and there was marked paradoxical movement of the sternum on inspiration. X-ray examination showed a rotation of the heart into the left chest. Angiocardiogram revealed no filling defect. E.C.G. was normal and the circulation time using dehydrocholic acid was seven seconds. In July, 1952, the deformity was repaired. The result is shown in Fig. 3. At her last follow-up, 10 months after operation, there was no recurrence of deformity, her posture was excellent, and she had no disability.

Case 2.—A boy aged 5 had been subject to "bronchitis" all his life. The deformity was first noticed when he was 2½, and it had progressed since. In all respects he seemed a healthy boy except for his recurrent chest infections. On examination a well-marked deformity was seen. On inspiration there was a severe degree of paradoxical movement of the sternum. Repair was carried out. He had a well-formed substernal ligament, and when this was divided the xiphoid and recti sprang away. The mistake was made of not being radical enough; the third costal cartilage should have been removed on either side. His follow-up from the cosmetic point of view was disappointing in that there was some overgrowth of the third costal cartilage. There was no paradox, and since his operation nine months previously he had had no further attacks of bronchitis; this was the longest period he had been free of chest infection.

Case 3.—A boy aged 10½ was completely symptomless. His parents requested the operation because they were a Service family and were anxious for the boy to go ultimately into the Services. Also, they lived in a families camp and

FIG. 4

FIG. 5

FIG. 4.—Case 3. This patient had no symptoms. FIG. 5.—Case 3. Photograph taken just before discharge.

had seen a previous case returned from the unit. Fig. 4 shows the degree of deformity. This boy had a marked paradox. Fig. 5 was taken immediately before his discharge and well illustrates the need for close supervision over the next three to five months.

Case 4.—A girl aged 13 complained of pain in the xiphisternal region associated with exercise. It was a sharp non-radiating pain. It had been present for one year. She became more breathless than her friends and at times found it difficult to keep up with them. Because of a murmur in her heart the school doctor had years previously told her that she had heart trouble. Examination showed typical funnel-chest deformity. There was a systolic murmur over the mitral area. The deformity was repaired; the murmur has now disappeared, and she indulges in full activities without any discomfort.

[Since this paper was submitted five additional cases have been repaired. They have all done well and no complications have arisen.]

Summary

The current concepts of pectus excavatum are briefly reviewed.

A prophylactic operation is advised at an early age to prevent a progressive and permanent deformity. The two main indications for surgery are cosmetic and symptomatic. The technique employed requires no external traction or added internal support. In infancy the dividing of the xiphisternal joint and freeing of the sternum from the diaphragm correct the deformity. Older subjects require the added resection of all deformed costal cartilages and a transverse wedge osteotomy of the sternum.

Ten patients treated by this method are presented. There were no deaths or complications. The early results are satisfactory and encouraging. It is necessary to be radical and to excise all the deformed cartilages.

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ANTIHISTAMINE THERAPY

WITH SPECIAL REFERENCE TO SKIN DISORDERS

BY

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During the past five years a separate out-patient clinic has been held twice a month for the purpose of studying the administration and overall value of the antihistamine group of drugs. Most of the patients attending the clinic have had urticaria. The main problems connected with the use of these drugs can be dealt with under headings of administration, ill-effects, and skin disorders affected.

The Drugs Available

The following drugs of the group are available for oral use in this country.

Official Name	Proprietary Name
Antazoline	Antistin (Ciba)
"	Histotab (Boots)
"	Ben-a-Hist (Bencard)
Bromazine	Ambodryl (Parke, Davis)
Chlorcyclizine hydrochloride	Histantin (Burroughs Wellcome)
"	Di-paralene (Abbott)
Diphenhydramine hydrochloride	Benadryl (Parke, Davis)
Mepyramine maleate	Anthisan (May & Baker)
Methaphenilene hydrochloride	Diatrin (Warner)
Phenindamine hydrogen tartrate	Theophorin (Roche)
Promethazine hydrochloride	Phenergan (May & Baker)
Tripeleannamine hydrochloride	Pyribenzamine (Ciba)
Meclozine dihydrochloride	Ancolan (B.D.H.)
None	Aetidil (Burroughs Wellcome)
None	Synopen (Geigy)

"Dibistin" (Ciba) is a mixture of antazoline and tripeleannamine.

"Avomine" (M. & B.) and dimenhydrinate ("dramamine," Searle) contain antihistamines but are primarily used for travel sickness.

There is not much information available about the equieffective doses of the various drugs. In conjunction with Professor W. A. Bain, I carried out comparisons of various drugs in their effects on induced histamine weals in man. It was then found that for single doses 40 mg. of promethazine was equivalent to 275 mg. of mepyramine and 600 mg. of antazoline (Bain, 1949). With repeated doses the drugs with a long action, such as promethazine, will build up a greater effect; and after a week's therapy promethazine, 40 mg., was found to be equivalent to mepyramine, 560 mg., given in a 24-hour period.

The specific histamine antagonism is apparently the same with all the drugs, but the nature and degree of side-effects vary. It is the incidence of the latter, when equieffective doses of the drugs are compared, that usually determines which is the most suitable drug. In a clinical assessment (Bain, Hellier, and Warin, 1948) it was shown that the incidence of drowsiness was greater with diphenhydramine than with mepyramine. When promethazine given in a single dose at night was compared in this respect with mepyramine given three times a day, the side-effects were less, and most patients preferred promethazine (Bain, Broadbent, and Warin, 1949). Recently a similar comparison has been undertaken, using promethazine in a single dose at night and chlorcyclizine given twice a day. Forty-nine patients with persistent urticaria were treated with the drugs in turn, and the dose in each case was adjusted to a level giving approximately the same degree of reduction of the wealing. Nineteen patients had some side-effects with one or both drugs. In seven of these they were less or nil when on chlorcyclizine, in two they were less or nil on promethazine, and in 10 there was no difference. In this clinical comparison chlorcyclizine, 75 mg., gave approximately the same effect as promethazine, 25 mg.

From the preliminary tests it was shown that antazoline was a relatively weak antihistamine, and it has not been used in the clinical work. Tripeleminamine has a similar structure to mepyramine and its effects are about the same.

Meclozine, phenindamine, and methaphenilene do not appear to have any useful advantage over the others, but, together with the recent additions, bromazine, "actidil," and "synopen," my experience with these drugs has been limited, and no clear comparison seems to be available.

In the clinic the main drug used has been chlorcyclizine, but a few patients have had promethazine or mepyramine, and in some cases diphenhydramine has been used when the additional sedative action has been required.

Practical Points in Administration

The dose of the drugs required to suppress weals varies greatly. Apart from the question of body weight and age it has been shown that individual patients vary considerably in the degree of histamine antagonism given by the same dose of one of the drugs (Bain *et al.*, 1948). Thus the same degree of histamine antagonism given in one patient by, for example, 300 mg. of mepyramine a day may be given in another by 900 mg. If a patient shows a small antihistamine effect with one drug of the series, a small effect will generally be given by the other drugs. In the practical administration of the drugs the variation in response is usually overcome by giving the patient an average dose, and if the symptoms are not controlled the dose is raised until either the desired effect is brought about or side-effects become too great.

In addition to this variation in individual response to the drugs the strength of stimulus evoking the treated disorder will vary from patient to patient. If the tendency to urticaria is very great even in a patient relatively sensitive to the antihistamine, it may be impossible to reach a high enough dose of the drug to control the eruption. This is more often seen in the acute attacks of urticaria.

The strength of the stimulus may also fluctuate in the same patient. For example, urticarial weals satisfactorily

suppressed by certain doses of an antihistamine may suddenly reappear coincident with additional psychological stress, or other factor. In such a case higher doses of the drug may again suppress the weals (Warin, 1950a).

Judged by the response of the induced histamine weal, children are relatively insensitive to antihistamines, and consequently a larger amount than the usual proportional age reduction of the dose is necessary to get an effect on weal formation.

The frequency of administration will vary with the length of action of the drugs: promethazine has a long action, and if given in a single dose may control the urticaria throughout the 24 hours. However, in some patients on a single dose the weals return towards the end of the 24-hour period. This could, of course, be controlled by giving a second dose, but can also often be controlled by increasing the single nightly dose. Chlorcyclizine is relatively long-lasting and it seems satisfactory to give the drug twice a day. With mepyramine it is usually necessary to give the dose three or four times a day.

Chronic urticaria quite often fluctuates regularly throughout the 24-hour period, appearing or becoming worse in the evening or in the early hours of the morning. When this is so the drugs should obviously be given to allow the maximum antihistamine effect at this time. The time taken from ingestion to full effect is about two to four hours with most of the drugs. Therefore, for example, in a patient who has a persistent slight wealing but exacerbations in the late evening, the best method of administration might be to use chlorcyclizine, 50 mg. in the morning and 100 mg. at tea-time. In a patient requiring large doses of an antihistamine one may be able to avoid unpleasant side-effects at work or during the daytime by so adjusting the times of administration.

The antihistamine drugs vary in the rapidity of onset of action after ingestion. The new drug actidil apparently reaches its maximum effect more quickly than the others, and it may prove to be the drug of choice when a rapid effect is required.

Often the type of patient who suffers from a persistent urticaria does not sleep well, quite apart from any itching, and in these cases it may be worth while giving at night one of the antihistamine drugs, which usually produces a drowsy effect. Diphenhydramine and promethazine are perhaps the best for this purpose, and, indeed, recently they have been used deliberately as mild sedatives. The drugs can be mixed, and a quite useful combination is chlorcyclizine, 50 mg. twice daily, with diphenhydramine, 50 mg. at night.

The dose should always be gradually reduced before discontinuing treatment. Otherwise, if the tendency to urticaria remains unchanged, the patient may find a sudden and full return of the rash very distressing.

Sometimes the conditions treated are periodic, with intervals of a few weeks between attacks, and in these cases it may be as well to start off with a period of regular daily administration, but later on it is often satisfactory to give the patient a supply of the tablets to take for a few days as soon as the attack begins.

Ill-effects of Antihistamines

The main side-effect of the antihistamines is drowsiness. As has been discussed, this is commoner with some drugs, and is, of course, more often encountered when large doses are employed. It is very difficult to assess the overall incidence of drowsiness. On direct questioning practically all intelligent sensitive patients having average doses will have noticed a little drowsiness. The danger of drivers and workmen in hazardous occupations taking the drugs is of course present, but has probably been overemphasized. Under such circumstances the first dose should, if possible, be taken at a week-end or, if more urgent, in the evening after returning home. In the clinic a number of public transport drivers and a motor-cycle "speedway" rider have been treated for long periods.

Many other side-effects have been described; these include dryness of the mouth, headache, blurred vision, dysuria, nightmares, depression, and other mental changes.

A curious effect is that of a twitching sensation, which is usually felt more in the legs. The muscles ache and the patient is constantly moving and stretching the limbs. Restlessness and a desire to get up and walk about are often felt. This side-effect was first noticed with promethazine (Warin, 1950b), but during the past two years it has been noted with chlorcyclizine and also with diphenhydramine. The symptoms may not be described by the patient, but are not uncommon if specifically inquired about.

Mepyramine and tripeleminamine sometimes give rise to nausea, vomiting, abdominal colic, and diarrhoea. These side-effects are uncommon if it is remembered to give the drugs with or after meals. In potential epileptics the drugs occasionally produce fits (Churchill and Gammon, 1949).

Death associated with convulsions has been recorded in 14 cases when large overdoses have been swallowed accidentally by children. In only one of these children did the amount taken approach the therapeutic dose. This occurred in a child aged 14 months who died after accidentally taking mepyramine tablets, the dose of which was unknown, but assessed at 2-300 mg. (Prain, 1950).

Wyngaarden and Seevers (1951) mention reports of three cases of haemolytic anaemia and nine cases of agranulocytosis. In one of the latter the patient, who had mepyramine for three months, died (Glassmire, 1951). Bénard and others (1947) report the case of a patient who died with jaundice and anaemia, but this did not appear to be definitely related to the small dose of "anergan" administered.

Considering the vast amount of the drugs used throughout the world, these few cases have little significance, and it seems that in general these substances are relatively free from serious toxic effects in therapeutic doses, even when administered for prolonged periods. Some patients in the clinic have now received regular and continuous treatment for three to four years without any deleterious effects. There is no definite evidence that tolerance to the antihistamine effect of the drugs occurs. Certainly the drowsy side-effects often become less after a few days and patients may think that they are becoming tolerant to the drugs. It is also possible that the tendency to urticaria becomes greater and gives rise to an increase in weals in a patient in whom the rash was previously reduced, so creating an impression that tolerance was developing. However, the degree of reduction of the induced histamine weal after many months' treatment is unaltered (Warin, 1948).

Skin Disorders Affected

Acute chronic and papular urticaria, dermatographism, and the urticarial response from stings and bites can all be affected. The weals may be completely suppressed or they may just be reduced in number and size according to the level of antihistamine effect obtained. If the underlying stimulus to the urticarial reaction is considerable, as may occur with drug or food urticaria, or if the patient is relatively resistant to the drugs, as, for example, in children with papular urticaria, the weals may not be obviously affected by the doses commonly prescribed.

Although it is not intended here to discuss in detail the clinical value of suppressing or reducing the weals in urticaria, the main conclusions might be mentioned. When the attack is self-limited, as in acute or recurrent urticaria, symptomatic relief with the drugs will have an obvious place in treatment. In chronic urticaria the weals are reduced or suppressed only so long as the drugs are given, and treatment may have to be continued for many months. The period that the underlying tendency to wealing lasts is probably neither shortened nor prolonged by such treatment, but as in most cases considerable relief is obtained

it is thought that antihistamine treatment has an important place in the management of these cases.

It is very difficult to decide how much giant urticarial swellings are affected by antihistamines. In such giant urticaria (angioneurotic oedema or Quincke's oedema) the oedema is largely in the subcutaneous tissues. These swellings may or may not occur in association with chronic urticaria. Clearly they do not respond to antihistamines as well as the ordinary dermal weals, and when both conditions are present the dermal weals can often be completely suppressed while giant swellings may still occur. Fifty-two cases with recurrent giant swellings have been treated, and, although it is very difficult to institute adequate controls in a condition with such irregular manifestations, 40 patients have had a reduction in the number and size of swellings when on antihistamines. Furthermore, there was usually a reduction in the severity and length of time the swellings were present if the drugs were given only at the earliest possible stage in an attack. It therefore seems that, although not affected as much as dermal weals, subcutaneous swellings are reduced.

A type of wealing may occur in association with certain other eruptions, including dermatitis herpetiformis, erythema multiforme, and actinic prurigo. An attempt to assess the effect of antihistamines on these conditions has been made, the antihistamine effect being checked by noting the reduction of induced histamine weals and using a mild sedative in the control periods (Warin, 1950a). In 10 cases of dermatitis herpetiformis it was concluded that, although one or two patients appeared to be improved, in general no specific action on this condition could be demonstrated. Since then a number of cases have been treated, and it has appeared that the cases benefited have been those in which the weal element of the rash has been a prominent feature. Ten cases of actinic prurigo were also assessed in a similar manner: although conclusions were not definite there was apparently some effect from antihistamines. It has proved very difficult to decide whether or not erythema multiforme lesions are reduced.

The eczematous dermatitis reaction affects the epidermis chiefly, but in some cases the skin is raised and tense owing to an associated dermal oedema. In my experience it is only this latter type of the eczematous dermatitis reaction which is affected, and then only with regard to the dermal oedema. The drugs have been used to reduce pruritus from various causes, but it is only the type associated with wealing, as in urticaria, that can regularly be affected.

From time to time it has been claimed that certain other eruptions are affected by the drugs, but as experience becomes wider the number of conditions benefited becomes smaller and it may well be shown eventually that the only conditions affected are those in which wealing is part of the eruption. Halpern (1952) has suggested that the main effect of antihistaminic substances is on the neuromuscular mechanism of certain small vessels. As wealing is dependent on the dilatation of small vessels in the dermis, it would seem likely that the main action of the drugs is to antagonize the dilatatory action of histamine on the dermal vessels and to a less extent on the subcutaneous vessels.

Summary

The antihistamine drugs available in this country are listed and compared.¹

Certain practical points in administration of the drugs are mentioned.

Ill-effects of the drugs are discussed.

The skin disorders affected are discussed, and it would seem possible that the only conditions of the skin which are benefited by antihistamines are those in which wealing is part of the eruption.

I would like to express my thanks to Dr. C. D. Evans for so kindly referring many patients to me.

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INCIDENCE OF ALLERGIC DISEASES IN GENERAL PRACTICE

BY

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The symptoms of allergic disorders depend upon the antigen-antibody reaction in the shock organ. Von Pirquet defined allergy as an "acquired specific altered capacity to react." Even after 50 years of research in this field, Pepys (1953) points out that this statement is still valid.

The findings of a collagen lesion in serum sickness, periarteritis nodosa, lupus erythematosus, and rheumatic fever, and the improvement in these conditions after cortisone or A.C.T.H. therapy, suggest that allergic reactions might play some part in their aetiology. We decided to investigate the incidence of five of the common allergic diseases in our practice—namely, bronchial asthma, allergic rhinitis, urticaria, atopic eczema, and drug allergy.

The practice, an industrial one comprising about 4,000 patients, is carried on from two surgeries. Details of attendances and treatment are recorded daily in each surgery. The period of this investigation was from September 1, 1952, to September 1, 1953.

Diagnosis of the Allergic Diseases

Only a brief account of the diagnosis and differential diagnosis of allergic diseases is given.

The general practitioner has the best opportunity of diagnosing common allergic diseases. A careful history-taking is most important, and should include the main complaints, details relating to the cause of illness, past medical history, family and social history, environmental background, and history of previous treatment. History-taking has been emphasized by Tuft (1949), Herxheimer (1952), Sheldon *et al.* (1953), and other allergists. The therapeutic application of adrenaline and ephedrine in acute attacks of asthma and antihistamines in allergic rhinitis and urticaria is helpful in establishing the diagnosis.

We agree with Freeman (1950) that x-ray examination of the chest in asthma is not essential. Laboratory investigations, skin tests, and estimations of vital capacity are more useful for the management of the patients than for diagnosis. Cases of chronic bronchitis and emphysema were excluded.

In allergic rhinitis a history of recurrent attacks of rhinorrhoea, sneezing, itching in the eyes, nose, and pharynx, and a general feeling of fatigue are the complaints. Examination reveals bluish oedema of the nasal mucosa and sometimes polypi. Sheldon *et al.* point out that sore throat and enlargement of cervical lymph nodes are not common

in allergic rhinitis. The finding of large numbers of eosinophils in nasal smears helps in doubtful cases.

Urticaria may be acute or chronic: the acute type generally disappears within a few days or weeks; chronic urticaria may continue for months or years (Tuft, 1949; Sheldon *et al.*, 1953). The patient complains of an itching or burning sensation. The diagnosis is made on the finding of weals, which may vary in size and shape.

Atopic eczema was diagnosed by the finding of superficial cutaneous eruptions involving the flexural surfaces; adequate history is very important (Vickers, 1952; Sheldon *et al.*, 1953).

Drug allergy presents a great problem. A memorandum on the sensitivity of antibiotics (*Med. Offr.*, 1953) emphasizes the importance of this subject. Reports of deaths attributed to phenylbutazone have appeared in the medical and lay press. Penicillin may cause dangerous or even fatal reactions (Pick and Patterson, 1953; Siegal *et al.*, 1953). Drug allergy may develop after ingestion, parenteral injections, or contact with the offending agent, and it may manifest itself in the immediate or delayed type of reaction (Rackemann, 1953; Pepys, 1953; Sheldon *et al.*, 1953). The manifestations of drug allergy are various, the commonest being the skin lesions. The most serious, however, are agranulocytosis and thrombocytopenia, and thiouracil is the common cause of the former and "sedormid" (Grant, 1953) of the latter. Diagnosis depends on history, general examination, and cessation of symptoms on stopping the offending drug.

Differential Diagnosis

The diagnosis of straightforward cases of allergic disease, like many other medical or surgical conditions, is not difficult. The elderly hypertensive and arteriosclerotic patient with incipient cardiac failure gets attacks of dyspnoea; the child with recurrent attacks of bronchitis and bronchiolitis presents wheezing and cough. Periarteritis nodosa or Löfller's syndrome (Rubin, 1947) brings on asthma-like attacks. Here the eosinophil count is of great value. Bronchogenic carcinoma is getting common, and we encountered one patient suffering from it who self-diagnosed asthma.

Septal deflections, enlarged turbinates, enlarged tonsils and adenoids, infective sinusitis, and the common cold are the conditions mistaken for allergic rhinitis.

Children like to scratch the itchy urticaria weals; urticaria should then be differentiated from scabies or chickenpox.

In atopic eczema the secondary changes resulting from scratching and infection may lead to a variety of skin abnormalities: erythema, papules, wealing, scaling, pigmentation, and lichenification. Cases of seborrhoeic dermatitis and contact dermatitis were excluded.

Results of Observations

Table I shows the age and sex incidence of the five allergic diseases. Table II gives the percentage incidence of allergic diseases. Table III shows the duration of symptoms for each group. Drug allergy is of special interest

TABLE I.—Age and Sex Incidence of Allergic Diseases

Age	Asthma		Urticaria		Allergic Rhinitis		Atopic Eczema		Drug Allergy	
	M	F	M	F	M	F	M	F	M	F
0-1 ..	1		9	8			1			
2-4 ..	6		11	4	1		2			
5-9 ..	4	2	5	5		1	2			
10-14 ..	3	2	5	5	2					
15-19 ..	4		2	2		1				1
20-29 ..	3	2	1	2	2		1	2	1	
30-39 ..	6	9	4	1	6	4	6	1	2	2
40-49 ..	4	3	1	2	4	4	5	2	1	1
50-59 ..	4	9		3	1	3	1	1	1	2
60-69 ..		5		1	1		3			2
70+ ..	1			1						
Total ..	36	32	38	34	17	13	18	9	4	8
	68		72		30		27		12	