AN APPROACH TO THE IDEAL ANTIHYPERTENSIVE

(A Clinical Research Review)

THE newer diuretic agents of the chlorothiazide group possess definite antihypertensive properties, particularly when given with established antihypertensive drugs. A combination of a new diuretic, flumethiazide, with the standardized whole root of Rauwolfia serpentina has been found to represent a therapeutic advance of considerable importance in the treatment of hypertension.

Flumethiazide, which is the trifluoromethyl homologue of chlorothiazide, causes excretion of sodium equal to that seen with chlorothiazide, but its excretion of potassium is lower than with other saluretics. Moyer et al[1] observed that "By contrast to hydrochlorothiazide, the primary effect of flumethiazide is on natriuresis and not chloruresis. The latter compound also has less effect on potassium excretion than do chlorothiazide and hydrochlorothiazide." The diminished excretion of potassium is particularly important for patients with hypertensive cardiac disease or patients on digitalis. Excretion of bicarbonate with flumethiazide is also lower than with chlorothiazide, so there is less likelihood of producing acidosis. Homeostasis is better maintained and this is a prime consideration in long-term antihypertensive therapy. Flumethiazide was synthesized and developed by Squibb who have introduced it in combination with rauwolfia under the name Rautrax.

The rauwolfia preparation employed in Rautrax tablets is Raudixin, the clinical applications of which have been described by Gilchrist,[2] Galambos,[3] Leslie[4] and other investigators. Raudixin represents the neural-antihypertensive agent described as the "rauwolfia preparation of choice."[5] This standardised whole root of Rauwolfia serpentina is less likely to produce depression, Parkinson-like symptoms or over-sedation than any of the rauwolfia alkaloids used alone. The combination of flumethiazide and Raudixin provides an example of truly significant therapeutic potentiation.

Although Rautrax contains the saluretic which causes less potassium loss than occurs with chlorothiazide or hydrochlorothiazide, potassium supplementation is still considered desirable, especially when therapy extends over prolonged periods. Potassium chloride is provided in Rautrax to help make up for any differences that may occur between potassium intake with food and potassium loss. This is particularly important for patients with cardiac involvement. Fixed inclusion of potassium in the daily antihypertensive dose is most convenient and safest for these patients.

Because it is safe, effective, well tolerated and simple to administer Rautrax closely approaches the ideal antihypertensive. It is indicated in mild to severe hypertension and is especially useful for patients with hypertensive cardiac disease and latent or overt heart failure, because of loss of oedema fluid. The suggested initial dosage is 2 to 6 tablets daily in divided doses. For maintenance therapy 2 tablets in divided doses daily have proved adequate in many cases, the maintenance range being 1 to 6 tablets per diem.

Decreased unwanted reactions are a main feature of Rautrax. As with any potent diuretic of the class to which flumethiazide belongs, hypochloraemic alkalosis with or without hypokalaemia may occur in some individuals in spite of the supplementary potassium chloride provided. Cirrhotic patients have been reported to be particularly prone to the development of hypokalaemia. For this reason, cirrhotic patients or those with rigidly restricted sodium intake should be watched for early signs of fluid and/or electrolyte disturbances. Care is needed in treating patients with severely damaged kidneys and low urine output. However, there are no absolute contraindications to the use of Rautrax which offers new and more effective means of controlling high blood pressure with added safety and convenience for the patients.

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Heat, exertion, trauma. Morgan[30] stated that heat, and exertion which produces heat, could rise to cholinergic urticaria; and that this is probably induced by the liberation of acetylcholine through the parasympathetic nervous system with a secondary release of histamine.

Light. Wolf[29] suggested that light altered the tissue-protein constituents of the skin, rendering them antigenic, and Ehrlich[31] agreed that light urticaria was an allergic rather than a photo-dynamic phenomenon on the fact that passive-transfer reactions were positive although all agents failed to relieve the patient. Partington[32] also found that the reaction in man due to ultraviolet light was not influenced by antihistamines. Epstein,[33] in an interesting study, referred to work on the mechanism of solar urticaria, differentiating that due to visible light, where the passive-transfer test was negative, and that caused by ultraviolet light, where this test was positive and the condition helped by antihistamine therapy. Claesson *et al.*[34] thought that the active substances in the action of ultraviolet light on the skin could not be clearly defined nor could the participation of histamine or histamine-like substances be confirmed. From their experimental investigations they concluded that the mediator substance in the skin was 5-hydroxytryptamine or some similar agent.

Infection

The question of the existence of true bacterial allergy is a controversial one. While positive tuberculin, mallein, lepromin and similar skin reactions, as well as the association of streptococcus products with rheumatic fever, indicate sensitivity to the corresponding microorganisms, it is not so easy to establish scientifically that the bacteria of the respiratory or gastro-intestinal tract are in fact responsible for the usual allergic manifestations which characterize hay fever, vasomotor rhinitis, asthma, eczema, etc. There is thus reason for the doubt that bacterial sensitization is responsible for urticaria, although the possibility of the production of histamine or histamine-like substances by their metabolic activities under certain circumstances cannot be overlooked.

Dutton,[35] some 12 years ago, concluded from his studies of chronic urticaria that low-grade chronic infection was the commonest aetiological factor. There is, however, little agreement with this view. Kahn and Grothaus[22] did not find the correction of infected foci of value. Similarly Siegel and Bergeron,[7] in their study of 115 cases of urticaria and angioneurotic oedema in children and young adults, did not observe a cause-and-effect relationship on removal of infections or infestations; and Mitchell *et al.*[8] also felt that focal infection was not significant. In our experience, whilst we always recommend search for and elimination of foci of infection, we have not often found laboratory evidence of such infections in persons with chronic urticaria.

Infestation with animal parasites has been reported in aetiological association with urticaria—especially the intestinal worms (ascaris, oxyuris, tapeworm); amoebiasis and hydatid disease have also been held responsible. Cohen and Criep[36] referred to previous reports of urticaria occurring with malaria and infestation with roundworms and flatworms, and described their own findings of chronic urticaria of undetermined aetiology in 28 patients where 19 had an associated amoebiasis. Thomas and Rideout[37] also quoted evidence of urticaria accompanying malarial paroxysms and disappearing after the administration of antimalarial drugs. They described a patient with vivax malaria where the initial paroxysm was accompanied by giant urticaria and oedema of the glottis, which reappeared in the second paroxysm.

The finding of blood leucocytosis would be helpful in confirming a state of infection, and eosinophilia if present would lead to the suspicion of the presence of animal parasites.

Psychological

There is considerable difference of opinion about the part played by emotional factors in skin lesions, including urticaria, but there is little doubt of this association, even if not in a primary role.

Graham, Wolf and Wolff[38] showed that changes in tissue sensitivity occurred with varying life situations and emotions. They demonstrated that the arterioles and minute vessels of the skin exhibited dramatic changes in function during experimentally-induced alteration in feeling states. Certain persons during periods of resentment in reaction to symbols of assault exhibited dilatation of arterioles followed by transudation of fluid resulting in oedema of the skin. Further, under these circumstances the skin exhibited increased sensitivity to a host of foods, pollens, drugs and simpler chemical agents. Kaywin,[39] in the study of emotional factors in urticaria, concluded that the onset of attacks was precipitated by a particularly frustrating experience in a shy, withdrawn, easily-embarrassed, passive, dependent and immature person. Graham[40] stated that dramatic life situations responsible for attacks were almost exclusively those in which the patient developed resentment when he saw himself a victim of unjust treatment about which he could do nothing.

Urticaria Associated with Other Diseases

Winkelmann[26] drew attention to the occurrence of chronic urticaria in association with certain systemic diseases including mastocytosis (urticaria pigmentosa), carcinoma, lymphoma, liver disease, rheumatoid states, and obstructive jaundice. In addition, transient urticaria is sometimes found in myelogenous leukaemia where the blood histamine level is high. Wolf[29] referred to its occurrence also in Loeffler's syndrome, periarteritis nodosa and Hodgkin's disease.

TREATMENT

In the treatment of the acute urticaria attack, antihistamine therapy is used successfully except perhaps in that due to penicillin. Loveless and Dworin,[41] as well as Steinhardt,[1] reported control in about 80% of cases. It is wise to persevere with antihistamine administration for a week or two after the urticaria has disappeared. Parker[42] found that in 20 cases not responsive to antihistamine alone the patients benefited by combined calcium-antithistamine therapy.

Adrenaline or ephedrine is indicated in acute forms of urticaria, and ACTH or corticosteroids may be essential in severe forms of angioneurotic oedema.

Complaint by the patient of accompanying gastro-intestinal discomfort may be revealing, because nausea, vomiting, colic and diarrhoea may be further evidence of a food idiosyncrasy. Foodstuffs considered aetiologically responsible should of course be avoided by the patient.

A thorough physical examination is essential in each case of urticaria, more especially to find any underlying disorders and to determine the presence of foci of infection serving to keep alive urticarial manifestations. In this connection especial attention should be paid to dental, nasopharyngeal, gastro-intestinal, gall-bladder, prostatic, cervical and other infections.

As has been shown above, infection as an aetiological agent in urticaria is not accepted by everybody. Nevertheless

there is a possibility that during an infected state the tolerance to histamine produced by allergic or other mechanisms may be lowered. Laboratory aid should be invoked in the search for animal parasites or unusual bacteria, and in the examination of the blood for eosinophilia and leucocytosis.

Close attention should be given to the question of drugs in the aetiology. The patient should be questioned about the recent therapeutic administration of penicillin or other antibiotics. It should be remembered that urticaria may appear as a late sequel perhaps weeks after penicillin has been given. As the patient may not be acquainted with drugs medically administered he should be asked about recent illnesses or operations where medicaments of some kind might have been given. It is wise to refer to 'medicines' rather than to 'drugs' in this connection because in the latter expression he would not be likely to include laxatives, sedatives, headache powders, sleeping tablets, tranquillizers, nerve or health tonics, and similar household remedies.

In the control of chronic urticaria it is important not to be obsessed with the idea that the condition is of necessity an allergic disorder. An indication will usually be obtained from a detailed history of the patient whether there is an allergic basis or whether endogenous physical, infective, endocrine or pyschological factors are predominant. A family history of allergy or a personal history of asthma, hay fever, sinusitis or atopic eczema may confirm a suspicion of an allergic origin in a particular case. Further careful questioning, supported by skin testing if necessary, will suggest inhalant factors or foodstuffs responsible for the condition. If so, these should be avoided if possible or specific desensitization against the inhalant sensitivities should be carried out.

In chronic urticaria histamine desensitization is generally not of much value, although it has been found of benefit in urticaria due to penicillin and it should be tried in the so-called physical allergy where urticarial wheals are associated with pressure, heat, cold, light or friction.

Saline purgatives may be required both to reduce fluid in the tissues and to remove irritating foreign substances from the gastro-intestinal tract.

Walzer,[44] in his studies of the experimental wheal, demonstrated that it was induced faster when alcohol was ingested with or before the specific whealing food. This may be an indication for the patient to avoid alcohol, with its vasodilating effects, as well as stimulating foods.

Vitamin K by mouth was recommended by Black,[43] who found a diminished level of prothrombin, sometimes notably so, in 65% of 156 chronic urticaria patients studied. There was relief in 60% of the cases, particularly in those patients showing a prolonged coagulation time.

The possibility of overt penicillin ingested in milk or other dairy products should be borne in mind.

If, after thorough investigation, allergic, infective or other causal agents cannot be detected, consideration should be given to the possibility that stress factors are responsible for the skin manifestations.

The therapeutic approach to the psychogenic basis of physical disorders is, of course, a study in itself. As a rule there is no need for specialized psychotherapeutic measures. Encouragement of the patient to talk of his condition will generally reveal to the experienced physician a broad picture of his emotional state and an attempt should be made in the course of further sessions to assess its nature and significance. This type of interview conducted with patience and understanding will in itself benefit the patient, and every effort should be made in the course of these talks to give him an understanding of the fact that both physical and emotional stresses may be productive of the same type of bodily reaction. It must be remembered, however, that the stress state itself need not be the sole cause of the skin trouble. It may well be that under such circumstances urticaria may result from drugs or infections, as well as from allergens which would probably be tolerated without symptoms under normal conditions.

SUMMARY

The clinical and pathological aspects of urticaria and angioneurotic oedema are described.

Attention is drawn to the relatively low incidence of urticaria in the African (Bantu) population.

The aetiology of urticaria is discussed as an allergic disorder associated with the release of histamine or histamine-like substances in the characteristic antigen-antibody reaction of allergy and as a manifestation of their release by other mechanisms.

A classification of the possible causative factors of acute and chronic urticaria and angioneurotic oedema is given and explanatory comments made on some of the more important *exogenous agents* (inhalants, ingestants and contactants) and *endogenous factors* (physical, infective and psychological) involved.

The treatment of the acute attack and the approach to the control of chronic urticaria are suggested.

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