HISTAMINE IN ANAESTHESIA
A Short Survey

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SUMMARY
A brief account is given of the relevant pharmacology and physiology of histamine, followed by a review of some of the recent literature relating to the release of histamine by drugs in anaesthetic use.

The question naturally arises, to what extent need the anaesthetist take the possible release of histamine into account when assessing the likely effect of any drug on his patients. It would appear that the only circumstances in which he need take any note of histamine release are when morphine and curare are used in the asthmatic and when trimetaphan is used to induce hypotension.

Before discussing histamine in its relationship to anaesthesia, it is necessary to consider briefly the background picture of histamine in general.

THE CHEMICAL STRUCTURE OF HISTAMINE
There is a large number of physiologically active amines; among them are adrenaline and the sympathomimetic amines, acetylcholine and the cholinergic amines.

In addition, there are two important amines known to be liberated from cells as the result of injury or allergic reactions, but playing an as yet uncertain part in injured tissue. These are 5-hydroxytryptamine and histamine.

Histamine, β-iminazolylethylamine, is formed in the body from its precursor, the amino-acid histidine, by the action of the enzyme histidine decarboxylase.

Chemically the various antihistamines have the presence of an ethylamine grouping

-CH₂ CH₂ N=

in common. This grouping is, however, present in other amines which have no striking antihistamine activity. The ethylamine grouping is found in the histamine molecule, and so in the antihistamines it may represent that portion of the molecule which competes with histamine for cell receptors (Micks, 1957).

The antihistamines may be regarded as competitive antagonists. Nearly all the antihistamine drugs have the following general formula R—X—C—C—N (Wilson and Schild, 1959) where the nucleus R is composed of one or more aromatic or heterocyclic groups; and the component X may be (a) nitrogen or (b) oxygen or (c) carbon. They belong largely to two groups—the ethylenediamine derivatives, and the ethanolamine derivatives, both of which contain an ethylamine grouping:

\[
\begin{align*}
\text{Histamine:} & \quad \text{H} \quad \text{H} \\
\text{Histidine:} & \quad \text{C} \quad \text{C} \quad \text{N} \\
\text{Mepyramine maleate (Neo-antergan):} & \quad \text{H} \quad \text{H} \\
\end{align*}
\]

In the following formulae for the comparison of the structure of histamine with the antihistamines, the ethylamine grouping has been placed in a bracket for purposes of recognition.

(i) The ethyl diamine derivatives, where in the above general formula X = N:

\[
\begin{align*}
\text{Histamine:} & \quad \text{H} \quad \text{H} \\
\text{Histidine:} & \quad \text{C} \quad \text{C} \quad \text{N} \\
\text{Mepyramine maleate (Neo-antergan):} & \quad \text{H} \quad \text{H} \\
\end{align*}
\]
Histamine.

Promethazine hydrochloride (Phenergan).

(ii) The ethanolamine derivatives, where in the above general formula \( X = O \):

Diphenhydramine hydrochloride (Benadryl).

Adrenaline and noradrenaline may be regarded as physiological antagonists to liberated histamine, modifying its effects by a reversing action (Feinberg, Malkiel and Feinberg, 1950). Both adrenaline and noradrenaline contain the ethylamine grouping.

The triple response can be elicited by the injection of histamine into the skin. It consists of a red line at the site of inoculation, due to the dilatation of the capillaries by direct action, a flare due to dilatation of arterioles by means of an axon reflex, and a weal due to increased capillary permeability, and the marked arteriolar dilatation which provides the fluid (Keele and Neil, 1961b).

Keele and Neil (1961a) point out that histamine is widely distributed in mammalian tissues, but the highest concentrations occur in skin, intestine and lung, that is at surfaces where the organism is in contact with the outside world.

Histamine is found in the tissue mast cells. Feldberg (1954) in a review article on some physiological aspects of histamine says that unfortunately very little is known about the mast cells, but that the histology textbooks state that they are present in groups or clumps in the connective tissue around the small blood vessels and contain granules which stain with basic aniline dyes, like the basophil leucocytes, but the two types of cells are independent of one another.

The granules of these cells contain heparin and histamine—possibly bound in a loose chemical combination. It is possible that the organic acid heparin is bound to the base histamine.

The intragranular histamine is readily released when the granule membrane is ruptured by physical or chemical means, and it then becomes physiologically active (Keele and Neil, 1961a). It is of interest to note that a mast cell tumour of a dog contained the highest recorded content of tissue histamine, and the triple response can be elicited with ease in the skin lesions produced by a benign mastocytoma (urticaria pigmentosa in man) (Riley, 1956).

It must be pointed out, however, that the mast cells are not the only cells in which histamine is found.

**THE PHYSIOLOGY OF HISTAMINE IN MAN**

Histamine causes arteriolar dilatation, in addition to capillary paralysis which leads to a fall of blood pressure and a rise of heart rate. Smooth muscle is contracted throughout the body including the muscle coat of the bronchioles, intestine, spleen and uterus. It increases glandular secretion, and this is the basis of the histamine test for gastric juice.

The triple response can be elicited by the injection of histamine into the skin. It consists of a red line at the site of inoculation, due to the dilatation of the capillaries by direct action, a flare due to dilatation of arterioles by means of an axon reflex, and a weal due to increased capillary permeability, and the marked arteriolar dilatation which provides the fluid (Keele and Neil, 1961b).
ANAPHYLAXIS AND HISTAMINE
The chief symptoms of anaphylactic shock show a marked difference in different species; on the other hand, the symptoms of anaphylactic shock resemble those of histamine poisoning in the same species (Wright, 1952.) Thus both conditions, that is to say anaphylactic shock and histamine shock, produce intense bronchoconstriction in the guineapig which can lead to death (white emphysema).

In the dog both substances produce a constriction of the hepatic veins leading to congestion of the liver, and resulting in the collapse and death of the dog, as perhaps 60 per cent of the blood is trapped in the portal system.

In the rabbit both produce a constriction of the pulmonary arterioles, with dilatation of the right side of the heart.

The particular site at which histamine or anaphylactic shock affects different species of animal is known as the "shock organ" for that species.

The above, however, is not the whole story, for there remains a phase in the anaphylactic contraction of smooth muscle which does not appear to be due to histamine, as this phase is not antagonized by antihistamine drugs (Hawkins and Rosa, 1956). The substance producing the phase of anaphylactic contraction, not antagonized by antihistamines has been given the name "slow reacting substance" or SRS, a substance so named because it causes a slow contraction of smooth muscle.

TYPES OF HISTAMINE RELEASING AGENTS
Schachter (1952) discusses the clinically known fact that many drugs, diverse in their pharmacological properties, can evoke a common syndrome bearing considerable resemblance to experimental protein anaphylaxis. This fact, he notes, led to the inclusion of drugs of this type in the broad category of allergy and its designation as drug allergy, although frequently the reactions were on first contact, the substances were non-protein in nature, and there was a failure to detect antibodies in the reacting subjects. Theoretical objections to this classification, on the grounds of the non-protein nature of the antigen, were subsequently overcome, to some extent, by experiments which led to the concept of haptens or partial antigens, in which a compound antigen is formed from a drug or part thereof in combination with tissue protein. The hypothesis still fails to explain the facts that there is frequently no evidence of previous contact with the drugs concerned and that antibodies are not in general demonstrable. The finding that many of these "anaphylactoid" drugs are actually primary histamine liberators modifies these difficulties in so far as prior sensitization need not be regarded as a sine qua non of the human reaction. Thus in addition to reactions in which the subject becomes sensitized to the drug acting as a partial antigen, reactions to first contact could occur on the basis of primary histamine releasing properties of the drug. It is possible, Schachter continues, that drugs such as sulphanilamide and dinitrophenol, which do not possess primary histamine releasing properties, evoke reactions only after sensitization.

Table I (Paton, 1956) classifies the compounds which release histamine. Groups 5, 6 and 7 on the list include some of the agents of interest in anaesthesia, particularly number 6, the so-called "histamine liberators".

<table>
<thead>
<tr>
<th>Types of histamine-releasing agents.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Proteolytic enzymes</td>
</tr>
<tr>
<td>5. Large molecules</td>
</tr>
<tr>
<td>7. Monobasic compounds</td>
</tr>
</tbody>
</table>

Key: Tween 20 is a wetting agent; P.V.P. is polyvinylpyrrolidone; for compound 48/80 see text.

(Reproduced from Paton (1956) in Histamine, Ciba Foundation Symposium, by kind permission of the author and publishers.)
To quote Paton (1956), "it seems that any compound possessing two or more basic groups carried on, and separated by, a sufficient aliphatic or aromatic scaffold is liable to have the property of releasing histamine".

Table II (adapted from Paton, 1956) is a list of some basic "histamine liberators", including several which are in common anaesthetic use.

In a further elaboration of the nature of histamine release by simple chemical compounds Paton (1957) gives much information of value. He points out that the first main conclusion from a survey of the known histamine releasing agents is that basicity (already noted) predisposes to it. Only the "large molecule" group, the detergents, tween 20, bile salts, neoarsphenamine, and chlortetracycline provide exceptions, and with all of these different processes of releasing may be involved.

It is obvious, Paton continues, that basicity alone does not confer activity. The inactivity of ethylamine and hexamethonium illustrates this. But the replication of basic groups seems invariably to induce histamine release, provided their spatial relationship is sufficient. Reviewing the work on compounds which include diamines (NH₂(CH₂)₂NH₂), diaminides, diguaindines and diquaternary salts (CH₃N+(CH₂)₉-N(CH₃)₃, it seems to follow that any compound containing basic groups separated by more than 5 or 6 atoms (the optional number seems to be 8–14) has a strong chance of being highly active. The situation is curiously analogous to the requirements for neuromuscular block.

Paton further points out that polybasicity is not essential for action. Trimetaphan, morphine and the substituted benzamidines are all monobasic compounds and are all active in the release of histamine. It is noticeable, however, that of the monobasic compounds, the active ones consist of a basic group attached to substituted aromatic rings.

The nature of the basic group is also important in histamine liberation. Comparing similar series such as aliphatic bistrimethylammonium compounds (such as, for example, decamethonium) with homologous diamines, the former are very much less active. All quaternary salts are not, however, equally active. For instance d-tubocurarine is considerably more active in the release of histamine than decamethonium. If quaternary salts tend to be less active, probably by virtue of their complete ionization, other features of their molecules (possibly simple increase of hydrocarbon bulk) can restore activity again.

Histamine liberation, then, appears when basic groups in a molecule are repeated at sufficiently spaced distances, or when single basic groups are attached to substituted aromatic rings; too low or too high basicity depresses activity, but bulk and complexity of a molecule favour it.

The question naturally arises as to how these mono- and polybasic compounds release histamine. MacIntosh and Paton (1949) and Paton (1957) suggest a possible answer. The theory put forward is that the release of histamine by the simple basic substances involves a process of ionic exchange. The appearance in the blood of a tissue acid, heparin, as a result of histamine liberator action made reasonable the hypothesis that histamine may be...
Normally attached to some tissue acid and then freed by ionic exchange with the liberator, the freeing being accompanied by some disruption of the binding of the acid so that it, too, was available for diffusion into the circulation. The discovery by Riley and West (1953) that histamine and heparin are, in fact, associated in the tissues increases considerably the interest in this approach.

As might be expected on this theory, it is those bases which are comparable in strength to histamine, or stronger than it, which are active in its release. The characteristics of the bases which are effective in producing release in vivo readily seem to be, as already noted, twofold: either they are dibasic (or polybasic) compounds in which the basic groups are separated by a predominantly hydrocarbon moiety, or else they are benzamidine or phenylethylamine derivatives with polar ring substituents remote from the basic group. In each case some structural analogy exists with the structure of histamine (viewing it either as a dibasic compound, as an amidine, or as an aromatic ethylamine).

The idea that the histamine releasing action should increase with increasing basicity of the compound must be modified, of course, when quaternary substances are concerned. Here the problem of entry into the cell becomes of importance, since, in general, quaternary salts only slowly penetrate cellular membranes. It was found, in fact, that decamethonium, the quaternary analogue of decamethylenediamine, was only slightly active, a result indicating that the activity of the compound depends not only on basicity but also on its ability to enter the cell. On the other hand, not all quaternary salts are of equal activity and d-tubocurarine has proved considerably more effective as a histamine liberator than decamethonium or gallamine. The principal structural difference between the two drugs is the presence of a relatively complicated aromatic structure in d-tubocurarine as against a simple aliphatic chain in decamethonium. It might be supposed that the abundance of lipophilic material in d-tubocurarine goes some way to overcome the quaternary nature of its polar groups, enabling it to enter the cell somewhat more readily than a more or less purely quaternary molecule such as decamethonium. Paton concludes that these considerations of structure and action are at present suggestive only.

The reason for the slow penetration of cell membranes by quaternary salts is their complete ionization. To enter a cell substances need to be fat soluble. (There are exceptions—glucose, Na+, etc.) Ionized substances, though highly water soluble, have a low fat solubility and are therefore confined to the extracellular space.

Among the primary histamine liberators mentioned in group 6 of table I (Paton, 1956) is a substance called compound 48/80. This synthetic substance is a very potent histamine liberator in some animals. It is a polymer amine, a condensation product between formaldehyde and p-methoxy-phenethyl-methylamine (Uvnäs, 1958). Another polymer amine, PK3010aa, has been synthesized that differs from compound 48/80 in that it has two methyl groups linked to the nitrogen (Uvnäs, 1958). The two polymers are shown in figure 1.

![Polymer histamine liberators](Reproduced from Uvnäs (1958) in the Journal of Pharmacy and Pharmacology by kind permission of the author and editors.)
It can be seen that these substances have Paton's requirements for a histamine liberator, that is two or more basic groups separated by a sufficient aliphatic or aromatic scaffold.

Uvnas (1958) expresses doubts as to whether histamine liberation can be explained merely on an ion exchange basis, by substances penetrating the cell and granular membranes and, once inside the granules, simply replacing histamine from an acid group. He says that several arguments can be advanced, against the displacement theory to which Paton has subscribed, as being valid for the action of compound 48/80. To Uvnas the fact that 1 molecule of 48/80 releases several molecules of histamine appears to be a serious obstacle to a displacement theory.

Paton (1956) himself raises this difficulty of compound 48/80 being more active than it should be, in releasing something like 10 molecules of histamine to each basic nucleus of compound 48/80. In his opinion this objection need not be taken too seriously, since he points out one can find elsewhere examples of one drug competing with ten or more times its molecular weight of another drug. He concludes that it only presents a difficulty if a completely static idea of the reaction is adopted.

Another counter-argument raised by Uvnäs (1958) to the displacement theory appears to carry more weight, at least as far as compound 48/80 is concerned. Compound 48/80 is an amine. Placed in an acid medium it will ionize, its lipid solubility will decrease and hence its ability to penetrate the cell will decrease. Conversely its ability to penetrate the cell membrane should increase with decreased ionization in an alkaline medium. In other words, the more alkaline the medium, the greater should be the disrupting action of 48/80 on the mast cells. As shown in figure 2 (Uvnäs, 1958), this is not the case. Pieces of rat mesentery were incubated with 48/80 at various pH values. The disruptive action of 48/80 on the mast cells showed a peak around pH 7.8 and lower values were reached on either side of the optimum value. The tertiary amine PK3010aa shows a similar pH curve. The slope of these curves is reminiscent more of an enzymatic process than of an ion exchange mechanism. (The increased disruption at a pH higher than 9.2, which includes the control, is probably due to alkalinization.)

On the other hand, the disruptive action of decylamine shows no pH peak but increases continuously with rising pH. Uvnäs notes that this observation is consistent with the assumption that

![Figure 2](https://academic.oup.com/bja/article-abstract/34/6/397/294945)

The influence of pH on the disruptive action of 48/80 on rat mesentery mast cells. Barbitone buffer. ..... 48/80 0.5 μg/ml, PK3010aa 1 μg/ml, decylamine 10 μg/ml, control.

(Reproduced from Uvnäs (1958) in the Journal of Pharmacy and Pharmacology by kind permission of the author and editors.)
decylamine may act according to the displacement theory. The more alkaline the medium, the less ionized does decylamine become. Its lipid solubility increases and thereby its ability to penetrate the mast cell membranes.

Hägberg and Uvnäs (Uvnäs, 1958) have put forward a theory supported by experimental evidence that there is a lytic enzyme attached to the mast cell surface. This enzyme is normally inactive because it is blocked by an inhibitor. In their theory this inhibitor is removed by the histamine liberator, thus releasing the active enzyme which attacks the cell’s membrane. It is postulated that the liberator removes the inhibitor from its attachment to an NH₂ group of the lytic mast cell enzyme.

To sum up, there are two main theories to explain the action of primary histamine liberators: according to one, the histamine liberator enters the cell and because of its basicity releases histamine from its weak ionic linkages with a tissue acid, e.g. heparin; and according to the other, the liberator activates a lytic enzyme on the cell surface by removing an inhibitor from an NH₂ group of the enzyme, thus activating the enzyme.

Looking at table I, from Paton (1956), one is struck by the apparent paradox that an antihistamine can release histamine. Presumably a substance which is so chemically similar to histamine that it can occupy and block the receptor mechanism for histamine can also, and for the same reason of chemical similarity, liberate histamine from its loose chemical complex with a tissue acid.

Again in table II, from Paton (1956), there is another apparent paradox in that the sympathomimetic amines are listed as histamine liberators, even though they may be regarded as physiological antagonists to liberated histamine. Amphetamine, for example, may be viewed as an aromatic ethylamine. It thus fulfils Paton’s requirements for a histamine releasing agent, even though “physiologically speaking” its action will be to reverse the effect of the liberated histamine.

THE HISTAMINE RELEASING AGENTS WHICH CONCERN ANAESTHETISTS

Relaxants (diquaternary ammonium compounds).

In 1936 West reported in the Lancet that, when using curarine chloride by continuous intravenous drip in the treatment of tetanus and postencephalitic Parkinsonism, bronchospasm was one of the hazards. To overcome this he recommended prompt endotracheal intubation and injection of adrenaline.

In 1935 Anrep and Barsoum working in the laboratory found that tetanus of a skeletal muscle evoked by stimulation of its nerve is accompanied by the appearance of measurable amounts of histamine in the venous blood emerging from the muscle. An attempt was made to determine if direct stimulation of a curarized muscle also produced a similar effect, which led to the discovery that the administration of curare even without stimulation of the muscle is followed by a far greater liberation of histamine than is ever observed during the contractions of normal muscle (Alam et al., 1939).

In 1939 the classical experiments on the release of histamine by curare were carried out by Alam et al. Using the gastrocnemius of a dog, they found that the fall of histamine content of the muscle was roughly comparable with the amount collected from the venous effluent.

They also found that systemic curare caused a rise in the blood histamine. The release of histamine by the muscle did not depend on the paralyzing action of curare on the motor nerve endings. The effect was observed also after degeneration of the muscle nerve.

Subsequently, in 1946, Comroe and Dripps carried out experiments with curare on humans, and reported that intracutaneous injections of d-tubocurarine chloride produced weals and flares. Intraarterial injections into the brachial artery, while the arm veins were occluded, were also carried out. Immediately after injection the artery was occluded for 1/2 minutes. This resulted in huge weals and flares sometimes covering half the forearm.

In the following year similar experiments were reported by Grob, Lilienthal and Harvey (1947). They produced oedema of the limb as well as weals. They also found that prior injection of the antihistamine pyribenzamine prevented the formation of weals.

In 1949 MacIntosh and Paton described a number of organic bases which liberate histamine, and in 1950 Wilson, Gordon and Raffan, using the dimethyl ether of d-tubocurarine iodide as op-
posed to d-tubocurarine chloride in a hundred major intrathoracic operations, reported that clinically there appeared to be less release of histamine with dimethyl tubocurarine iodide. This impression was partly based upon the fact that a collapsed lung or lobe of a lung was much more easily inflated by the anaesthetist when the dimethyl ether of d-tubocurarine iodide was used. Using the latter drug they found that the pressure necessary to reinflate the lung was much less. They did not state how the pressure was measured.

In 1952 Sniper injected various muscle relaxants intradermally and measured the weals which resulted. His results can be seen in table III.

<table>
<thead>
<tr>
<th>Relaxant</th>
<th>Size of weal in sq.mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum</td>
</tr>
<tr>
<td>d-Tubocurarine chloride</td>
<td>270</td>
</tr>
<tr>
<td>Dimethyltubocurarine iodide</td>
<td>220</td>
</tr>
<tr>
<td>Gallamine triethiodide</td>
<td>190</td>
</tr>
<tr>
<td>Decamethonium iodide</td>
<td>115</td>
</tr>
<tr>
<td>Control</td>
<td>55</td>
</tr>
</tbody>
</table>

(Reproduced from Sniper (1952) in Brit. J. Anaesth., by kind permission of the author and publishers.)

Fifteen milligrams of d-tubocurarine chloride were taken as equivalent in potency to 6 mg of dimethyltubocurarine iodide, 120 mg of gallamine triethiodide, and 3 mg of decamethonium iodide. Ten patients were used for each muscle relaxant and ten for the control.

In experiments with intradermal injections of suxamethonium, Bourne, Collier and Somers (1952) showed that it is a weak histamine liberator having about one-hundredth the activity of tubocurarine. Although suxamethonium is a poor histamine releasing agent, it is emphasized that large doses of the drug may be given, and therefore care may be required in allergic patients.

Of interest is table IV (from Riley and West (1953)), which shows the effect of the histamine liberators on the histamine content (µg/g tissue) and relative mast cell content of rat tissues. The histamine liberators were stilbamidine (a trypanocidal diamidine) and d-tubocurarine.

Control values were first established for the mast cell content and the amount of extractable histamine in the omentum, mesentery, and subcutaneous tissues of the normal rat. A fresh series of rats was then injected intravenously with stilbamidine and d-tubocurarine. Their results indicated that both stilbamidine and d-tubocurarine bring about a reduction in the content of histamine and mast cells, tubocurarine being more effective. When there were very few or no mast cells left (value 0) they considered it possible that some of the released histamine was still retained in the tissue.

Foldes, Wolfson and Sokall (1961), using the non-depolarizing long acting neuromuscular blocking agent toxiferine in a series of 157 patients, state that in contrast to d-tubocurarine, signs of histamine release or ganglionic effects were not observed after its use. Toxiferine is a bis-quaternary ammonium compound.

Wylie and Churchill-Davidson (1960) draw attention to the experiments of Mongar and Whelan (1953) as being of interest to anaesthetists. These authors infused d-tubocurarine into the brachial artery of two conscious subjects. In neither case was there any marked increase in plasma histamine in the venous return from the arm, nor was there any flushing or wealing of the skin of the forearm.

Larger doses were then given to anaesthetized subjects. With doses as large as 30 mg (equal to about 3,000 mg intravenously) the histamine in

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Control Histamine</th>
<th>Mast cells</th>
<th>Stilbamidine Histamine</th>
<th>Mast cells</th>
<th>d-Tubocurarine Histamine</th>
<th>Mast cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omentum</td>
<td>18</td>
<td>++</td>
<td>10</td>
<td>+0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Mesentery</td>
<td>10</td>
<td>+</td>
<td>5</td>
<td>+0</td>
<td>5</td>
<td>+0</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>16</td>
<td>++</td>
<td>10</td>
<td>+</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

(Reproduced from Riley and West (1953) in the Journal of Physiology, by kind permission of the authors and editors.)
the plasma did not rise above 20 μg/l., and local signs such as flaring and wealing were very slight.

Mongar and Whelan suggest that it is unlikely that relaxant doses of d-tubocurarine administered intravenously for clinical purposes, where concentration in the blood would be less than one-hundredth of that present in the forearm in the above experiments, are ever likely to produce side effects due to the release of histamine.

It was not until higher concentrations in the tissues were achieved by the rapid injection of 10–50 mg of d-tubocurarine followed by the arrest of the flow that definite rises in plasma histamine were obtained. In these experiments there was marked flushing, wealing and discoloration of the skin of the forearm and hand. To obtain this degree of histaminaemia in the general circulation when infusing only a small fraction of the weight of the releaser into about 100 times the blood volume the substance would have to be a very potent histamine liberator indeed.

Wylie and Churchill-Davidson conclude, concerning d-tubocurarine and histamine release, that the evidence in man remains contradictory; but they make the point that it is always possible that the same dose of a drug may act differently from patient to patient, and that in view of the possible connection between d-tubocurarine and bronchospasm, it would seem sensible to use a depolarizing relaxant for all patients with an allergic condition.

**Trimetaphan.**

Payne (1955), when using trimetaphan, found that certain effects developed which could be attributed to histamine release. He carried out two series of investigations.

He estimated the acid content of the gastric secretions in six patients to whom trimetaphan was given, and repeated it in another series to whom no trimetaphan was given. Patients undergoing operations not requiring muscle relaxation were investigated, and no drugs known to release hista-
mine were used. After the induction of anaesthesia with thiopentone a stomach tube was passed, the stomach emptied, distilled water added, and gastric samples withdrawn.

All the patients to whom trimetaphan was given showed a secretion of free acid which resembled that following a hypodermic injection of histamine (fig. 3).

In a series of ten cats a polythene catheter was passed into the right ventricle to measure the pressure.

Immediately following the injection of trimetaphan, there was a marked rise in the right ventricular pressure, sometimes to three times the resting value, and simultaneously there was a sharp fall in blood pressure. These results were similar to those obtained following the intravenous injection of histamine acid phosphate in 1-mg doses.

Paton (1957) says that it seems possible that the characteristic action of trimetaphan represents the effect of repeated histamine releases, presumably on a background of modest ganglionic block.

Morphine and Pethidine.
Every anaesthetist is familiar with the triple response sometimes produced along the course of a vein used for the intravenous injection of pethidine.

Finer and Partington (1953) showed that this triple response can be modified and reduced by previous treatment with an antihistamine drug (diphenhydramine), given orally 2 hours prior to the intravenous injection of pethidine.

They also studied in the cat the effect of pethidine on the blood pressure. The fall in blood pressure following the intravenous injection of pethidine lasted from 45 to 90 minutes. Recovery from the hypotension was not hastened by the antihistamine drug mepyramine, but did prior treatment with mepyramine modify the blood pressure response.

The experiments in the cat indicated that, at least in this animal, the hypotensive effect of pethidine was not due solely to the liberation of histamine. They concluded that it seems likely that in man also some factor other than histamine liberation is involved in the production by pethidine of severe hypotension and collapse.

Feldberg and Paton (1951) discussing the effect of morphine on the blood pressure in the cat arrive at a similar conclusion. They found that the depressor action of morphine was associated with the appearance of small amounts of histamine in the plasma, but these amounts were insufficient to account fully for the effect on the blood pressure. They point out, however, that the well recognized collapse very occasionally following morphine and codeine, particularly when given by the intravenous route, the hypersensitivity of the skin in certain patients to opium preparations, the pruritus and sneezing of the opium addict, may all be attributed to the release of histamine.

They agree with Herxheimer (1950) that it is very possible that the hypersensitivity to morphine shown rarely by patients suffering from bronchial asthma is due to the release of histamine to which substance these patients are particularly sensitive.

On reference to Herxheimer one finds, however, that he does not recommend the complete abolition of the use of morphine in asthmatics, as he feels there are some cases of asthma where sedation is urgent and that the barbiturates have not the desired effect, but in these cases he stresses that morphine must never be given without adequate cover of adrenaline.

As a result of a clinical observation, that the weak antihistamine drug cyclizine chloride unexpectedly antagonized some of the actions of morphine, Gershon and Shaw (1958) investigated the action of certain antihistamine substances, and other drugs, on narcosis induced by morphine in animals.

They found without exception that the antihistamine drugs tested restored consciousness to dogs given morphine. The administration of histamine before morphine results in an increase in the rapidity of the onset of narcosis. The action of an antihistaminase (isoniazid) and the actions of antihistamine drugs were consistent with this result. Paradoxically histamine injected during narcosis transiently improved the level of consciousness. They conclude that it would appear that at least part of the pharmacological action of morphine is mediated by release of histamine. They point out, however, that the improvement brought about in a morphine-treated dog by the antihistamine drugs was brief and required large doses, and they note that it is possible that the beneficial effect was due not to the antihistamine activity, but to an additional central action.
Dextran and Polyvinylpyrrolidone

Dextran is a polysaccharide produced by the fermentation of sucrose by the micro-organism leuconostoc mesenteriodes.

Halpern (1956) injected dextran into albino rats, producing generalized disorders characterized by erythema, pruritus, oedema, dyspnoea, haemocoagulation, and vascular collapse. Previous adrenalectomy aggravated the vascular collapse. The common feature was an alteration in the permeability of the small blood vessels.

Figure 4 shows that about 5 minutes after the intravenous injection of 180 mg of dextran the average plasma histamine value rose from 36 μg/l. to 931 μg/l. The maximum level of 1,440 μg/l. was reached 15 minutes after the injection.

Table V, from Halpern (1956), is interesting in that it shows the relation between the molecular size and the toxic effects of dextran in rats. In clinical practice, polymers of molecular weight ranging from 35,000 to 150,000 are commonly used. It will be noticed that it is the polymers of this range which give the highest percentage of toxic reactions in rats. It must be understood that the action of dextran is specific for albino rats.

The intravenous injection of the synthetic colloid polyvinylpyrrolidone by Halpern (1956) caused in dogs general disorders characterized by erythema, violent pruritus and fall of arterial blood pressure together with gastric hypersecretion. The depressor effect was accompanied by a rise in portal venous pressure and an increase in the size of the liver.

Just as in the albino rat there was a rise in the plasma histamine level after the intravenous injection of dextran, so in the dog there was a comparable, though not as great, rise in plasma histamine, after the intravenous injection of polyvinylpyrrolidone. It was found that prior injection of mepyramine did not prevent the gastric hypersecreting action of polyvinylpyrrolidone, although it abolished almost completely all other disorders.

Again it must be understood that the action of polyvinylpyrrolidone is specific for dogs. This substance is no longer used in clinical practice because of its possible carcinogenic properties (Brewer, 1959).

Halpern found that antihistamines and particularly promethazine were very effective against almost all the toxic effects produced by polymers on the small blood vessels of intact animals. However, in adrenalectomized rats, which were extremely sensitive to dextran, although promethazine raised consistently their resistance to dextran it was unable to restore their resistance to normal, while it did restore to normal the resistance of these animals to histamine.

Halpern noted a lowering of toxicity of dextran in adrenalectomized animals, whose histamine had been depleted prior to adrenalectomy. Just the same degree of decrease in toxicity was observed when the adrenalectomized rats were pretreated with promethazine. Halpern concludes that it

<table>
<thead>
<tr>
<th>Molecular weight</th>
<th>Percentage incidence of toxic reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>6,000</td>
<td>0</td>
</tr>
<tr>
<td>35,000</td>
<td>25</td>
</tr>
<tr>
<td>100,000</td>
<td>100</td>
</tr>
<tr>
<td>230,000</td>
<td>65</td>
</tr>
<tr>
<td>2,000,000</td>
<td>0</td>
</tr>
</tbody>
</table>

(Reproduced from Halpern (1956) in Histamine, Ciba Foundation Symposium, by kind permission of the author and publishers.)
seems, therefore, that two factors intervene in the toxicity of dextran in adrenalectomized rats: histamine is one, but it is only partly responsible for the toxicity. The part which is attributable to histamine can be neutralized by promethazine or prior depletion of histamine. The second factor must be of a different nature, possibly related to the slow reaction substance (Halpern, 1956).

Discussing plasma expanders, Hewer and Lee (1957) note: “Reports of reactions to dextran come to hand from time to time and it would appear that this plasma expander can be antigenic to man and can produce precipitins and also skin sensitivity. The degree of sensitivity as measured by skin tests seems to bear no relationship to the systemic reaction, while a second infusion after 21 days does not enhance the sensitivity. Thus a look-out should be kept for these reactions in all patients who receive dextran, but as they are seldom serious they in no way preclude the use of this very useful agent. Reactions are more frequent in non-anaesthetized than in anaesthetized patients and take the form of the usual allergic lesions such as urticaria, skin rashes, oedema, and irritation of mucous membrane of the upper respiratory tract. They are often ameliorated by the intravenous injection of antihistamine drugs.”

In a report to the National Research Council, U.S.A. (1952), it was pointed out that the sera of a small fraction of population will agglutinate one or more strains of the organism leuconostoc mesenteroides. It was further pointed out, however, that the presence or absence of agglutinins to this organism does not provide a basis for systemic reactions to dextran.

It is possible that, in man, reactions to dextran have occurred because of this organism rather than due to dextran acting as a macromolecular histamine releasing agent as in table I.

REFERENCES


**SOMMAIRE**

Après un bref résumé des propriétés pharmacologiques et physiologiques importantes de l’histamine, l’auteur passe en revue une partie de la littérature récente portant sur la production d’histamine par des médicaments employés en anesthésie.

Bien sûr, la question se pose de savoir jusqu’à quel degré l’anesthésiste doit prendre en ligne de compte la production possible d’histamine quand il évalue l’effet probable de n’importe quel médicament sur son malade. Il semble apparaître que les seules circonstances dans lesquelles il doive peut-être compter avec une production d’histamine sont l’emploi de morphine et de curare chez un asthmatique et quand le triméthaphane a été employé pour produire une hypotension.

**ZUSAMMENFASSUNG**

Die für die praktische Anwendung und Nutzenübung wichtigen pharmakologischen und physiologischen Aspekte des Histamins werden kurz beschrieben, worauf eine Übersicht über einen Teil der neueren Literatur zur Ausschüttung von Histamin im Zusammenhang mit zu Anaesthesiezwecken verwendeten Medikamenten folgt.

Es ist klar, daß sich dabei die Frage ergibt, in welchem Ausmaße der Narkotiseur bei der Einschätzung der diesbezüglichen Wirkung aller betreffenden Pharmaka auf seine Patienten die potentielle Ausschüttung von Histamin ins Kalkül zu ziehen hat. Es scheint wohl so zu sein, daß die einzigen Umstände, unter denen wir das Freiwerden von Histamin ins Auge fassen müssen, die Anwendung von Morphium und Curare bei asthmatischen Patienten sowie jene von Trimetaphan zum Zwecke der Blutdrucksenkung darstellen.