TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in current use.

Antihistamines

Antihistamines have a simple chemical structure, similar in some respects to other important classes of drugs. Their pharmacological actions are therefore closely related to those of these other drugs, and indeed it has never been possible to manufacture an antihistamine without other actions. However, many of these are useful, and, in certain circumstances, are the basis of therapeutic use. The great variety of available antihistamines is due to the many uses to which they are put and the ease with which the chemical criteria for antihistamine activity can be satisfied. The few antihistamines discussed in this review are selected representatives from the main classes of drugs of antihistaminic action, but should be suitable for the great majority of therapeutic needs.

Pharmacology

Absorption is rapid from the gastrointestinal tract and from injection sites. Effects begin within 15-30 minutes and continue for a varying length of time, 4-6 hours for most preparations. These drugs are excreted as unidentified metabolites in the urine, having undergone hydroxylation and glucuronide conjugation in the liver. An enterohepatic circulation exists for the hepatic metabolite of mepyramine. Caution is advised in giving antihistamines to patients with hepatic disease. There is every reason to expect an increased rate of metabolic breakdown in patients receiving barbiturates

Antihistaminic Actions

By definition, antihistamines antagonise the actions of histamine, and they do so by competing with histamine for the occupation of receptor sites. This is a competitive antagonism, quite different from the reversal of histamine effects by adrenaline, which acts on different receptor systems. Not all the effects of histamine can be antagonized to the same extent. Thus the smooth-muscle stimulating effects—the cause of bronchospasm—and the direct nerve-stimulating effect—the cause of the flare in the triple response and of pruritus—are almost completely antagonized. Antihistamines also reverse the vascular effects, such as the dilation of capillaries and the increase in their permeability.

The histamine-induced gastric acid production is not inhibited by antihistamines, though their secondary vagolytic effects reduce the amount of the response, which is partially vagus dependent.

Other Actions

Potentially desirable.—The basic structure of antihistamines is similar to the active part of atropine, its related alkaloids, and synthetic substances with peripheral and central atropine-like properties. A similar relationship can be seen to the local anaesthetics. Peripheral atropine-like properties, including dryness of the mouth, blurring of vision, and tachycardia, are well marked. The central effects, including both depression and stimulation of the C.N.S., convulsant and anticonvulsant properties, and suppression of motion sickness and tremor, are present to a variable extent. Local anaesthetic properties, including antidysrhythmic actions, are also present. Table I includes an attempt to quantify these various side-effects, but the value of such predictions is reduced by the considerable individual variation of response.

Anticholinergic actions are least marked with mepyramine and cyclizine. Diphenhydramine and promethazine regularly cause severe dryness of the mouth, blurring of vision, and palpitations. Neither drug should be given to a patient with glaucoma. Urinary symptoms are less troublesome.

Antihistamines share the ability of atropine alkaloids, especially scopolamine, to depress spontaneous activity in the electroencephalograph and reduce activation responses to light and hypothalamic and reticular activity. However, restlessness can also occur, and it must be concluded that mechanisms controlling spontaneous cortical activity are separate from those regulating consciousness. Stimulation of the higher centres causes alertness and convulsions may result in higher dosage or in patients with a focus of cortical excitability. Antihistamines should never be given to major epileptics. There is nothing paradoxical in a drug possessing both sets of actions. Depression of subcortical regions results in sleep and in higher dosage respiratory depression. The stimulant actions are less frequent, tend to occur in children, and may be seen in early overdosage. Most antihistamines, notably promethazine and diphenhydramine, cause somnolence. Mepyramine and chlorpheniramine are said to be less sedative, but there may be personal variation of response. Phenindamine is not sedative.

Antiadrenaline and antiserotonin actions are most marked in promethazine, in which they perhaps contribute to the sedative effects. Cyproheptadine, structurally quite similar to imipramine, has potent antiserotonin actions, and in addition to antihistamine actions it is useful in the carcinoid syndrome and in certain variants of migraine.

The valuable properties of antihistamines in motion sickness and tremor cannot be separated from ordinary atropine-like side-effects, but limited specificity has been achieved with cyclizine and meclozine, which are potent antiemetics without excessive atropine-like actions. Promethazine is also a potent antiemetic. Diphenhydramine and phenindamine have mod-

TABLE I.—*Side-effects of Antihistamines*

	Peripheral Atropine like Effects	Central Effects				Local Anaesthetic	Gastro-intestinal Effects	Other Effects
		Sedation	Stimulation[1]	Anti-emetic	Anti-Parkinsonian			
Mepyramine	+	+	+	0	0	++	++	
Antazoline	+	+	+	—	—	++	—	Antidysrhythmic
Diphenhydramine	+++	+++	+	++	++	+	0	
Chlorpheniramine	++	+	+	—	—	—	—	
Triprolidine	+	+	+	—	—	—	—	Photosensitization
Cyclizine	+	+	+	+++	—	—	+	Possibility of teratogenicity
Meclozine	+	+	+	+++	—	—	+	Photosensitization
Promethazine	+++	+++	+	++	+	+++	+	Adrenaline antagonism
Phenindamine	++	0	++	—	++	—	—	Serotonin antagonism
Cyproheptadine	++	++	+	—	—	++	—	

KEY: +++ Well marked effect. ++ Moderate effect. + Effect present 0 Effect not present.
— Information not sufficient to permit assessment, but unlikely to be striking.
1. Especially in children.

erate antitremor activity but are not the best available drugs for parkinsonian tremor.

All conventional antihistamines are local anaesthetics. This is an unobtrusive side-effect possessed notably by promethazine, mepyramine, and diphenhydramine. Antazoline, also a potent local anaesthetic, has quinidine-like cardiac actions of therapeutic interest.

Generally undesirable.—Loss of appetite, nausea, vomiting, epigastric distress, constipation, and diarrhoea have all been reported. These are not all readily explicable, but doubtless the combined effects of somnolence and lack of saliva and gastric secretion contribute to anorexia. Epigastric pain could well be a result of histamine release, as could diarrhoea, but the more usual constipation is an atropine-like action. Cyproheptadine is an appetite stimulant.

All antihistamines seem capable of sensitizing, especially in contact with the skin, and then particularly with exudative lesions, such as eczema. Similar risks are present with aerosols and nasal sprays. Photosensitivity is common with the phenothiazine antihistamines and is reported with triprolidine. The latter also has an interesting property of absorbing ultraviolet light, and has therefore been used as a sun-burn protective. Nevertheless, topical antihistamine lotions and creams are amongst the most common causes of iatrogenic skin eruptions seen in outpatient clinics by dermatologists, and their use should be discouraged.

Blood dyscrasias are not common, but agranulocytosis, thrombocytopenia, and haemolytic anaemia have all been reported.

Being sedative, antihistamines potentiate sedatives. The depressant effects of alcohol and morphine-like drugs are increased. Monoamine oxidase inhibitors should not be given to patients on antihistamines or vice versa for fear of atropine-like crises, as seen with imipramine and MAO inhibitors.

The piperazine antihistamines, cyclizine and meclozine, have been associated with teratogenicity, and this has been proved in at least one animal species. These potent antiemetics are therefore unsuitable in the first trimester of pregnancy.

The fatal adult dose of antihistamines may be as little as 20-30 tablets of one of the common drugs. The picture is dominated by atropine-like features, with convulsions, hallucinations, and later, respiratory depression. Dryness of the skin, pyrexia, and dilatation of the pupils are easily recognizable, especially in children. Absorption is so rapid that gastric lavage is usually too late. Symptomatic measures are indicated to control hyperpyrexia, convulsions, and respiratory depression, for which assisted ventilation may be required.

Uses of Antihistamines

Antagonism of histamine.—When histamine plays a part in the clinical syndrome produced by an immune reaction, that part of the syndrome, and that part only, can be antagonized by an antihistamine. Histamine-release is most common when there is cellular damage, but as this can happen in most immune reactions there is no specific reaction type for which antihistamines are likely to be beneficial. The tissue in which the reaction takes place is much more of a guide to the role of histamine; reactions involving the skin and upper respiratory tract have important histamine contributions. In more general reactions histamine plays at least some part in the vascular mechanisms.

Cutaneous manifestations in immune reactions are common, and the aspects most benefited with antihistamines are urticaria and pruritus. Erythema and angio-oedema are less satisfactorily antagonized. Urticaria occurs in penicillin and salicylate reactions, with pollen sensitivity, and in certain food allergies. When the only evidence of sensitivity is in the skin, good results are obtained from administering an antihistamine systemically and stopping the allergen, if this is possible. When a more general reaction with bronchospasm or profound hypotension is present, as in a well developed penicillin anaphylaxis, antihistamines are less useful. They cannot reverse the bronchospasm, which is due to slow-reacting substance, and they only partially reverse the vascular effects (there is a non-histamine component) and at a slow rate. Thus an antihistamine is only supplementary to the adrenaline required in general anaphylaxis.

Again, in serum sickness antihistamines dispel the urticaria but rarely benefit the arthralgia or pyrexia. Patients with high skin reactivity, as in neurosis or mastocytosis or with urticaria pigmentosa, react excessively to minor stimuli. An antihistamine reduces dermographism and the flushing in the skin of the neurotic and unduly sensitive. The pruritic aspects of exanthematous drug eruptions and contact dermatitis are treatable with an antihistamine, but in neither is the visible lesion benefited. Withdrawal of the drug in the former case and topical steroids in the latter are usually curative.

Excellent results are obtained in the pruritus and oedema of insect bites. The erythematous aspects of some other lesions are quite well controlled, but little benefit is found in erythema multiforme and exfoliative dermatitis. Generally beneficial results are obtained in angioneurotic oedema, but it must be understood that an antihistamine is less satisfactory than adrenaline when the site of the angio-oedema is life-endangering.

The other situation in which immune reactions provide a predominantly histamine response is the upper respiratory tract. Thus an antihistamine is very effective in seasonal hay fever, especially at the start of the season when the allergens are in low concentration. It may be necessary to add a low dose of a steroid later in the season. Less benefit is found in perennial vasomotor rhinitis. There is no substance to the claim that antihistamines are beneficial in the common cold, but the atropine-like actions may reduce rhinorrhoea with symptomatic benefit.

Antihistamines are useless in asthma, including pollen asthma, and have a role in the treatment of bronchospasm only in the isolated and rare condition in which histamine is released from the mast cells in response to certain drugs such as dextran, polyvinylpyrollidine, D-tubocurarine and pentamidine. While it might be good practice to give an antihistamine to a patient about to receive dextran or D-tubocurarine, the established reaction is better treated with adrenaline.

Antihistamines are beneficial in transfusion reactions not due to ABO incompatibility or to pyrogens. The more severe reactions are less satisfactorily controlled. It is good practice to administer an antihistamine prior to transfusion in a patient who has previously had trouble.

Antihistamines are given routinely to prevent undesirable actions of histamine in the maximum histamine test meal. This test is now little performed since derivatives of gastrin became available.

Other actions.—Promethazine and diphenhydramine are useful *sedatives*, which may be of benefit to a hospitalized patient with a drug reaction or receiving a transfusion. Both of these drugs are also popular as preoperative medication, when the sedative and anticholinergic properties are desirable.

The role of antihistamines in *cardiac arrhythmias* is uncertain in view of the effectiveness of intravenous local anaesthetics and other established drugs. However, a drug with sedative, anti-emetic, and antiarrhythmic properties can be excellent background therapy. Atropine-like action is also useful in certain forms of bradycardia.

Promethazine is a potent *anti-emetic* as far as morphine induced vomiting is concerned. Cyclizine and meclozine are also capable of reversing morphine nausea, but are ideal for *motion sickness*, when their lack of sedative effect is suitable for outpatient use.

The antihistamines have no place in the treatment of epilepsy and parkinsonism, but the drugs that are used usually have some antihistaminic activity.

Drug Combinations

There is an enormous variety of combinations of drugs including an antihistamine, but those for topical use on the skin, in the eye, and in the upper respiratory tract are contraindicated because of the risks of sensitization.

Of the combinations for oral administration there is little to be said for those containing a mixture of antihistamines. Those containing atropine are rendered unnecessary by the wide variety of histamines with atropine-like activity. The combination of an antihistamine and an antitussive has no place. There are few indications for the simultaneous administration of an antihistamine and a steroid hormone, but a combination is undesirable in that flexibility of dosage is impossible. Dimenhydrinate is not a drug combination in the true sense but is a theophylline derivative of diphenhydramine; it does not seem a specially advantageous compound.

A case can be made for the combination of an antihistamine and a sympathomimetic in cases when upper respiratory congestion has an allergic component. The most popular non-barbiturate sedative is a combination of methaqualone and diphenhydramine. However, there is evidence of abuse in certain young people, and methaqualone may increase vascular permeability leading to pulmonary oedema in overdosage or in those predisposed.

Dose and Means of Administration

Table II indicates the recommended dosage of the selected antihistamines, the usual duration of action, and the available oral and parenteral preparations available. No attempt has been made to include various topical preparations for use on the skin, in the eye, as nose drops, or as aerosols. The risks of sensitization are considerable and unjustifiable; the oral or parenteral route offers comparable or superior results in any situation when a topical antihistamine might be prescribed. There is unlikely to be added benefit from exceeding the recommended dosage, but the side-effects would undoubtedly become more troublesome. Dosage in children is calculated on the following basis:

Up to one year, 1/6 to 1/4 adult dose; 1 to 5 years, 1/4 to 1/3 adult dose; 5 to 12 years, 1/3 to 1/2 adult dose; over 12 years, 3/4 adult dose. A dose of 5ml. of the elixirs named in Table II is equivalent to 1/2 adult dose.

TABLE II.—*Dosage of Antihistamines*

	Duration of Action (Hours)	Forms in Which Available			Recommended Dose mg.	
		Tablet Size mg.	Injection mg./ml.	Elixir or Syrup mg./ml.		
Mepyramine	4-6	50 100	25	5	100	3-4 times daily
Antazoline	4-6	100	Ampoules Available	—	100	3-4 times daily
Diphenhydramine	4-6	25	10	2·5	25-50	3-4 times daily
Chlorpheniramine	4-6	4	10	0·4	4	3-4 times daily
(Slow Release)	(8-12)	12			12	1-2 times daily
Triprolidine	4-6	2·5	—	0·4	2·5	3-4 times daily
(Slow Release)	(8-18)	10	—		10	1-2 times daily
Cyclizine	4-6	50	50	—	50	3-4 times daily
Meclozine	12-18	25	—	—	25	1-2 times daily
Promethazine	6-12	10 25	25 50	5 5	25 25	1-2 times daily 1-2 times daily
Phenindamine	6-8	25	—	— at present	25-50	2-3 times daily
Cyproheptadine	4-6	4	—	0·4	4	3-4 times daily

Conclusions

Whether an antihistamine is given to antagonize histamine or for some side benefit, undesirable effects must be anticipated. The considerable variation that exists in the response to antihistamines, especially with regard to the sedative side-effects, means that trial and error dictates the choice of drug. Especial care must be taken to ensure that the patient realizes the potential danger of driving, with the double risk of sedation and blurring of vision.

Antihistamines are not the panacea for all ills. Their variety is not equalled by their usefulness. Practitioners are advised to restrict their prescribing to a selected few antihistamines and to limit their use to conditions in which real benefit is likely to occur.

ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Analgesics and Peptic Ulceration

Q.—*What analgesics are suitable in cases of osteoarthritis associated with recurrent peptic ulceration, and how should the analgesics be administered?*

A.—The problem is that all analgesics with "anti-rheumatic" effects—that is, those which are likely to be the most effective in controlling pain from chronic arthritis—are contraindicated in patients with recurrent peptic ulceration. There are, however, analgesics which do not cause gastric irritation, and these should first be tried. Ibuprofen can be given orally in a dose of 200 mg. three times a day. Paracetamol combined with codeine phosphate is sometimes effective, but the constipating action of codeine is undesirable in the elderly. Pentazocine may be given by intramuscular injection in a dose of 30 mg. three times a day.

If the pain is not controlled by any of these agents then, with some risk in a patient with peptic ulceration, indomethacin suppositories can be tried. Another agent which can be used cautiously is aloxiprin in an oral dose of 1.8g. four times a day. Both this drug and indomethacin must be stopped immediately should the patient complain of dyspepsia or other gastro-intestinal disturbance.

When the site of the arthritis makes intra-articular injection possible (for example, the knee joint) injection into the joint of hydrocortisone (25 to 37·5 mg.) often brings considerable benefit. The injection should be made before treatment by the physiotherapist. The period of relief from pain varies, and it may last from a few days to several months.

Inheritance of Diabetes

Q.—*What is the likelihood of the children of a marriage developing diabetes mellitus when the father and mother are both free from the disease but the mother's mother and the father's father both had diabetes of the late-onset variety?*

A.—There would be an increased risk of late-onset diabetes developing in the children of this marriage, but the increase would probably be only of the order of four or five times the random risk. There would probably be little or no increased risk of early-onset diabetes.

Long-term Diuretic Therapy

Q.—*Is aching in the thighs and calves in a patient regularly on a thiazide diuretic, together with potassium supplements, likely to be due to lack of potassium, and, if so, how can it be treated?*

A.—This is not an uncommon symptom in patients on long-term diuretic therapy. In my experience, it is not usually related to potassium deficiency but rather to depletion of salt and water. Obviously under these circumstances it is difficult to correct while maintaining a diuretic effect.

Three possible manoeuvres may help, however. One is to reduce the dose of diuretic used. A second is not to restrict the patient's salt intake while on diuretic therapy. Thirdly, if diuretics are being used for a hypotensive effect, changing treatment to a small dose of an adrenergic neurone-blocking drug such as alpha-methyldopa might be a suitable solution.