, that his trouble is most likely of an allergical nature; and it may reveal the specific material which excites the attack. One cannot depend on the latter phenomenon to any great extent.

Duke estimates that only twenty-five percent of chronic cases can be correctly diagnosed through skin tests of any sort.[3] This percentage is even lower in food sensitive cases, which includes many urticarias. Schloss showed that the skin reaction in an egg-sensitive patient was only positive a few days each month, although the egg was being ingested continuously. Blackfan, O'Keefe, Shannon, Stuart and Farnham, Rackemann, and Alexander are other authors who have commented on the negative results obtained with many skin tests, especially in food sensitive patients.

In using skin tests for diagnosing we must remember that a negative test does not eliminate that substance as an excitant; that a positive test is of little diagnostic value without clinical corroboration; that a single individual may

be susceptible to many different materials; that a small delayed reaction may mean as much as large definite reactions. This does not mean that skin testing is to be disregarded, as it should be carried out in all urticaria suspects, remembering to qualify the results.

In searching for material factors (as opposed to Duke's physical allergens) two methods of skin testing are usually used at present. The cutaneous, or scratch, method is the more common. It is not useful in children, nor in patients sensitive to pollens, and other air-carried substances, and to materials that are very irritating. This method often fails in food sensitive patients, where the intracutaneous method is the one of choice. The latter gives more positive reactions and also more false reactions, (i.e. positive reactions in non-susceptible patients).

Walker was the fist to advocate the cutaneous method. The testing may be done on the forearm, upper arm, back, or upper leg; after cleaning and drying the surface. Location of the test depends on the number of substances to be used and the patient. In babies and children the back is preferable; in females the thighs; and in men the arm.

The allergens should be placed in longitudinal rows far enough apart so that a positive reading will not cause overlapping and confusion. The skin is scarified with a knife, going through the corneum but not deep enough

to draw blood. The dry powdered foreign materials being tested are placed on the scarified areas; a drop of tenth normal sodium hydroxide solution is placed next to the powder; then the solid and the liquid are mixed into the scratch with a small sterile applicator or toothpick. Solutions, one-tenth percent to one percent, are more easily used.

The intracutaneous method was advocated by Cooke and is more useful with food allergens. Sterile extracts, standardized in varying strengths, are injected intracutaneously, 0.01 to 0.04 cubic centimeters being used. Care must be taken to get between the layers of skin and not under it, because of the danger of a general reaction. Small gauge needles and tuberculin syringes should be used. It is best to run a control test with the type of extracting fluid used. Methods of preparing these extracts for both cutaneous and intracutaneous tests have been described in detail by Coca, Wodehouse, and others. Drug houses also offer them to the profession.

Duke reads as positive only those reactions which have a wheal with pseudopods, surrounded by an irregular area of hyperemia. Rowe interprets results as 0,1,2,3,4 plus, depending on the size of the wheal, surrounding erythema and extent of pseudopod. Vaughan and Shannon have pointed out that small erythematous areas may also indicate a hypersensibility.

The Prausnitz and Kustner method of indirect skin testing may be used where direct testing of a patient is inadvisable for some reason. (As in dermatographism, atopic eczema, extreme sensitiveness, in patients where direct testing gave multiplicity of positive reactions, etc.) Walzer has developed this technique quite extensively.

He draws five to ten cubic centimeters of blood from the patient, centrifuges it, draws the serum off and sterilizes it. A non-allergic patient is injected intradermally with one-tenth cubic centimeter of the patient's serum in sixteen spots about four centimeters apart on each upper arm. After two to four days, when evidences of irritation have subsided, the spots are injected intradermally with 0.02 cubic centimeters of the extracts of the allergens. In two to four days more the same spots may again be used for testing, if the first tests were negative. Any excessive reaction of the sensitized spot as compared to the control may be regarded as positive. Walzer has also used a variation of this routine wherein he gives the allergens orally rather than by intracutaneous injections.

In any of these methods there is the danger of constitutional reactions of a serious nature. Adrenalin should be kept at hand and used if a patient develops coryza, asthma, generalized erythema or itching of the skin.[2] They should

never be allowed to leave sooner than twenty to thirty minutes after the testing has been completed.

Opthalmic and nasal tests are seldom used in urticaria. They may be of value in those rare cases where a pollen or other air-carried substance is responsible for the rash, but are not of enough value to be outlined here.

Inhalation methods are useful for testing rather simply for hypersusceptibility to animal hair, feathers or emanations from vegetable matter. It likewise is rarely used in urticaria and is never very successful.

Subcutaneous tests are most useful in confirming a diagnosis. If a substance gives a positive reaction it can be injected subcutaneously when the patient is free from urticarial symptons. If an urticaria is initiated, the diagnosis is confirmed. Small dosages must be used in such instances.

Skin tests are of value only in cases of true allergical urticaria where the allergens have caused the formation of reacting substances in the patient's tissue. Mc Bride and Schorer,[101] Pulay,[80] Peshkin,[58] Greenbaum,[54] Goldsmith,[13] and others would agree that numerous cases could not be diagnosed with this method, and the general examination would have to suffice.

Rowe has suggested the use of trial diets in diagnoses because skin tests are prone to give "false positive" and

"false negative" reactions. When food allergy is definitely suspected and skin reactions are negative, or if symptoms are not relieved by diets based on positive skin reactions, the prescence of various food sensitizations may be determined by using elimination diets. These are the same as the diets used in treatment of urticaria and are outlined in great detail by Rowe.[4] They may be used only in cases due to food.

Attempts to use precipitin and complement-fixation reactions in determining exciting factors have not met with much success and are of no practical value.

Widal originated a complex laboratory method for use in diagnosing urticaria patients, which is rather impractical.[5] It is called the "crise hemoclasique" and is defined as a rupture of the equilibrium of the blood which may occur when an allergic patient comes into contact with a specific allergen. It is characterized by a lowered blood pressure, a drop in the leucocytic count, a change of refractometric index of the blood, and a change in the clotting time.

Duke's work in physical allergy has opened a new field in the diagnosis of urticaria. He tests his patients with the material substances mentioned (pollen, epithelium, food, etc.) and also with physical agents such as ice, cold baths, refrigerated air, hot baths, dry air, moist air, currents, sunlight, actinic rays, physical exercise, and changes in

air pressure. These methods have aided him in diagnosing previously obscure cases of urticaria. Weiss, Wilson, Alexander, Blaclford, and others have substantiated his work.

Duke gives the diagnosis of contact reactions and reflex-like reactions under different headings. Contact reactions caused by light, heat, cold, and mechanical irritation are usually noted by the patient. Small areas of skin may be exposed to the different substances to make a diagnosis (characterized by erythema, swelling and itching). Some difficulty may arise from delayed reactions which will not appear for some time after the testing is completed.

Diagnosis of reflex-like reactions, due to heat, cold, or light is simple if the reactions are initiated promptly upon exposure. In delayed cases the diagnosis is uncertain and the symptons must be compared with a known case. A one-thousand watt nitrogen lamp (for heat), ice rubs, hot and cold compresses may be used in attempting to excite the reactions. The patient should exercise vigorously during any of these tests. The rare cases due to mental exertion (i.e. heat originated by the exertion) will have to be determined by the history.

The differential diagnosis of urticaria should offer little difficulty. Evanescent wheals of various sizes and shapes with a surrounding area of hyperemia and itching, should suggest the ordinary forms of urticaria. These

points plus the general distribution on covered portions of the body, differentiate it from erythema multiforme.

Pemphigus and dermatitis herpetiformis might offer difficulty in the rare forms of urticaria that have vesicles. Preceeding wheals, the history and the course of urticaria would rule these out. Pediculosis, scabies and irritations of other animal parasites may give scattered wheals but not the other eruptive features of urticaria, unless in a person hypersensitive to the bite or such animals.

The "nettle rash" type of urticaria might be confused with measles. The former always itches or burns and seldom is accompanied by fever, sore throat or eye symptons. A history of a previous attack is often obtainable in urticaria. Prescence of allergy in the family history would also be of value in determining an urticaria.

Localized edema from chronic infections or local interference with venous blood return might rarely be confused with angioneurotic edema. This condition would last several days while the allergical edema would soon dissappear.

Syphilis, of course, could produce a rash similiar to urticaria. Itching would probably be absent in syphilis. The blood Wassermann and continuation of the lesions would designate a syphilitic manifestation.

The acute exanthemata of childhood must be differentiated from lichen urticaria. The lesions usually are decidedly different than the lichen eruption. Lack of constitutional symptons would often rule out the urticarial manifestation. It would be very seldom that the two conditions could not be readily differentiated.

In summarizing the methods of diagnosis we find that a careful family and personal history are essential. Observations made by an intelligent patient regarding his disturbance are very valuable. Physical examination, laboratory proceedures and roentgen examinations are most useful in determining contributory factors. Specific tests are invaluable in some cases but are quite prone to errors and misinterpretations; and a diagnosis should never be based on the results of these tests alone. Removal of the suspected agent with consequent relief from symptons, or reproduction of symptons during a well period by bringing the patient into contact with the suspected allergen, is essential for a final diagnosis.

TREATMENT

In discussing the treatment of urticaria we find that the literature varies markedly at different periods, depending a great deal on the particular theory of urticaria that is in vogue at the time. It would seem wise to remember that each author has obtained results with his particular mode of treatment in his individual cases. It is

possible that all of the treatments mentioned in the literature have some justification, although the cases may have cleared spontaneously and not through the efforts of the enthusiastic physician.

A great deal of the earlier therapeutics as outlined in the literature seems a bit far-fetched, while some is consistent with present day trends. As early as 1830, Badgley stressed the importance of diet in treating urticaria, along with laxatives to keep the gastro-intestinal tract clear and warm salt water baths to relieve some of the pruritic discomfort.[126] In 1883, Anderson suggested the use of trial diets and changes of environment in treatment.

Such lotions as vinegar, vaseline, soda, chloroform, witch hazel, glycerine of lead, phenol, cologne water, tar, chloral, and camphor were recommended to be used locally for the pruritus. Baths of salt, soda, potassium sulphurate, hydro-naphthol soap, etc. were suggested for the same use.

Sulphuric ether, quinine, arsenic, salol, belladonna extract, ergot, pilocarpine, menthol, antipyrene, potassium bromide, and atropine were tried as internal medicaments to combat the urticaria.

Application of an electric current to the spine was endorsed by Anderson[121] and Jackson[120] for improving the

general condition of the nerves. One author applied high-frequency currents for fifteen minutes to all the effected areas of the skin, giving a total of six treatments.[114]

The French had a novel method of placing cotton over the lesions and then bandaging tightly to prevent any further development.

Mitchell used collosol manganese in urticaria because ot the supposedly destructive action of that compound on the invading toxin.[82] Marcovici suggested venous puncture in persistant urticarias, drawing off two-hundred cubic centimeters of blood and infusing one pint of warm normal saline.[56]

In general, the earlier method of treatment was the use of a bland eliminative diet, laxatives, baths and lotions for the itching, various internal medicaments (some for constitutional defects and some for their supposedly direct action on the urticaria).

Modern methods of treatment are along five lines, as outlined by Duke; avoidance or removal of the exciting factor; avoidance or removal of contributory factors; specific protein treatment; non-specific protein treatment; and symptomatic treatment.

Avoidance of the cause is difficult in urticaria because foods are the most common factors and they are the most difficult allergens to apprehend by skin tests.

Also, a split protein may be the offendor and it may be present in any number of the more common and substantial foods.

If a specific food is found to be the exciting factor it may be avoided in the diet. Vaughan has prepared a detailed list of substitutes for the more common foods (as wheat, eggs, cottonseed, pork, milk, cocoa, etc.) which can be utilized for hypersusceptible patients, without forcing them to use an unbalanced diet. He suggests that foods belonging to a given biologic group be avoided if symptons persist, even though only one or two members of that group gave positive skin tests.

Elaborate elimination diets are stressed by Vaughan, Rowe, Balyeat and others for patients in whom no specific diagnosis was made. They recommend a diet which contains none of the more common foods and none which are known to be frequently allergenic. The patient is kept on such a regime for two weeks and if symptons disappear, new foods are added cautiously, at the rate of one or two per week. The offending food or foods may thus be apprehended, and eliminated, making the proceedure useful in both diagnosis and treatment. Details of such diets may be found in the works of authors referred to.

Vaughan advances this general preliminary diet which may be used if there are no contraindications in the way

of skin tests or history:

Fruits; pineapple, fig, bluberry, huckleberry

Cereals; none

Bread; Ry Krisp (Ralston)

Green Vegetables; endive, gumbo, artichoke

Starchy Vegetables; sweet potatoe

Meat; lamb

Beverage; tea

Condiments; olive, cranberry

Desserts; rhubarb, sliced pineapple

Nuts; chestnut, filbert, pistachio

Miscellaneous; sugar, salt, maple syrup

Other authors use a more radical preliminary diet, such as milk alone or dry toast for two or three days, later adding the simple foods one at a time.

Other allergens such as pollens, dust, animal emanations or products may require that the patient change his environment. Climatic miasms also might necessitate such a change.

Individuals sensitive to products elaborated in chronic foci of infection should be treated by removal of the foci. Vaccines may be used if the foci cannot be apprehended. In antitoxin hypersensitiveness the horse serum is probably responsible and some other form of serum should be used.

Specific protein treatment has not proved satisfactory in urticaria. In the rare cases where pollens have been

responsible, results have been good. In desensitizing urticaria patients to other forms of allergens the results are disappointing. Duke has tried to desensitize to milk and egg, with some success. He theorizes that the whole food may be harmless to a patient while the split-products could serve as allergens. So he concludes that cutaneous desensitization of the whole food would be impractical. Oral administration is the best method.

Van Leeuwen suggests two methods by which this may be done. First, a very small dose of the foodstuff may be taken three-quarters of an hour before eating a meal which contains the food. The second form consists of taking a very small quantity of the foodstuff and gradually increasing the dose. Either method has been known to give desensitization in rather rare instances.

In desensitizing to those allergens which it is practical to do so, especially pollens, we start with one-tenth cubic centimeter of that dilution of the extract which has just failed to give a positive skin reaction. (Ranges from 1:5000 to 1:500,000). The dose is increased progressively at each injection. Sometimes it is doubled each time, again it is increased only by a stated amount such as two-tenths cubic centimeter. The frequency of treatment , size of dosage, and rapidity of dosage increase all depend on the response of the patient to therapeutic meas-

ures. Extreme care must be taken to gaurd against a general reaction and treat such promptly if it does occur.

Non-specific treatment is an attempt to lessen the patient's sensitiveness to allergens in general and not to any specific substance. It is probably of more benefit in urticaria than are the specific methods and is advisedly used in those cases where the exciting factor cannot be found, or where there is no response to other modes of treatment. It would be ideal to find one substance which would cause this desensitization to all allergens. None has been discovered but several valuable adjuncts are known.

Peptone given in capsules forty-five minutes before meals was found to lessen allergical symptons. Pelin and Smith obtained good results in a few cases by giving two-tenths to five-tenths grams one hour before meals.[67] Brown uses a sterile thirty-three percent solution consisting of equal parts of peptone, siccum, glycerine, and water. He gives one minim intradermally, then two minims, then three, increasing the dosage one minim each time until sixteen minims are being given. This dosage is maintained continuously, giving one or two treatments each week.[46-48]

This method seems to get results only where food is responsible for the attack; probably by stimulating secretion of digestive juices so that the food is more completely

digested and s plit-protein radicals are not absorbed into the circulation. A cup of broth or bouillon half an hour before meals does the same thing, according to Vaughan.

The latter author has also used peptone injections both intravenously and intramuscularly. It produces a "shock" with chill and fever, which seems to relieve the symptons of urticaria, (as well as of other allergical manifestations). He recommends gradually increasing the interval between doses until it is given once every seven or ten days. Relief is obtained in about fifteen percent of the cases. Pagniez and vallery Rodot, Swann, Williams, and Rackemann believe in this method of treatment with slight variations.

Protein shock has also been suggested in treatment of urticaria, using either typhoid vaccine or sterile milk. (Peptone does not produce a true protein s hock). The degree of the reaction may be accurately controlled by premature tests with small quantities to determine susceptibility of the patient. Duke suggests using colon bacilli subcutaneously or intravenously to produce the shock.

Vaccines are useful in cases of urticaria where foci are factors. Rackemann believes they are of little value. Vaughan, on the other hand, believes they are beneficial and describes two kinds. First, those to specifically desensitize persons suffering from bacterial allergy; second,

those to immunize persons who are not bacteria-sensitive but have urticaria from some other cause and are carrying chronic bacterial infection. Total number of injections varies decidedly and should be given in increasing doses, about once every one or two weeks. Vaughan quotes contemporaries who agree with him that vaccines have their place in the treatment of allergical phenomenon, including urticaria; but most confine such efforts to cases with a definitely suspected bacterial hypersusceptibility.

Symptomatic treatment was about the only form of therapeutics endorsed by early authors (as given previously). Later developments have produced new methods which are quite useful and beneficial. Innumerable drugs have been recommended by various physicians but only a few have shown consistent effects.

Adrenalin is the one remedy which almost always gives some measure of relief. It is effective, when applied either locally or subcutaneously, in aborting severe attacks of acute urticaria. Balyeat recommends ten minim doses repeated in one-half hour if necessary, after emptying the stomach with a pump or an emetic. It should be given in the smallest possible doses which will give the desired clinical effect, and be injected slowly. It may be used for indefinite periods without noticeable ill effects. Keith,[72] Churchhill,[33] and Goldsmith[13] are others who recommend it.

Atropine and ephedrin have also been recommended by various authors. Duke believes the latter may be used in place of adrenalin because its effect lasts longer, although it seems to be less potent in reducing symptons. Kesten treated seventeen cases of chronic urticaria and angioneurotic edema with ephedrine; seven were completely cured and two were improved.[53]

G. T. Brown gives ephedrine hydrochloride in capsules or tablets (three-eighths to three-fourths grains). He believes it is extremely beneficial. Atropine has been used for a long time, with fair results. Anderson suggested its benefits as early as 1883.[121]

Van Leeuwen, Brown, Lancashire and others advocate the use of calcium salts in urticaria to relieve the symptons. Some authors are more radical than others and would use it in all cases. Brown presents a rational proceedure to be used only in those patients in whom a low normal calcium or definite calcium deficiency has been found by laboratory methods.

He gives calcium lactate and parathyroid orally where there is a low normal calcium, and the same plus air-cooled quartz lamp treatments in a definite deficiency. The calcium lactate if given in five gram doses, on an empty stomach, stirred into a glass of water. This is taken one-half hour before breakfast and a second dose at bedtime.

Children are given twenty-five grains of the lactate three times daily, one-half hour before meals.

Calcium may also be administered intravenously, using a sterile ten percent solution and giving two to five cubic centimeters, two or three times per week.

The dessicated parathyroid dosage is one-tenth grain for adults and one-twentieth grain for children, given in tablets three times faily, one-half hour before meals. Warfield agrees with this method.[19]

The quartz lamp treatments are given with a mercury vapor ultraviolet light, increasing the time of exposure and decreasing the distance, with each treatment. A mild skin reaction is to be obtained with each exposure.

Dessicated thyroid should be used in patients with a low metabolic rate, given in one-tenth to one grain tablets, three times daily, one-half hour before meals.[46] Ravitch suggested the use of this gland extract in 1907.[111]

Dessicated whole ovary or corpus luteum may be administered where ther are symptons of ovarian hypofunction along with the urticaria. Dessicated whole suprarenal gland may be tried in cases with a definitely low blood pressure. Pancreatin is occassionally useful in cases with definite food sensitization. It is given in five grain tablets with enteric coating, one to two tablets after each meal.[46]

Brown has also outlined many treatments for conditions occuring simultaneously with urticaria in which drugs are used and result in some degree of relief from the urticaria. Among these are sodium bicarbonate (one teaspoonful daily) if the urine is strongly acid; Fowler's solution where there is a low red blood count; iron, if the hemoglobin percentage is low; salines, such as sodium phosphate, every morning for patients with an abnormal intestinal flora. Vallery-Rodot[62] and Hirshberg[117] suggest combating hyperacidity, when present with urticaria, with sodium bicarbonate, either orally or intravenously. These measures are not to be used routinely but only in cases where such conditions complicate the urticaria.

Vaughan has used ten percent sodium chloride intravenously in some cases, with little or no results. Van Leeuwen thought sulphur injections were of some benefit.

Among other methods to relieve the symptons we find Menagh and Goss using gall bladder drainage. Menagh obtained results in fifty percent of his chronic urticarias by using this proceedure.[55]

Golden[30] and Lancashire[79] suggest psycho-therapy to remove psychic causes which may be responsible. Harrison reported a case due to menstrual disturbance which he cured by injection of a solution prepared from the soiled menstrual pads of the patient.[8] Nephritis, diabetes, and other constitutional diseases, of course, must be looked for and treated.

The itching in urticaria, which is often most severe, may be relieved by such antipruritic methods as; cold baths, either plain or soda; sponging the skin with alcohol, or a saturated solution of menthol in alcohol; calamine lotion containing phenol or menthol. Ice compresses may be applied to the localized swellings of angioneurotic edema.

Sedatives may be utilized in cases where the itching causes insomnia. Mixed bromides, fifteen grains at a dose should be prescribed to be taken at bedtime. If there is nervousness, they may be used two or three times daily. Barbitol derivatives are highly recommended by many for this same purpose.

Since Lewis' theory of histamine as the basic etiological factor, Rulison and Lichenstein have introduced a new method of therapeusis. They decided to diminish the patient's response to the histamine, or prevent its release in excessive concentration. They were unable to do the first, but have obtained some good results by following along the lines of the second method. They attempted to make the tissue cells less permeable so that less histamine would be released. Following the theory of Peterson and Wallis, that the permeable cell has a small amount of calcium in proportion to the potassium, they gave calcium to decrease the permeability and maintain the calcium-potassiom equilibrium.

Eustis believes that the histamine comes from putrefactive action of bacteria on histidine in the gastro-intestinal tract. Therefore, he attempts to use a low histidine diet and change the intestinal flora. Calomel, rhubarb or phenolphthalein are given to help prevent absorption of the putrefactive material. Then cereals, fruits and vegetables (excluding peas or beans) along with acidopholus buttermilk are used as a diet for three or four days. Later, meats, eggs, peas and beans may be added. If indican appears in the urin (denoting absorption of putrefactive material) the diet is returned to its original status and a new start is made. The author reports uniformly good results with this regime.

Treatment of urticaria resulting from physical allergy is best discussed separately because of its recent innovation. Duke suggests full doses of adrenalin subcutaneously in contact cases which occur promptly upon exposure. Light sensitive patients must protect themselves with dark clothing, veils, gloves, etc. Pink or brown powders may afford slight protection. Mild cases may gain some tolerance by subjecting increasing areas of skin to the sunlight. Cold sensitive patients should avoid exposure, seek warm climates and avoid cold drinks and baths. Application of cold water to gradually increasing areas of skin may give slight desensitization.

Treatment of patients with reflex-like reactions may be along several lines. Avoidance of specific and contributory factors is essential. Heat from pathological conditions in the body will often initiate an attack and so must be remedied. Desensitization by increasing doses of the specific substance often gives some relief. Adrenalin, atropine or sedatives have the same benefit here as in other urticarias.

In giving these variations in treatment we have observed numerous measures, some of which can apply generally and others which are of benefit only in specific cases. Also, many details have been omitted which would be useful in such specific cases. Generally speaking, it is impossible to lay down a definite routine which may be followed in treating a given case. Each patient is an individual problem which must be worked out in the minutest detail; and even then treatment may be of no avail.

In summarizing we can say that avoidance or removal of the specified allergen is the best method of treatment. Specific protein treatment is best if the allergen is known but cannot be entirely avoided. Non-specific protein treatment is sometimes beneficial where the allergen is undetermined. Adrenalin is the best measure for relief of acute urticarial symptons, until other methods may be employed. Types of physical allergy causing urticaria are to be treated by special methods. Treatment based on the

theory that histamine is the basic factor of urticaria is relatively new and untried, but has recieved some favorable comment.

Advance of therapeutic methods has been shown by specific and non-specific protein desensitization, more elaborate trial and elimination diets, and introduction of a very few useful drugs.

PROGNOSIS

The prognosis of urticaria varies markedly with the specific type being treated. In the acute types with a determined exciting factor the outlook is good. Rackemann had twenty-seven patients whose attacks came after certain foods were ingested, followed acute infections, or were associated with a chronic infection which could be treated. Twenty-one of these recovered completely, three were improved (have outbreaks when they do not follow dietary restrictions) and three did not respond to treatment.

Authors who have reported small series of cases, or single cases, of acute urticaria invariably have shown complete cures.

Chronic urticaria gives a less favorable prognosis. Rackemann had a series of eighty-seven such patients. In thirty-one of these the urticaria disappeared and had not returned in two years. In thirty-two more the symptons were greatly improved. In the other twenty-four cases the

condition was not changed during the two year period. Of course, the etiology of the urticaria determines its outcome, to a large extent.

Hazen found twenty-eight urticaria patients who had a positive Wassermann. These were given regular anti-syphilitic treatment and twenty-three of them were relieved of their symptons.[105]

Menagh's series of one-hundred and sixty-six cases had etiological factors including foods, other proteins, biliary tract involvement, and some unknown factors.[25] Of the entire group seventy-five were cured, sixty-four were improved and twenty-seven were unchanged by treatment. Of the group with biliary involvement as the etiological factor over thirty-five percent were cured and eighty-five percent were improved by treatment, consisting of vaccines, drainage, diet, and surgery.

Eichenlaub recorded a series of fifty-eight cases with the etiology determined in fifty of them.[70] Of these fifty patients, twenty-nine were cured, thirteen were improved, six unchanged, and two were lost trace of.

From these results we can conclude that chronic forms of urticaria will respond to treatment in over eighty percent of all cases where etiology is established. A complete cure can be expected in about thirty-five percent of such instances.

Lichen urticaria and urticaria pigmentosa are two of the chronic forms in which prognosis is very poor indeed. Fortunately these types occur comparatively rarely. The lichen urticaria usually disappears at puberty but responds poorly to treatment before that time.

Angioneurotic edema has a prognosis that compares with the common forms of chronic urticaria. In this form of the disease we find the only reports of death due to urticaria. They are rare indeed, and have occured in patients giving a positive family history of angioneurotic edema. Griffith, Kreiger, Fritz, and Wason have reported such instances. Edema of the glottis was probably responsible in all of the cases.

In general, the prognosis of urticaria depends on the thoroughness of the physician's work, and the intelligence and cooperativeness of the patient.[6] The physician must have the desire to persevere and unearth all of the etiological factors, and then to treat them sanely by methods of choice.

The patient should be willing to continue treatment for a long period of time even though the results seem to be discouraging. He may have to avoid certain factors for his entire life, which may inconvenience him no small amount. In other instances, a period of avoidance may create a tolerance which will allow him to recontact the factor without

a return of symptons.

A permanent cure depends on avoidance of the etiological factor or desensitization to it. Prognosis, then, in the final analysis depends on the ability to determine these factors and avoid them or be sensitized to them.

CONCLUSION

Urticaria is a specific skin disease marked by transient eruptions of wheals and is, in most cases, a true allergical manifestation. In a few instances, however, the disease may not involve an "allergen-reacting substance" interaction.

Numerous factors may initiate the attacks and many endogenous conditions are supposed to predispose to them. Recently, a histamine like substance has been found which is supposed to be released in the tissues by action of the exciting factors and cause a transudation of fluid into the tissue, with resultant wheal formation.

The condition is recognized by various sized wheals with surrounding hyperemia, itching or burning, and occassionally by such general symptons as fever, vomiting, nausea, and other gastro-intestinal disturbances.

Treatment is based on avoidance or removal of the exciting factor, avoidance or removal of contributory factors, specific protein treatment, non-specific protein treatment, and symptomatic treatment to relieve immediate distress of the patient.

Prognosis of urticaria is good in acute types of the disease but less favorable in the chronic forms.

CASE HISTORIES

The following case histories, taken from the literature, are recorded to illustrate the various forms of urticaria, since specific types were not discussed in detail in the body of this paper.

Case I: Acute Urticaria

"A man, aged 29, seen at 2:30a.m., had wheals from fifteen to twenty centimeters in diameter over the body, legs, arms and face. The eyes were closed from swelling of the lids. The wheals were still growing and showed numerous large pseudopodia around the periphery. In the center of these wheals were small puncture wounds that apparently were due to insect bites. The administration of epinephrine, ephedrine and cold baths caused the wheals and the intense itching that accompanied them to disappear after a few hours. Investigation of the bedding showed numerous bedbugs.

The patient stated that he felt fine when he went to bed. He noticed a slight biting, then intense itching and turned on the lights. His eyes swelled shut within a few minutes.

The next morning the left eye still closed, but the

remainder of the wheals had disappeared except for a slight induration around the puncture wounds. Just within the border of the left eyebrow there was a puncture wound. The tissue around this was indurated and reddened.

The past history revealed that the patient had had urticaria on several occassions after eating strawberries for several successive days. He did not recall having been bitten by bedbugs before. There was no history of asthma or hayfever in his family."[33]

Case II: Chronic Urticaria (with a "physical allergen as the exciting factor).

A woman, aged 53 years, who had been constantly subject to hives for over twenty-five years. At first there was merely a persistant itching, which lasted for a hour or two and then a definite wheal formation began. For several years the hives occured only on vigorous exercise but for the past fifteen years have come on with only moderate exertion. Warm water baths and too warm clothing also caused the hives to appear. Skin tests attempted lately gave positive reactions to everything tested.

On physical examination a moderate dermatographism was found. Some emphysema, slight cardiac enlargement, a soft systolic murmur, and a blood pressure of 178/94 were the other positive findings.

Laboratory findings were within normal limits.

Exercise, warm baths and excessive body covering caused the appearance of a rash.

The patient was treated by warm baths. At first she stayed under the shower for five minutes, and this time limit was increased daily. The temperature of the water was also raised a little each day. These baths were discontinued after three weeks and ten days later the symptons returned. The baths were resumed and for the next six weeks no symptons had been complained of, even though the patient exercised as much as she cared to.[25]

Case III: Urticaria Hemorrhagica

The patient was a 46 year old male. He had been in good health until six years previous, when his left hand suddenly began to swell and a patchy red eruption appeared on the right leg. By the next day the eruption was on all the extremities and was associated with their swelling and with joint pains. This subsided in three weeks and recurred at intervals of ninety days. Hematemesis, hematuria and bloody stools accompanied the attacks. He was diagnosed four years ago as a purpura hemorrhagica patient and a splenectomy performed. The symptons recurred nine months later and once again recurrences were noted at irregular intervals. "Colds" were said to precipitate the attacks.

Extensive laboratory work was done with the blood.

foci of infection were searched for. The prostatic secretion was found to contain streptococcus viridans and staphylococcus albus. These cultures were injected into rabbits and forty-eight hours later small hemorrhages were found on their thighs.

This was thought to be an example of hemorrhages occuring into the skin as the result of an allergical reaction, with the patient being hypersensitive to the bacteria, or their products.[31]

(It is possible that this rare form of urticaria is merely an exaggeration of the usual urticarial reaction, in which a transudation of fluid occurs from the lymph or blood vessels into surrounding tissue. In hemorrhagic urticaria, plasma and serum elements may pass intact through the capillary walls to the tissue, causing purpuric spots).

Case IV: Urticaria Pigmentosa

A Mexican girl, aged 9 months, developed an urticarial rash over the buttocks at 6 months of age. The rash faded in a few days and in the next week a reddish-brown, nodular eruption appeared. The nodules were about one-eighth to one-fourth inch in diameter and appeared on the arms, legs, trunk and neck. Marked dermatographia was elicited. No pruritus could be demonstrated. Enlarged glands were found in the groin, axilla and neck. Family history and

Wassermann were negative. The thymus was not enlarged.

Microscopically the nodules contained mast cells, melanin pigment. Surrounding the blood vessels and the base of the papillae were several layers of oval cells with round nuclei containing dense chromatin. The connective tissue was hyaline in character.[134]

Treatment has been unsatisfactory in these rare cases of urticaria pigmentosa and none was recorded in this case.

Case V: Urticaria Factitia

A boy, aged 8, whose father had been subject to asthma for a great many years, had been subject since infancy to hives which would follow scratching of the skin.

The rest of the history, physical examination, laboratory, and roentgen examination were negative. Skin test were all negative.

A slight scratch of the skin caused a whaal to form. Rubbing with a smooth object vigorously would not produce the hives. Freezing the skin with ethyl chloride resulted in a wheal. Other physical allergens gave negative results.

Reaction of the skin exhausted it locally so that it would not respond to further application of the irritating agent.

The administration of epinephrin (0.5 cubic centimeter subcutaneously) did not prevent reactions.[3]

Case VI: Lichen Urticaria

"A child, age 4 years, has a severly itching disorder of the trunk and extremities of two and a half month's duration. The mother states that the itching is so severe that it keeps the child awake a large part of the night and that there seems to be little or no irritation during the day.

She states that by looking at the eruption at present we can have no conception of the way it appears at night, in that during the night she notices numerous places which resemble mosquito bites and that these are not now present.

The child has an older brother and sister and a younger brother, none of whom is affected.

The mother further state that she is able to relieve the child somewhat by bathing the parts with a solution of soda.

So far as she knows the child is in every other respect perfectly normal. She has always followed the instructions of the Infant Welfare as regards the diet of her children."[38]

Case VII: Angioneurotic Edema

A 15 year old, Porto Rican boy had been in good health until ten days before admittance to the hospital. He noticed pain in the ankle, knee, elbow, and shoulder joints at that time. Also, the upper lip and nostrils began to

swell.

His family history was negative. He gave no history of previous allergical manifestations, relating to himself.

Physical examination showed edema of the lip and nostrils. The mucosa of the left antrum was thickened. A systolic murmur and diastolic murmur were heard. Both elbow joints, right knee joint, both ankle and both hip joints were tender and swollen.

The Wassermann and urinalysis were negative. The white count was 17,000. A diagnosis of active rheumatic heart disease with rheumatic polyarthritis was made. He was placed on salicylates for three weeks. Five weeks later the temperature was back to normal. Pain and swelling of the joints disappeared. The leucocyte count became 6,500. Edema of the upper lip persisted, as did an eosinophilia of from two to twelve percent.

Extensive skin tests gave only a one-plus reaction to old tuberculin and a two-plus reaction to streptococcus hemolyticus.

Later, the ova of Trichocephalus dispar were found in the feces and anthelmintic treatment started. Edema of the upper lip had subsided somewhat but there was still an eosinophilia of about four percent.

Six months after the onset of the rheumatic fever and angioneurotic edema, there was still a swelling of the upper lip present. No ova were found at this time. There were no further attacks of polyarthritis.[135]

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