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H-2 HISTAMINE RECEPTORS

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Since the chemical synthesis of histamine by Windaus & Vogt (1) in 1907 and the classic researches of Sir Henry Dale and his colleagues starting in 1910 (2, 3) on its physiological effects, a huge literature has accumulated on the chemistry, natural occurrence and distribution, and involvement of histamine in a wide variety of actions and organs (4). It was not until effective antagonists were synthesized in 1937 by Bovet & Staub (5) that some of these actions could be classified. What soon became evident was that certain effects of histamine could not be antagonized by any of the large number of available antihistamines. The most prominent of these actions were gastric acid secretion and cardiac chronotropism. Ash & Schild (6) in a classic paper recognized the implication in those exceptions and postulated a diversity of receptors for histamine action, labeled the receptors sensitive to mepyramine H-1 receptors, and defined their pharmacologic characteristics. They left open the question as to whether the non-H-1 receptors constituted single or multiple subclasses. The important invention of a second class of histamine antagonists by J. W. Black and his colleagues (7) defined a class of receptors, the H-2 receptors that are not affected by the classical H-1 antihistamines such as mepyramine. What has followed in the 6 years[1] since that invention is the development of specific H-1 and H-2 agonists and antagonists and, by their use, the further definition of H-1– and H-2–mediated actions.

The purpose of this review is to present both the evidence on which current classifications of actions of histamine into H-1 and H-2 are based and the therapeutic applications of the H-2 antagonists.

We review more than H-2 receptors because H-2 receptors are commonly intertwined with the H-1 receptors in similar or opposing actions. Even

[1]This review was written in July 1978.

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more, this chapter overviews the actions of histamine as understood from the analytical use of the receptor-specific agonists and antagonists that have largely become available since 1972. The review then concerns itself mainly with histamine between 1972 and 1978. A very few key references are drawn from earlier publications, but much of what is known about histamine in the pre-H-2 era is contained in the monumental compendium edited by Rocha e Silva (4) and published in 1965. This valuable source covers the history, chemistry, isolation, and occurrence of histamine; its pharmacology, metabolism, and physiological significance; and the release of histamine. Much of the recent history of histamine, especially that related to the H-2 receptor antagonists, is summarized in three symposium reports (8–10).

PHARMACOLOGY AND CHEMISTRY

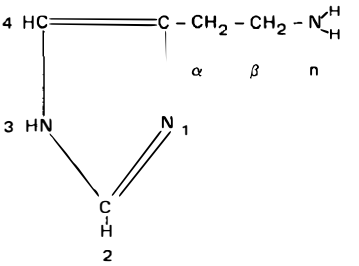
Initial Pharmacologic Evidence

Black and co-workers (7) first defined the H-2 receptors by an extensive systematic examination of several agonists (Figure 1)[2] and antagonists on H-1 and H-2 histamine responses. The test systems used included contraction of isolated guinea pig ileum and of rat stomach (both H-1); gastric acid secretion in perfused rat stomach, contraction frequency of isolated guinea heart muscle, and electrically stimulated rat uterus (all H-2).

First Black et al found that methyl substitutions provided two compounds with single receptor specificity: 4-methylhistamine for H-2 and 2-methylhistamine for H-1. The evidence from the use of the antagonist burimamide further strengthened the definition of the H-1 and H-2 receptors. The drug reversibly and competitively blocked the action of histamine and 4(Me)H on gastric acid secretion and on cardiac muscle, with parallel shift of the dose-response curves to the right. The calculated dissociation constant (K_b = 7–8 μM) was about the same for various actions of histamine or 4(Me)H. Burimamide failed to block the cardioaccelerator action of isoprenaline (β_2 adrenergic), or the H-1 histamine or carbachol effect on ileum. Burimamide and 4(Me)H were thus shown to be selective for the H-2 receptor.

Further studies in man, rat, cat, and dog showed that burimamide blocked gastric acid stimulation by pentagastrin and by food in the gut, but not vagally or cholinergically (carbachol) stimulated acid secretion. These results seemed to clearly establish a role for the intermediation of the H-2

[2]Abbreviations: 2-methylhistamine, 2(Me)H; 3-methylhistamine, 3(Me)H; 4-methylhistamine, 4(Me)H; N-methylhistamine, N(Me)H; N-di-methylhistamine, N'N'(Me)$_2$H; 2-(2-pyridyl)-ethylamine, PEA; and 2-(2-thiazolyl)-ethylamine ThEA.



Substitute (Me)	none (Histamine)	1	2	3	4	α	β	N'(Me)	N'N'(Me)$_2$	4, N'N'(Me)$_3$	4, N'(Me)$_2$
H-1	++	0	++	0	±	0	0	++	++	0	
H-2	++	0	±	0	++	0	0	++	0	++	

Figure 1 Modification of histamine by methyl substitutions in various marked locations to illustrate the principles of H1 and H2 receptor-specific compounds.

receptor in parietal cell stimulation by histamine, by gastrin (pentagastrin stimulation of ileal contraction was not blocked), and by food, but not apparently by acetylcholine.

Subsequent work in many stomach preparations with metiamide and cimetidine have failed to show that cholinergic or vagal or any other primary stimulus of acid secretion bypasses H-2 receptor blockade with metiamide or cimetidine, strengthening the argument for a critical role for histamine or for the H-2 receptor in the stimulation of the parietal cell. Several other inconsistencies involving pepsin secretion, species differences, and drug interactions now require more careful interpretation of the pharmacology of the H-1 and H-2 receptor specificities and actions. Moreover, recent studies in a wide variety of tissues allow some insight into cellular pathways of action of H-2 agonists and antagonists.

Chemistry

The development of H-2 antagonists is an exercise in chemical logic by the team at Smith, Kline & French Laboratories, which is described by Durant et al (11–15) and by Ganellin et al (16).

Since H-1 antagonists had none of the blocking actions desired, it followed that their structure (substitutions for the imidazole ring) was not a good starting point. By modifying first the imidazole ring, using a small nonpolar methyl group the team at Smith, Kline & French found that 4(Me)H retained gastric acid secretory activity but had no antagonist non-H-1 activity, and that 2(Me)H had predominantly H-1 receptor specificity

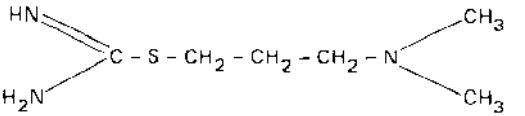


Figure 2 Dimaprit, a new nonimidazole specific H-2 agonist. The name *dimaprit* is derived thus: *DI-M*ethyl-*A*mino-*PR*opyl-*I*so-*T*hiourea (14).

(Fig. 1). They then systematically modified the side chain, but over a period of several years involving over 700 compounds synthesized and tested (17), the breakthrough came when guanyl histamine was found to have slight antagonist action against histamine stimulation of guinea pig atrium. By lengthening and further modifying the side chain, *burimamide* (7) was produced and its effects as an H-2 antagonist with no agonist activity was reported in detail by Black and his colleagues (7). Because burimamide was still a rather weak antagonist, was ineffective orally, and caused marked side effects in animals, especially when given with histamine, the side chain was further modified both by replacing a methylene group ($-CH_2-$) with a thio ether (–S–) link in order to make it electron withdrawing and by substituting an electron releasing group in the 4 position of the imidazole ring to favor the tautomeric form A of imidazole seen in histamine. This gave *metiamide* (Figure 3). Because of agranulocytosis produced by the latter, the thio urea sulfur atom (–S) was replaced by a cyanoguanidine (–N.CN) to provide a compound (*cimetidine*) (Figure 3) with the same H-2 antagonist activity but less likely to have bone marrow effects. This has been borne out so far in extensive clinical testing and in the first year of worldwide clinical use. The chemical comparisons between metiamide and cimetidine are given by Durant (11, 15). Though they are chemically similar, some biological differences do exist and should be reconciled for the various actions that may be prematurely classified on the basis of one antagonist or agonist (for example, burimamide is an α-adrenergic releaser and raises the blood pressure). This is especially relevant if we are to characterize further types or subtypes of H1 or H2 receptors according to the conditions of the testing.

The marked chemical distinctions between H-1 and H-2 receptor antagonists are outlined in Figure 3. The H-1 antagonists have aryl or heteroaryl rings that need not have any structural relationship to the imidazole ring. The aryl rings confer lipophilicity [with high octanol/water partition coefficients (p), e.g. for diphenhydramine $p = 2500$, compared to $p = 0.2$ for histamine and $p = 0.07$ for cimetidine]. The aryl rings probably act in hydrophobic binding. The H-1 antagonists resemble histamine in possessing a side chain (usually ammonium) which is positively charged at physiologic pH. In marked contrast, the H-2 antagonists are hydrophilic. They bear a

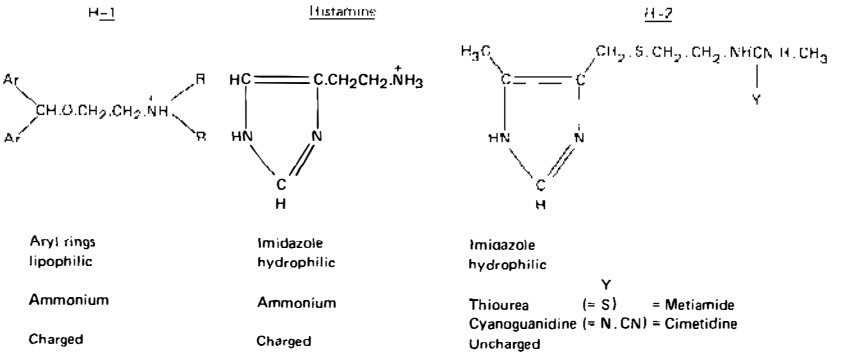


Figure 3 Essential chemical differences between histamine and its principal antagonists after Durant et al (11) and Ganellin et al (16).

structural relationship to histamine in having an imidazole or 4(Me) imidazole ring but differ in having a side chain which, though polar, is uncharged. These differences confer considerable receptor selectivity. The H-1 recognition is conferred by the ammonium group and the H-2 site by the imidazole ring. Moreover, lacking a charge in the side chain the H-2 antagonists cannot mimic histamine; that is, they are not agonists. There is one report (18) which suggests that there may be a change in H-1 receptors to resemble H-2 receptors when guinea pig ileum is examined at 12–18°C. This requires confirmation with specific agonists, but if confirmed could be important in interpreting receptor specificities.

Receptor populations are now recognized as being subject to fairly rapid change, increasing when deprived of agonist such as following denervation of muscle or gland, and by the administration of β-adrenergic antagonists; however, in four gastric fistula dogs cimetidine was given 3 times daily for 10 days at a total daily dose of 50 mg/kg. Histamine dose-responsive gastric acid output (H-2), heart rate (H-2), and blood pressure fall (H-1 + H-2) before and one day after stopping cimetidine showed no difference in any of the three parameters, indicating that none of the H-2 receptors increased in number or affinity as a result of blockade with an H-2 antagonist (B. I. Hirschowitz, unpublished). This agrees well with a lack of rebound of gastric secretion in patients treated with cimetidine.

Absorption and Distribution

Cimetidine is rapidly absorbed from the small gut (ileum > jejunum) of man, dog, and rat. There are no sex differences (19). Blood levels in man are proportional to oral dose in the range of 100 to 800 mg, with peak blood concentrations reached in 60–120 min after oral dosing, and a blood half-life

of about 2 hr. The bioavailability of orally administered cimetidine is 75% compared to 100% after intravenous injection. The volume of distribution in four men averaged 52 liters. Cimetidine is distributed throughout the body except for brain (19), to which access is limited because of very low lipophilicity.

The plasma ^{14}C concentration decays by a two-compartment model with half-life 6.8 and 107 min respectively. After an oral dose in the fasting state, cimetidine is excreted rapidly via the urine (80–90% in 12 hr) where it appears largely in unchanged form. The rest appears in the stool by 48 hr (19).

In patients with renal failure (20) the half-life (Y) is inversely related to creatinine clearance X ($Y = -0.01X + 3.67$; $r = 0.69$, $p < 0.01$). Cimetidine is dialyzable at a rate less than half that of urea [60 ml/min, compared to 150 ml/min at a blood flow of 200 ml/min (12)]. Since it has a molecular weight of 252 and is only 15 to 20% protein bound (19), the rate of removal on dialysis is not surprising. The dosage then has to be adjusted accordingly.

GASTRIC SECRETION

Histamine is ubiquitously distributed in the animal kingdom, being present in all chordates except the stomachless carp. Though there is great variability in histamine content from tissue to tissue, only the gastric mucosa of all vertebrates is relatively rich in histamine; that is, there is a selective accumulation of histamine related to acid secretory cells. Gastric acid secretion is strongly stimulated by histamine in all vertebrates investigated, whereas in many fishes histamine has no effects on circulation or on smooth muscles of the gastrointestinal tract or uterus (21).

Histamine thus seems to serve a specific function relative to acid secretion. The failure to inhibit histamine stimulation of acid secretion by H-1 antihistamines defined this effect as H-2. This has been amply confirmed by the use of H-1 and H-2 receptor-specific agonists and antagonists.

The effects of burimamide, metiamide, and cimetidine have been studied on gastric secretion of acid, pepsin, and intrinsic factor in man and in various animals in vivo and in vitro under a variety of basal and stimulated conditions. With few exceptions the H-2 antagonists have been potent inhibitors of acid secretion in all species tested, and with all stimuli. This implies a critical role for histamine acting via an H-2 receptor pathway in the stimulation or secretion of HCl, but one that has not so far been better defined.

Pepsin secretion is not uniformly stimulated by histamine in all species; for example, man and the rat are stimulated, while the dog and the cat show weak stimulation at low doses and inhibition at higher doses (22), an effect

that is mediated by H-2 receptors as well (23). There is also less uniformity in the action of the three H-2 antagonists on pepsin secretion, to be discussed in detail below.

Intrinsic factor (IF) is apparently secreted from parietal cells and characteristically upon acid stimulation, say with betazole (24), has a sharp early peak lasting about 15 min and then is secreted at a low steady rate. The nature of the secretion suggests that IF is synthesized and accumulates very slowly in the parietal cell. The early peak is not eliminated by pretreatment with cimetidine (24), but the low, sustained secretion of IF in pentagastrin-stimulated secretion is reduced by cimetidine given i.v. at the same time (25).

Serum Gastrin

The H-2 antagonists have no direct effect on serum gastrin in man (26–29) or animals either in the basal state or with vagal stimulation (28–31). After food stimulation serum gastrin rises slightly in man, when intragastric pH is kept above 5 either by cimetidine or by intragastric titration (31). Six weeks of metiamide therapy in patients with duodenal ulcers (DU) had no effect on serum gastrin (32).

Gastric Secretion in Man

The effects of the H-2 antagonists on gastric secretion in man are largely known from experiments using metiamide and cimetidine.

Metiamide inhibits acid secretion in duodenal ulcer subjects whether unstimulated or stimulated by histamine, pentagastrin, insulin hypoglycemia, or liquid or solid meal (30, 33, 34). At an i.v. dose of 1 mg per kg.hr or an oral dose of 4 mg/kg, about 50% inhibition of stimulated secretion was noted. In at least two studies pepsin output was less reduced than acid output for vagal (35, 37) or pentagastin (36) stimulation and at the same blood levels.

Minimum effective blood levels of metiamide are $\sim$ 1.8 μmole/liter (35) and 50% inhibition occurred with 2.5 to 4 μmole/liter (34, 36), levels reached by oral doses of 200 to 300 mg by mouth.

Cimetidine replaced metiamide in clinical testing after the latter had caused a number of cases of agranulocytosis, one of which was fatal. Initial studies by Brimblecombe et al (38) indicated similar pharmacokinetics and potencies against histamine and pentagastrin stimulation for the two drugs, and subsequent testing in man with or without duodenal ulcer confirmed the efficacy of cimetidine against basal secretion during the day (39, 40) and at night (40, 41), with anacidity recorded 5–8 hr after a 300 mg oral dose. Postprandial acid output is also reduced by about 65% in the 90–180 min after the dose of cimetidine (38, 40, 42, 43). In both the nocturnal basal and

the meal-stimulated studies, pepsin secretion was much less affected than acid, with no decrease in pepsin concentration (41, 42), confirming earlier studies in duodenal ulcer with metiamide (35). Blood levels measured in the latter four studies quoted showed 50% inhibition of basal secretion at levels of about 2 μmole/liter (0.5 μg/ml), and 75–100% at levels 3–6 μmole/liter. The relation between blood level and percentage of inhibition is a rectangular hyperbola. Five patients were given total doses of 200, 300, and 400 mg and the mean peak levels were 2.4, 4.8, and 7.2 μmole/liter respectively with half-lives of 3.8, 2.3, and 2.5 hr respectively (41). The peak of blood levels is higher if cimetidine is taken before meals rather than with meals (44).

In these studies serum gastrin levels were unaffected by cimetidine (39–44). Gastric emptying as measured by infused markers was unaffected by cimetidine, though the amount of acid emptied into the duodenum was reduced because of the inhibition of acid secretion (42). In the same study the amounts of pancreatic and biliary secretion were unaffected by either the cimetidine or the reduced acid load in the duodenum. However, histamine stimulates bile flow and this is blocked (noncompetitively) by metiamide (45).

Cimetidine is a noncompetitive inhibitor (V_{max} and K_m both reduced) of pentagastrin-stimulated acid secretion (46). Vagally stimulated secretion, whether by sham feeding (47) or by insulin infusion (48), is strongly inhibited by cimetidine at a dose of 100 mg/hr i.v. Gastric distension which, like the previous two stimuli, stimulates acid secretion to about 50% of peak pentagastrin was also 90% to 100% inhibited by cimetidine. Caffeine-stimulated acid secretion is totally inhibited by cimetidine (49). Pepsin secretion was less affected than acid in the pentagastrin study (46), and not inhibited during insulin infusion (48).

Betazole-stimulated H^+, pepsin, and intrinsic factor (IF) were inhibited by cimetidine but basal output of pepsin and intrinsic factor were not reduced by the same 300 mg oral dose (50). The IF data in the latter study differ from those of Burland (24) who found no effect on pentagastrin-stimulated IF secretion.

Thus the H-2 antagonists block acid secretion in normal man as well as in those with duodenal ulcer in the basal state and after stimulation by the vagus, by food, pentagastrin, caffeine, and betazole. The inhibition of pepsin secretion is less marked, especially after pentagastrin and vagal stimulation, and in the basal state though betazole stimulation of both acid and pepsin are equally blocked by cimetidine as one may expect from a specific antagonist (51).

Though I could find no dose-response studies done in man using histamine stimulation with and without cimetidine, the evidence would suggest that in man histamine is a direct stimulant of acid, pepsin, and intrinsic

factor secretion. Appropriate kinetic analysis of the effects of H-2 blockers on histamine stimulation of all three products would determine how specifically each is stimulated via H-2 receptors. The noncompetitive and incomplete block of stimulation of acid secretion stimulated by pentagastrin and the lesser effect on pepsin stimulation does not favor histamine as the direct intermediary for pentagastrin action on the stomach, any more than inhibition of pentagastrin or other stimulation by atropine means cholinergic intermediation. Evidence from animal work to be cited below would suggest rather a system of linked receptors in which acetylcholine, gastrin, and histamine are interdependent. The role of the histamine receptor seems to be more critical to the parietal cell than to the peptic cell.

Gastric Secretion in Animals

All three H-2 antagonists have been extensively studied with various stimuli in animals including intact dog (7, 52), cat (29), rat (53), and even the Atlantic cod *Gadus Morhua* (54), and on isolated stomach of dog, cat, rat, mouse, guinea pig, frog, and necturus.

In general, where appropriately studied by dose-response techniques, the inhibition of histamine-stimulated acid secretion by H-2 receptor antagonists has been competitive in all species (7, 52, 55, 56). Pentagastrin stimulation in some studies was competitively inhibited and in others noncompetitively. Carbachol-stimulated secretion was resistant to both burimamide and metiamide (7, 55), but urecholine-stimulated secretion was inhibited noncompetitively by metiamide (57) and cimetidine (58).

An interesting difference emerged from the effect of these agents on pepsin secretion. Burimamide seemed to have slightly more effect on pepsin than on acid secretion. Metiamide, while inhibiting acid secretion by vagal or cholinergic stimuli, greatly *potentiated* the stimulation of pepsin by these agonists in dogs both with vagus nerve intact (56–58) and with the fundus denervated (56).

Cimetidine on the other hand reduced both acid and pepsin secretion with all stimuli except histamine. While cimetidine competitively inhibited histamine-stimulated acid secretion, it produced a change in the pepsin dose-response curve from a biphasic one, in which low doses of histamine stimulated and higher doses inhibited secretion, to one which paralleled the acid output curve. This was interpreted (23) as showing that histamine has both stimulatory (low dose, high affinity) and inhibitory (high dose, low affinity) receptors, both H-2. Similar receptor characteristics may account for the dose reversal (inhibition at "supramaximal" doses) with all the gastric secretagogues for acid stimulation.

In the cat (13, 59) but not in man or the dog, there is some evidence that inhibition of acid secretion may be mediated by H-1 receptors, since an H-1 antagonist increases the response to histamine, normally lower, to the same

level as seen with specific H-2 agonists alone. In the dog there is no difference between histamine, and the specific agonists 4(Me)H (60), 4(Me-N-(Me)H, or dimaprit [Figure 2 (14)]. In man, the rat, mouse, and guinea pig there is no indication either of an H-1 inhibitory mechanism; that is, H-1 antagonists do not augment the gastric acid response to histamine. No systematic study of H-1 receptors and pepsin secretion has yet been published, though in the dog no effect (stimulatory or inhibitory) of the H-1 agonist PEA on gastric secretion of acid or pepsin was seen (B. I. Hirschowitz, unpublished).

Blood levels of metiamide and cimetidine have been shown in various animal and human studies to be the determinants of inhibition of basal, or meal-, pentagastrin-, or histamine-stimulated secretion with the best fit for the data being log-sigmoid; that is, inhibition seems to be related linearly to $\log_{10}$ blood concentration of the antagonist (e.g. 61, 62). The 50% inhibition concentration is about 2 μM in all studies, and the ED_{50} cases are 1–2 μM/kg i.v. bolus, 3–5 μM/kg.hr-1 i.v. infusion, and 10 μM/kg orally (62).

The effect of circulation and extrinsic innervation can be ignored in *isolated stomach* preparations that appear to be useful in the study of pharmacology of H-2 inhibitors, though much less sensitive than in vivo. In the isolated immature rat stomach (63) and the distended mouse stomach (64), acid is secreted dose-responsively with histamine, pentagastrin, acetylcholine, and dibutyryl cAMP. The action of histamine is potentiated by phosphodiesterase inhibitors (64). Metiamide competitively blocked histamine, noncompetitively blocked pentagastrin (64), but not di(Bu) cAMP. Atropine blocked acetylcholine and partly depressed pentagastrin effects but had no effect on histamine. In the isolated guinea pig stomach (65) cimetidine and metiamide were equally effective against histamine stimulation.

Cyclic AMP

Whether cAMP is a pathway for stimulation is unsettled. In the guinea pig stomach cimetidine is about 10 times more active than metiamide in blocking adenylcyclase stimulation by histamine, though adenylcyclase stimulation by other agents, e.g. NaF, was not blocked by H-2 antagonists (66, 67). Histamine-stimulated mucosal adenylcyclase from guinea pig was sensitive to both H-1 and H-2 antagonists, with K_m 10^{-4} vs 3×10^{-5} M respectively (68). In the dog, Scholes et al (69) showed stimulation of adenylcyclase in isolated viable cells by histamine and by 4(Me)H but not by 2(Me)H. Inhibition by both metiamide and burimamide (K_b 3.5×10^{-7} and 2.3×10^{-6} M respectively) but not by H-1 antagonists further characterized the system as H-2 receptor specific. Others (70) have found no evidence for a histamine-sensitive adenylcyclase in the dog. These and other inconsistencies are discussed by Amer (71).

It is still not clear whether the histamine-adenylcyclase experiments should be accepted at face value in the interpretation of the H-2–specific effects of histamine on acid secretion. There is a histamine-induced morphological change in the ultrastructure of the parietal cell which precedes acid secretion (72). A similar increase in microvillar surface area at the expense of tubulovesicles has been shown (73) to be related to cellular cAMP increases with theophylline when the latter is allowed to or is prevented from (by thiocyanate or anoxia) stimulating acid secretion, all in the presence of metiamide. The actions of histamine and other secretagogues may thus be divided into morphologic and secretory, the latter via an H-2 receptor–dependent mechanism. The receptor pathway for histamine-induced morphologic change was not identified by these studies, but is also presumably H-2.

The localization of ^{35}S burimamide, ^{14}C metiamide, or ^{3}H cimetidine by microautoradiography in the parietal cell cytoplasm of the dog and rat at a concentration 3–4 times greater than in adjacent peptic cells from 5 to 300 min after injection correlates with the apparent preference for acid over pepsin inhibition by these agents (74).

MUSCLE

Esophagus

Differences in techniques may explain the species differences in the effects of histamine on the lower esophageal sphincter (LES). In the monkey *Maccaca nemestrinas* and the Australian possum (*Trichosurus vulpecula*) histamine relaxes the LES by both H-1 and H-2 receptors and this effect is blocked by a combination of H-1 and H-2 antagonists (75). In the North American possum (*Didelphis virginiana*) which belongs to a different genus from the Australian possum, studies on isolated muscle strips from the sphincter (LES) and body of the esophagus showed excitation due to exogenous or endogenous (released by 48/80) histamine via H-1 receptors and relaxation via H-2 receptors (76). The H-1 effect predominated over the H-2 when histamine was given. The baboon demonstrates only H-1 excitatory effects of histamine on the LES (77). In man histamine has a biphasic effect on LES mediated only by the H-2 receptor with rather weak excitation at low doses and reversal of this effect at i.v. doses $>$ 20 μg/kg.hr histamine acid phosphate (78). Cimetidine does not antagonize the stimulant effects of gastrin (78, 79) or of a protein hydrolysate in the stomach (70) nor does it have any effect on the basal LES pressures in graded doses (50–400 mg p.o.) in normal man (80) or in those with abnormally weak sphincters.

Thus in species other than man the H-2 receptor has no effect (baboon) or mediates relaxation of the LES. In man there is excitation at low doses and reversal of this at even moderate doses. In vitro studies would resolve

the question as to whether there are two actions on the LES, e.g. excitation at low concentrations (high K_m) and inhibition (low K_m) at high concentrations or even whether those effects are direct at all on the esophagus. It also remains to be seen whether cimetidine has any effect on patients with hypertensive LES. A physiologic role for histamine in the LES seems unlikely.

Stomach

The rat stomach in vivo (7) contracts upon stimulation of the H-1 receptor. The isolated rat stomach also has been shown (81) to relax with stimulation of the H-2 receptor, e.g. by 4(Me)H, an effect that is competitively inhibited by metiamide. Bertaccini (82) reports that histamine has a marked spasmogenic effect on the rat pylorus which can be reproduced by H-1 or H-2 agonists. This action is not blocked by the respective histamine antagonist, but only by adrenalin, prostaglandin E_1, and papaverine. This anomalous histamine effect is yet to be explained.

Gastric Emptying

Gastric emptying of both liquids and solids measured by scintiscanning is unaffected by oral administration of 400 mg cimetidine given with the meal (83). This confirms other studies using intragastric markers (42) which showed that the fractional rate of emptying was unchanged even though a smaller actual volume left the stomach. Because the pH of gastric contents would be higher with cimetidine, one might expect food-stimulated serum gastrin to be higher (it is after 2 hr) (83). Moreover, if less acid enters the duodenum, less secretin would be released from the duodenum. If these two secondary effects cancel out, then it is likely that no effect of cimetidine on gastric emptying would be noted.

Intestine

Ileal contraction with histamine is a classic H-1 effect (6, 7, 61). The adult guinea pig ileum is more sensitive than rabbit ileum which is only sensitive to histamine before the age of 11 days (84). Burimamide reportedly potentiated the effect of histamine (85) though no direct evidence was produced that there was H-2 receptor–mediated relaxation or inhibition of contraction in guinea pig ileum. There are no data on histamine effect on duodenal, jejunal, or colonic motility.

Gallbladder

Waldman et al (86) have demonstrated that H-1 receptors mediate gallbladder contraction by histamine and that H-2 receptors mediate gallbladder

relaxation. Blockade of H-2 receptors augments the response to cholecystokinin, suggesting that they may modify the response to hormonal agents.

There have been no reports of histamine receptor studies of the bile duct or the sphincter of Oddi.

Genitourinary

There are neither inhibitory nor stimulating H-2 receptor actions in the guinea pig bladder or lower ureters that contract with H-1 receptor stimulation (87). The mouse vas deferens muscle is relaxed via an H-2 receptor–dependent pathway (88).

Uterus

Relaxation of rat uterine muscle was one of the non-H-1 effects which Black et al (7) used to demonstrate specificity of the H-2 receptor. Relaxation by various histamine analogues was in the same rank order as gastric acid stimulation, e.g. [4(Me)H > triazole > betazole] (89), none of which had an effect on cAMP of rat uterine muscle strips in one report (89) compared to another report in which cAMP appeared to be stimulated by graded doses of histamine (90) in proportion to the degree of inhibition of contraction.

Lung

The musculature of the respiratory tree is not pharmacologically uniform. Histamine excites the bronchial smooth muscle contraction via an H-1 receptor in various species including man, guinea pig, rabbit, goat, calf, pig, horse, and chicken (91). In asthmatic man bronchial muscle is more sensitive than it is in normal nonasthmatic man in whom constriction (H-1) and relaxation (H-2) are balanced (94). In the asthmatic children, atropine prevents histamine as well as acetylcholine-induced bronchoconstriction (93). Bronchial muscle in dogs is unaffected by H-2 agonists or antagonists, while that of the cat and sheep are relaxed by histamine, the former by an H-1 and the latter via an H-2 receptor. Tracheal muscle in the cat is relaxed by both H-1 and H-2 agonists but in the sheep is relaxed by an H-1 action (91). In the dog lung histamine constricts tracheal muscle even in the presence of metiamide (92), and this effect, as on the bronchi, is solely H-1 mediated (as it is in normal man) (75).

As in other actions, histamine is only one of several substances capable of constricting bronchial muscle and H-1 antagonists are only sometimes or only partly helpful in reversing the bronchospasm of allergic asthma. There is an unconfirmed preliminary report (94) of H-2–mediated relaxation of bronchial muscle in man, but H-2 antagonists have not been reported to have a deleterious effect in the use of other bronchodilators.

CARDIOVASCULAR SYSTEM

Histamine has multiple direct and indirect effects on the cardiovascular system. Effects on the heart include changes in rate, in rhythmicity and conduction; blood vessel effects result from action on the vascular smooth muscle. The consequences of the combined cardiac and vascular effects such as blood pressure and cardiac output changes in turn produce reflex effects, e.g. in pulse rate, that need to be taken into account in interpreting the effects of histamine.

The failure to completely block the hypotensive effect of histamine by H-1 antagonists first led Folkow et al (95) to propose the existence of more than one kind of receptor for histamine in the vascular system. The H-1 receptors defined by Ash & Schild (6) and the H-2 receptors delineated by Black et al (7) have now been both shown to be involved in the action of histamine on the cardiovascular system.

Vascular Effects

BLOOD PRESSURE Blood pressure effects of histamine have been measured in a number of species generally in anesthetized animals, frequently with single doses. Where appropriately measured by dose-response techniques in (anesthetized) dogs and cats, there is a maximum dose ratio displacement of the dose-response curve to the right of up to 10 by H-1 antagonists (96). Whereas the H-2 antagonists did not affect the depressor dose response to histamine, the combination of H-1 and H-2 antagonists caused very large displacement of the dose-response curve to the right (96–99). In cats either H-1 [2(Me)H] or H-2 [4(Me)H] agonists lowered blood pressure, effects which at very large doses were mediated by the other receptor. By contrast 2-(2-pyridyl)-ethylamine (PEA) and 2-(2-thiazolyl)-ethylamine (ThEA) acted only via H-1 receptor (15, 99).

Similar results have been reported in rats, guinea pigs (101), and monkeys (99). Earlier studies using burimamide should be reevaluated in the light of the findings of Ganellin et al (102) in pithed rats where burimamide increased the blood pressure—an effect that was blocked by phentolamine and prevented by adrenalectomy. This was interpreted as an effect due to the release of catecholamines. Related compounds tested showed pressor effects presumably due to catechol release in the rank order methylburimamide, > burimamide, > metiamide, > thiaburimamide, leading to the conclusion that the pressor effect was proportional to basicity of the compound due to the cationic (imidazolium) forms. In the sheep, small doses of histamine cause a fall in blood pressure and vasodilatation which is abolished by an H-1 antagonist but not by metiamide (103).

Studies with selective agonists for H-1 and H-2 receptors confirm these interpretations in anesthetized animals. Thus 2(Me)H, PEA, and ThEA all

reduce blood pressure in cats (99, 100) via H-1 receptors, and 4(Me)H does so via H-2 receptors in cats (99, 100, 104), dogs, rats, and rabbits (104). The effects of 2(Me)H, an H-1 agonist, spilled over at large doses on the H-2 receptor and those of 4(Me)H, the H-2 agonist, spilled over at large doses via the H-1 receptors (100). By contrast dimaprit (13) is a very selective H-2 agonist and lowers blood pressure (105) in anesthetized cats, dogs, rats, and rabbits. In the cat, blood pressure fell after dimaprit without any change in heart rate or cardiac output; that is, hypotension was related directly to a decrease in peripheral resistance. These effects were blocked by both cimetidine and metiamide.

Histamine has no direct effect on cardiac output by either receptor system, and this is so whether examined by appropriate agonists or antagonists (105, 106), though in anesthetized animals cardiac output might fall with hypotension if baroreceptors were rendered insensitive by the anesthetic.

PERIPHERAL RESISTANCE AND REGIONAL BLOOD FLOW Intravenously administered histamine produces peripheral vasodilatation, but the effect is not uniform in all tissues and not necessarily the same for any one tissue in different species.

VEINS Direct histamine action constricts veins by an H-1 receptor (97, 107).

GASTRIC BLOOD FLOW Gastric blood flow is usually measured by the clearance of aminopyrine that is trapped by lumenal acid. In the absence of acid secretion, this technique underestimates blood flow. Radioactive microspheres (106, 108, 109) provide a better estimate, especially in the nonsecreting stomach. Gastric mucosal blood flow increases with all stimuli of gastric acid secretion, more so with histamine than with pentagastrin or feeding at the same rates of acid secretion (110, 111). When stimulated acid secretion is inhibited by H-2 antagonists or by prostaglandins in the rat, increased blood flow persists (111) and PEA increases blood flow without stimulating acid secretion. Thus the rat gastric microcirculation is dilated via both H-2 and H-1 receptors. In the cat and dog the gastric blood flow effects of histamine are mediated via H-2 receptors (105, 106) and are not affected by the H-1 agonist PEA (106). It is still not clear whether the vasodilatation that accompanies secretion stimulated by secretagogues other than histamine is due to local histamine release or to other mechanisms, e.g. via a prostaglandin effect (112). Indeed it is still being argued whether acid secretion is mediated by histamine.

MESENTERIC Mesenteric blood flow, which is increased by histamine in the anesthetized cat, is reduced by H-1 antagonists (105, 110) with a maxi-

mum dose ratio shift of 16. Metiamide alone is without effect but when given with mepyramine causes a greater shift of the dose response to the right (105, 106). In the isolated perfused vascular bed of the cat terminal, ileum vasodilatation by histamine is blocked by metiamide with vasoconstriction by mepyramine-sensitive H-1 receptors. The vasoconstrictor effect was not demonstrated in the anesthetized cat. In general, vasoconstriction is demonstrated only in in vitro vessel preparations and is H-1 receptor mediated.

PORTAL BLOOD FLOW In anesthetized dogs hepatic portal blood flow is decreased by an H-1–mediated vasoconstriction, and hepatic arterial flow is increased by arterial vasodilatation also mediated by an H-1 receptor (107). Neither is altered by metiamide.

KIDNEY In the isolated blood-perfused dog kidney, histamine increased renal blood flow (RBF) from 137 to 181 ml/hr with the inner cortex getting the greater part of the increase. Renal function was unaffected by this change. Hemodynamic (vasodilator) effects were blocked by diphenhydramine but not by metiamide. The cat kidney perfused with blood behaved similarly but rabbit kidney is vasoconstricted with histamine (113).

Uterine blood flow in the conscious sheep is increased dose-responsively by intraarterial histamine. This effect is largely blocked by H-1 antagonists and very little by metiamide (103). Intravenously given histamine reduces uterine blood flow because of fall in blood pressure (134).

SKELETAL MUSCLE In man (114), the cat, and the dog, histamine dilates blood vessels of skeletal muscle (see 115), but is not involved in hyperemia following exercise (116). In very careful studies Rengo et al (117) have adduced evidence that histamine (H-1) may mediate reflex vasodilation in muscle, though Powell & Brody (97) do not find it so.

The action of small doses is blocked by H-1 antagonists, but larger doses are insensitive to this blockade. This led Folkow et al in 1948 (95) to postulate two kinds of histamine receptors in peripheral vessels. While H-2 antagonists have no effect by themselves, they augment the effect of H-1 antagonists and together abolish the vascular effects of histamine (97, 115, 118). Selective agonists confirm that stimulation of H-1 and H-2 receptors can each cause vasodilatation (13, 61, 97, 100, 118).

SYNOVIUM With ^{133}Xe clearance as a measure of blood flow, metiamide antagonized the vasodilator effect of histamine in canine joints (119). Mepyramine had no such effect and at certain doses caused vasodilatation by itself; this was also seen in rat gastric blood flow (111).

CORONARY BLOOD FLOW There are direct vasodilator effects of histamine on the coronary vessels (H-1) as well as secondary dilatation due to the myocardial metabolic activity (120). The overall coronary vasodilator effects of intravenously given histamine are partly reduced by H-1, somewhat more by H-2 antagonists, and abolished by pretreatment with both (100, 121, 122). The vasodilatation is also produced by H-2 agonists [4(Me)H and dimaprit], and to a much smaller extent by PEA (106, 121). Intraarterial histamine injection causes coronary vasodilatation in the dog (122). As above, H-1 antagonists block some of the response; H-2 antagonista are also incomplete, while both together abolish the effect of histamine (122). Neither antagonize the reflex coronary vasodilatation of reactive hyperemia (117).

CRANIAL CIRCULATION Histamine dilates the carotid vascular bed in the dog, partly by H-1 but mainly by H-2 receptor activation; as in other circulations it takes pretreatment with both types of antagonist to block the effects of histamine (123). In the monkey the effect of histamine on the external carotid circulation seems to be completely blocked by H-2 antagonists, while the internal carotid effects comprise both H-1 and H-2 receptors (124). In the cat, histamine produced vasoconstriction via H-1 receptor and vasodilatation via H-2 receptor. The H-1–dependent vasoconstriction is competitively inhibited in the external carotid circulation of the cat (125). The human temporal artery dilates with histamine, an effect that is blocked by burimamide (126). Theoretically, cluster headaches, which are thought to be due to histamine, should be responsive to combined H-1 and H-2 receptor antagonists. There are no reports of the combined use of these agents for histamine headaches.

IN VITRO EFFECTS Reports of vasoconstriction of blood vessels by histamine come largely from studies of isolated vessels, for example, cat ileal mesentery (115), cat extracranial vessels (125), rabbit aorta, portal vein, vena cava (115), and umbilical vessels of man, sheep, and monkey (115). This vasoconstriction can be blocked by H-1 antagonists. The same is true of pulmonary vasoconstriction by histamine (128).

PULMONARY CIRCULATION Except in the fetal sheep, where histamine given i.v. causes only pulmonary vasodilation (131), histamine given intravenously to anesthetized animals or to isolated heart-lung preparations causes both constriction and dilatation of the pulmonary vessels, the former dominating the response and abolished by H-1 receptor antagonists (128–130). The H-1 agonist 2(Me)H also produces vasoconstriction. The (residual) vasodilator effect after H-1 blockade of histamine effect is abolished by

subsequent H-2 antagonists. Pretreatment with H-2 antagonists augments the H-1 mediated vasoconstriction (129). These effects in the anesthetized dog and in heart-lung preparations could be reproduced in the conscious neonatal or adult sheep given histamine intravenously (132) but histamine given directly into the pulmonary artery of both adult and neonatal sheep had no effect (132). Also pentobarbital, Benadryl®, metiamide, and the ganglion blocker Arfonad® markedly attentuated the vascular effects of intravenous histamine in the conscious intact animal (132). This would suggest that the pulmonary vascular effects of histamine given intravenously are indirect and that the vasoconstrictor effect in the in vitro preparations are in keeping with histamine effect on other vessels studied in vitro (see above). Histamine causes pulmonary edema in conscious sheep by increasing vascular permeability through an H-1 action (133).

Studies such as those of Woods et al (132) using histamine and appropriate agonists and antagonists infused directly into the pulmonary artery need to be done in other conscious animals of various ages so as to rule out effects due to age and species differences.

Hypoxia produces pulmonary vasoconstriction which is not blocked by either H-1 or H-2 antagonists and which is increased by infusion of histamine (134). Histamine does not play a part in hypoxia-induced vasoconstriction.

Species Differences

RABBIT Whether in the conscious or anesthetized state, or in isolated vessels, bolus injections of histamine have a biphasic effect on vessels of the rabbit, first causing vasoconstriction and then vasodilatation. The vasoconstriction is H-1 mediated and the dilatation is H-2 mediated (135, 136). In the presence of H-1 antagonist only dilatation results from histamine given by bolus or infusion. This is seen in both the hind limbs of the intact animal (135, 136) and in isolated vessels of, for example, the ear (137), kidney (129), or mesentery (127). In the presence of H-2 antagonists, vasoconstriction is augmented (129). In the conscious rabbit, dilatation in the renal and mesenteric vessels has been reported to result from both H-1 and H-2 stimulation (138). Using specific agonists, blood pressure increases due to H-1 receptor-mediated vasoconstriction and falls due to H-2 mediated vasodilatation. The lack of histamine effect on blood pressure in the rabbit reflects the balance between the two effects, that is, an equal and opposite H-1 and H-2 effect.

CHICKEN Both H-1 and H-2 (H-1 $>>$ H-2) receptors mediate the vasodilator (depressor) effects of histamine on systemic arterial circulation and the venoconstrictor effects of histamine (139, 140).

OTHER SPECIES The species most widely studied, e.g. dog, cat, monkey, calf, and man, appear to be similar among themselves in most respects, though it is not always easy to compare, because the conditions of study are so different. Because of species-dependent pharmacologic diversity of histamine action, results in any one species have to be interpreted cautiously.

Histamine and the Heart

Histamine can be shown to have a number of effects on the heart, many of which can be shown in the intact animal, but not equally in all species. Since histamine is present in large quantities in cardiac tissue (141) mainly in mast cells (142), a possible physiologic role has been discussed (142, 143). It has, however, been difficult to always distinguish between the direct effects of histamine and the indirect which result from other effects of histamine, e.g. release of catecholamines [including incidentally that effect of some H-2 antagonists (102)], peripheral vasodilatation and fall in blood pressure, and changes in pulmonary circulation. Much of the work has thus been done on isolated heart preparations, most frequently from guinea pig.

Histamine increases the sinus rate–positive chronotropic effect; increases the amplitude of ventricular contraction–positive inotropic effect; impairs A-V conduction–negative dromotropic effect; increases coronary blood flow directly and indirectly (discussed above); and at high concentration induces ventricular arrhythmias. None of these effects are mediated by either cholinergic or adrenergic pathways, nor is histamine involved in cholinergic or adrenergic effects on the heart.

The sinus rate is increased by a direct action on the pacemaker cells which show an increased slope of diastolic depolarization with an increased rate of firing during histamine perfusion (144). This effect, which has been shown in guinea pig atria (7), in whole hearts in vitro, and in the intact animal is competitively antagonized by H-2 antagonists (7, 128, 142, 143, 145). Except for the report by Powell & Brody (97) who used very large doses of histamine and found that the chronotropic effect was blocked by mepyramine, H-1 antagonists have either no effect or augment the maximal response to histamine (128, 145, 146); this suggests (145) that there is an H-1 action which acts to reduce heart rate, though the H-2 positive chronotropic action is much more pronounced than the H-1 negative effect. The specificity of the H-2 receptor in the positive chronotropic effect is shown by the effect of 4(Me)H (7, 145), dimaprit (13, 14), and comparative lack of effect of 2(Me)H (7) and PEA (11, 15). The potency order of agonists is histamine $>$ 4(Me)H $>$ ThEA $>$ PEA (143) which is the same order as for rat gastric secretion (15), i.e. H-2 $>>$ H-1. In the dog 4(Me)H elicits a higher cardiac rate than histamine (145). Chronotropic effects are not seen

in all species. Thus in the cat dimaprit causes an H-2 mediated fall in blood pressure without significant change in the already maximal heart rate (105), and histamine in man sufficient to cause marked headache and prolonged PR intervals causes the heart rate to increase by less than 20 b.p.m. (147); I have also found that maximum histamine stimulation of gastric secretion in the presence of benadryl does not significantly change pulse rate or blood pressure in man.

The increase in force of ventricular and auricular contraction (positive inotropic effect) of histamine also appears to be H-2 mediated, since it is antagonized by metiamide, an effect that is attentuated by reducing the concentration of Ca^{2+} in the perfusing medium (148) using rabbit heart. The positive inotropic effect in guinea pig papillary muscle has been attributed to the slow inward Ca^{2+} current mediated by H-2 receptors (149) and cAMP (150). In electrically paced guinea pig atria the inotropic effect has been ascribed to H-1 action (151), but in isolated whole hearts, the inotropic effect of histamine is blocked by H-2 antagonists (152, 153). Agonist potency is in the same order as for chronotropism (143) (see above), and for rat gastric secretion (15). Part of the uncertainty of interpretation is that inotropism may increase with increase in heart rate [although it does not do so with isoproterenol induced tachycardia (97)] and the H-2 effect in whole hearts may be indirect. A-V dissociation results from progressive prolongation of A-V conduction by increasing doses of histamine, an effect also seen in man (147), acting by H-1 receptors (146, 154). The most selective H-1 agonist ThEA is also the most potent in prolonging A-V conduction with the least chronotropic effect, and, in sufficient dose will produce complete A-V dissociation. Ventricular-tachyarrythmias and idioventricular rhythm caused by histamine are preventable by H-2 antagonists (155). Enhanced automaticity of auricles as well as ventricles seems to be H-2 mediated (144). The potent potential effects of massive histamine release in anaphylaxis (156) can be appreciated from the multiple demonstrated effects.

The actions of histamine on the circulatory system still need to be placed in physiological perspective. Discrepancies in reported effects and receptor specificities probably stem in part from differences in species and preparation, from inadequate or excessive drug doses, from use of single doses and unappreciated other effects of some agents used. In general, histamine does not appear to be related directly or to be mediated by cholinergic or adrenergic pathways on the heart or blood vessels. Nevertheless, the demonstrated presence of large amounts of histamine in circulatory tissues, the histamine H-2-, but not H-1-, induced cAMP increases that parallel functional effects (153, 157), the mechanism for avid uptake of histamine (142), and the release of histamine under various physiological circumstances all suggest

that histamine may be important in cardiovascular function under physiologic or pathophysiologic circumstances. As in other tissues some effects are mediated by H-1, others by H-2, and some by both H-1 and H-2 receptors.

NERVOUS SYSTEM

Brain

Histamine may be a central neurotransmitter (158–161), and in many respects histamine systems in the brain are analogous to those involving other amines—serotonin, norepinephrine, and dopamine (162). In the several species studied, histamine is present in the brain in roughly the same distribution, being highest in the hypothalamus, especially the mammillary bodies and the supraoptic nucleus. The lowest levels have been found in the cerebellum and the medulla pons. Radiolabeled histamine does not cross the blood-brain barrier but is formed from the decarboxylation of histidine, which does cross the blood-brain barrier, by a specific histidine decarboxylase (HD) which exists in especially high levels in the hypothalamus, but is also present in other regions (163). Inhibition of the HD results in the very rapid depletion of histamine with a half-life of 0.5–5 min (164).

The major pathway for metabolism of brain histamine is by histamine-N-methyl-transferase (HMT) to 3-methyl-histamine [3(Me)H], an inactive analogue (Figure 1), and by a successive oxidative deamination by monoamine oxidase (MAO) to methyl imidazole acetic acid (MIAA) via the aldehyde.

The rapid turnover, especially in the hypothalamus (146), suggests that methylation could provide the inactivation process necessary to terminate the synaptic action of histamine. The response is modulated by the inhibition of HMT by 3(Me)H (165).

Much of the histamine and its synthesizing and degrading enzymes in mammalian brain is associated with subcellular particles that behave like synaptosomes, and histamine is stored in synaptic vesicles (166). There is also a slowly turning over pool of histamine, probably associated with mast cells (159). K^+ ions release histamine from brain slices by a Ca^{2+}-dependent process.

Events, for example, anesthesia, sedation, and stress, that affect other biogenic amines also similarly affect the release and turnover kinetics of brain histamine (162), and data from brain-lesioned animals in which there is reduction of histidine decarboxylase suggest the presence of histaminergic pathways (160). Evidence, much of it circumstantial, supports the suggestion that histamine has a role as a synaptic transmitter in the brain (161, 164).

Central Actions

Histamine intraventricularly or by localized injection in specific central loci has a number of reported effects including hypertension and tachycardia (167) via an H-1 pathway, sleep, central arousal, self-stimulation, hypothermia, enhanced water intake, increased respiration, and vomiting (161, 162).

Histamine exhibits both stimulation and inhibition on spontaneous or evoked electrical activity of central neurons. Cerebral cortical neurons (168), cerebellar Purkinje cells (169), and brainstem and spinal neurons (170) are usually inhibited, while hypothalamic neurons are usually excited by histamine (171). Both H-1 and H-2 agonists inhibit firing of cortical neurons (160). The effect of metiamide in blocking this appears specific. Central effects on blood pressure are not antagonized by metiamide, though the low lipophilicity (11, 15, 16) limits entry of metiamide into brain. Mepyramine blocked the pressor effect of histamine (167) but in the doses given into the ventricles it also blocks other centrally active pressors (172). Both H-1 and H-2 selective agonists can elicit pressor responses (167), each separately being less active than histamine. Since both inhibit histamine methyltransferase, they might indirectly affect endogenous histamine as well as having a direct effect on the receptors.

The centrally acting hypotensive agent clonidine is said to have an affinity for H-2 receptors (173). Centrally given cimetidine competitively antagonizes the effects of clonidine, which is also a gastric acid agonist. Finch & Hicks found no evidence in the conscious cat for interaction of clonidine and H-2 receptors (174). It is thus premature to invoke any central histamine action in hypotension or blood pressure control.

Histamine in the cerebral ventricle (ICV) also produced hypothermia which can be blocked by burimamide (175) given into the third ventricle; however, the results of routine studies with selective agonists and antagonists regarding temperature regulation are still confusing (161). Vomiting resulting from ICV histamine in unanesthetized dogs is mediated by both H-1 and H-2 receptors (176).

Tricyclic antidepressants block H-2 effects of histamine or H-2 agonists in the brain (177) and block the adenylcyclase stimulation by histamine (178), suggesting that histaminergic neurons may be involved in the actions of antidepressants. These observations may provide the unifying basis for understanding actions of diverse antidepressants. There is, moreover, a complex interaction between histamine and morphine receptors, in which l-histidine increases tolerance to withdrawal, as do both 2(Me)H and 3(Me)H, each being blocked by its specific antagonist, and histamine by both together (179). Weak H-2 agonists might, therefore, offer possible alternatives to current withdrawal treatments.

In the peripheral nervous system there is a dual action of histamine on the superior cervical ganglion of the rabbit where H-1 receptors mediate facilitatory and H-2 receptors inhibitory effects on ganglion transmission (180).

Brain Adenylcyclase and cAMP

Like other biogenic amines, histamine activates adenylcyclase in brain, leading to accumulation of cAMP (161, 181). It also enhances phosphorylation of proteins in brain slices (182). It is not yet possible to relate physiological function of histamine to the induction of adenylcyclase or phosphorylation of proteins. The evidence implicates a cerebral cAMP system as the postsynaptic receptor for an ascending histaminergic pathway in the rat (162). H-1 and H-2 histamine receptors appear to mediate both the inhibition of central neurons by histamine and the stimulation of adenylcyclase in brain slices.

In rabbit brain slices H-1 antagonists block the large increase in cAMP (183). The rank of potency of stimulation of cAMP by histamine and various analogues [histamine > N(Me)H, = N'N'(Me)$_2$H > triazole > betazole] (184) exhibited the same order as that of gastric secretion in dogs (185). Not all regions of the brain respond. The cerebellum, amygdala, hypothalamus, medulla pons, diencephalon, and brain stem do not respond to histamine, while rabbit or guinea pig cerebral cortex, hippocampus, thalamus, and striatum have two- to eightfold increases in cAMP with histamine (184, 186). These effects are all much potentiated by the presence of adenosine or norepinephrine, effects that are partly antagonized by H-1 antagonists (187). It even appears as though in the presence of adenosine the H-1 receptor develops an affinity for an H-2 agonist, e.g. 4(Me)H. The affinity for histamine is marginally affected by adenosine (188).

By contrast, brain slices from rat, mouse, cat, pig, or primates, including man, do not respond to histamine or exhibit only marginal increases of cAMP (162), though Green & Maayani (177) did find activity in rat hippocampus using a different system. Though the hypothalamus contains the most histamine in all species, in most of these histamine does not increase cAMP and excites rather than inhibits hypothalamic neurons, being inhibitory to most other neurons. In the chicken brain, cAMP stimulation by histamine is blocked by metiamide (189) and not potentiated by adenosine (190). In guinea pig cerebral cortical or hippocampal slices, histamine effects are partly (50–80%) blocked by either H-1 or H-2 antagonists while both together completely block the response (186). The response to either an H-1 (ThEA) or an H-2 (4(Me)H) alone is less than to histamine, the effect of each being blocked by the appropriate antagonist (162). Like the

α-component of norepinephrine response in brain slices (162), the H-1 effect is dependent on external Ca^{2+} or adenosine.

A most interesting recent report (191) showed that D-lysergic acid (D-LSD) and D-2 bromo-LSD (D-BrLSD) but not L-LSD are competitive antagonists of histamine in the activation of the H-2 receptor linked to adenylcyclase in the hippocampus and cortex of the guinea pig brain. D-Br-LSD is ten times more potent an H-2 antagonist than cimetidine, and D-LSD about equally potent. Neither psilocin nor mescaline had similar action. When both dimaprit and histamine were used, the pA_2 values of a series of H-2 antagonists were the same as for other H-2 effects on guinea pig atrium, rat uterus, and gastric acid secretion (7). H-1 antagonists were also active but at much higher concentrations. Antagonism of H-2 receptors could contribute to central and other pharmacological effects of D-LSD and Br-LSD, very likely acting in the hippocampus, where it is thought, histaminergic nerves terminate, and where histamine may act by blocking neuronal discharge (192). Moreover, there is a steric congruence between metiamide and D-LSD which could explain the H-2 receptor affinity of LSD.

HISTAMINE EFFECTS ON THE HEMOPOIETIC SYSTEM, AND IMMUNE RESPONSES

Histamine and other mediators are released from basophils and mast cells which have been sensitized by prior attachment of IgE to specific receptors on the surface. Once sensitized, the cell is activated by appropriate antigens. The release of mediators from these cells (degranulation) requires a subsequent step and is energy dependent, and also Ca^{2+} dependent. In vitro, two stages are distinguishable: The first involves IgE and antigen binding which activates the cell and the second involves Ca^{2+} which triggers the release (193). An increase in intracellular cAMP prevents the degranulation. Several agents inhibit release of mediators by increasing cAMP, including β-adrenergic agonists, prostaglandin E, cholera toxin, and histamine, the latter acting at low concentrations via an H-2 receptor. It has been suggested that histamine released locally by some cells could be involved in a feedback mechanism to limit further degranulation of other mast cells. Since H-2 antagonists block this action, the fear that they would allow a runaway release of mediators in hypersensitivity responses has been raised and tested in guinea pigs with tuberculin or dinitrofluorobenzene and subsequent challenge (194, 195) and in dog lung with ascaris challenge (92). In neither case was there any indication of an uncontrolled release of mediators as a result of several days of H-2 antagonist therapy. One report (196) showed an increase in erythema and induration of skin tests with streptoki-

nase-streptodornase in patients after six weeks of cimetidine therapy. In the clinical use of H-2 antagonists, no evidence of exaggerated cell-mediated immune responses has so far appeared. More subtle effects, such as on renal allografts (197), have not been adequately ruled out.

Histamine also has an effect on lymphocytes via H-2 receptors (193, 198). Specifically T lymphocytes produced in mice in response to injection of histoincompatible mastocytoma cells, appear in about one week and kill the mastocytoma cells. This cytolytic action is inhibited by histamine, acting via H-2 receptors. This action is mediated by cAMP and is competitively blocked by both burimamide and metiamide (193, 198). These receptors increase in number for about one week and then decline, so that the degree of inhibition of lymphocytotoxicity by histamine increases linearly with time to a peak and then recedes. Moreover histamine, also by an H-2 receptor action, inhibits the production but not the action on macrophages of antigen-induced migration inhibition factor (MIF) and of antigen-induced lymphocyte proliferation. H-1 antagonists have no effect on this system (179). Thus immediate hypersensitivity with histamine release may influence subsequent expressions of cellular immune reactions (194, 197).

Histamine also inhibits chemotaxis of leucocytes by an H-2 receptor–mediated pathway with an increase in cellular cAMP (199), an effect which is not affected by H-1 antagonists. Levamisole has the same effect as H-2 receptor stimulation. Other reports of inhibition of chemotaxis describe a histamine H-2–mediated effect in eosinophils (200) and basophils (201). Lysozomal enzyme release by zymosan from polymorphs is inhibited by histamine via H-2 receptor, leukocytes from asthmatics are less sensitive to histamine inhibition (202).

Bone Marrow

After the agranulocytosis produced in some animals (203) and in man (204–206) with metiamide, there is naturally great interest in understanding the mechanism so that such an effect might be predicted or at least detected early. Cimetidine was safely given to two patients who had metiamide-induced agranulocytosis (205, 207), indicating that the bone marrow effect was related to the structure of metiamide (presumably the thiourea moiety) rather than to H-2 antagonism (208). Byron has proposed (209, 210) that H-2 antagonism to the histamine triggering of the pluripotent bone marrow stem cell from the G_0-state into the DNA-synthetic phase of the cell cycle may be responsible for the effect of these drugs on bone marrow. So far the differences in effect between cimetidine and metiamide would tend to incriminate the thiourea rather than a general H-2 receptor effect in the agranulocytosis of metiamide.

MISCELLANEOUS EFFECTS OF H-2 AGONISTS AND ANTAGONISTS

Ovum Implantation

A combination of H-1 and H-2 antagonists prevented ovum implantation in rats (211). It is not reported whether histamine or any analogue affects ovum implantation, or whether uterine muscle activity plays a role in ovum implantation.

Adipocytes

Isolated canine adipocytes release fat when stimulated by histamine, as they do with norepinephrine. Both act by raising cellular levels of cAMP, and the effects are potentiated by theophyllin, and about 50% inhibited by insulin or prostaglandin E_1. Burimamide inhibited the histamine effect but not the norepinephrine effect, and propranolol inhibited the norepinephrine but not the histamine effects. H-1 antagonists had no effect on either agent (212).

Prolactin

Serum prolactin levels are elevated by an acute intravenous injection of cimetidine in normal man. There is no effect on thyrotropin, growth hormone, thyroxin, or triiodothyroxine (213). By contrast seven patients with Zollinger-Ellison syndrome (a syndrome in which gynecomastia not infrequently appears on cimetidine therapy) exhibited no change in serum prolactin levels on long-term cimetidine (215). This group includes two patients who had elevated prolactin levels before cimetidine. TRH-stimulated prolactin release was inhibited in four men by pretreatment with cyproheptadine (214). Prolactin is increased by a number of drugs and hormones; the mechanism is unknown and the explanation for the acute effect of cimetidine and the lack of chronic effect is unknown. Moreover, the connection between prolactin and gynecomastia is tenuous.

CLINICAL APPLICATION OF H-2-RECEPTOR ANTAGONISTS

Despite the extensive list of actions of histamine on H-2 receptors of almost every tissue so far described there is only one practical clinical application of the H-2 antagonists—the suppression of gastric acid secretion. The H-2 antagonists are very effective in this action in the basal state and with all stimuli of gastric secretion including food, gastrin, histamine, caffeine, distension, vagal, and other cholinergic agonists. The obvious application of the antisecretory effect is to the treatment of those diseases of the gastrointestinal tract in which acid and pepsin are thought to be, if not causative,

at least responsible for delayed healing or the failure to heal at all. These include duodenal, gastric and esophageal ulcer, recurrent ulcer after gastric surgery, reflux esophagitis, erosive gastritis, and duodenitis.

The first of the H-2 antagonists, metiamide, to be used in wide-scale testing resulted in a number of cases of agranulocytosis (204–207); at least one of these cases, in a patient with systemic mastocytosis (206), was fatal and led to its withdrawal from use. Until withdrawal, it had been shown to be more effective than placebo in short-term studies of duodenal ulcer symptoms (216) or healing (217) as well as in preventing recurrence in smaller, but longer-term studies (218, 219), though apparently requiring 3–4 doses per day rather than only one at night (218). Rapid relapse after treatment was noted (218).

Its successor cimetidine has been free of hematological side effects, even when given to two patients who had had metiamide-induced agranulocytosis (205, 207). Cimetidine underwent extensive clinical trials in a number of countries prior to its release on the market in late 1976 abroad and in mid-1977 in the United States under the trade name Tagamet®. For the most part the clinical trials, a number of which were multicenter, were randomized and double-blind and depended on endoscopy as the objective criterion of diagnosis and healing. These studies have also provided the first clear data on the short-term natural history of peptic ulcer. The results of these studies and related reports on some of the gastric secretory physiology and pharmacology is contained in the reports of the proceedings of two conferences on cimetidine (9, 10).

Duodenal Ulcer

Worldwide, some 70% of more than 600 patients with duodenal ulcer (DU) given cimetidine, 0.8 to 2.0 g/day p.o. in divided doses, were healed endoscopically in 2–6 weeks while only 37% of 300 patients given placebo were healed in the same time (220). In another study (221) which compared cimetidine with large doses of antacid for 4 weeks, similar rates of healing (60 vs 44%) and pain relief were obtained. This suggests that suppression of acid secretion was the mechanism whereby cimetidine promoted ulcer healing. A composite of data from several studies (220) provides a picture of the time it takes to heal duodenal ulcers. The time of observation is followed by the percentage healed with placebo and with cimetidine (i.e. week-PLAC vs CIM): 1 week, 18 vs 27%; 2 weeks, 29 vs 48%; 4 weeks, 42 vs 73%; 6 weeks, 41 vs 80%. This shows a roughly twofold better healing rate with cimetidine. It is rather curious that placebo healing rates in the United States and Australia are higher than in the UK and Europe both in cimetidine studies (Table 1) and in similar studies with carbenoxolone (222, 223).

Cimetidine, moreover, is not unique in the capacity to promote DU healing. In Table 1, compiled by Wormsley (224), at least nine drugs, with apparently different pharmacologic properties, have been reported to heal an average of 69 to 95% of patients with duodenal ulcer within a month or so.

The results so far suggest that from 3 to 6 weeks of cimetidine treatment is needed to heal 70 to 80% of duodenal ulcers but that in as many as 25% of patients treatment for longer than 6 weeks or additional measures, e.g. anticholinergics to suppress pepsin secretion, may be necessary to secure

Table 1 Comparison of healing rates of duodenal ulcer with nine different drugs[a, b]

Drug	Action	Country of trial	Ulcer healing at 4 wk (%) Drug	Placebo
Cimetidine[1]	H_2 blocker	USA[c]	76[d]	63
		UK	72	29
		Norway	85	60
		USA	81	57
Anisotropine methylbromide[2]	anticholinergic (+ inhibitor)			
Trimipramine[3]	antidepressant (+ inhibitor)	Norway	75	46
Gastrozepin[4]	tricyclic (+ inhibitor)	Germany	94	55
Carbenoxolone[5]	mucus	UK	69	22
	stimulant (?)	USA[e]	71	50
Glyptide[6]	antipepsin	USA	81[d]	60[d]
"De-Nol"[7] (tripotassium dictrato bismuthate)	ulcer coating (?)	UK	74	21
Aluminium[8] hydroxide	antacid	USA	76	40
15S, 15Me-PGE_2[9]	prostaglandin	Poland	75[f]	42[f]

[a] List compiled by Wormsley (224); reprinted by permission from *The Lancet*.
[b] References 1–9 cited by Wormsley (224):
1. Burland, W. L., Simkins, M.A. eds. 1977. *Cimetidine*. Oxford;
2. Bowers, J. et al 1977. *Gastroenterology* 72:1032;
3. Wetterhus, S. et al 1977. *Scand J. Gastroenterol.* 12:Suppl 43, p. 33;
4. Ludwig, H. 1977. *Therapiewoche* 27:1664;
5. Davies, W. A., Reed, P. I. 1977. *Gut* 18:78;
6. Butti, A., Personal communication;
7. Shreeve, D. R. 1975. *Postgrad. Med. J.* 51:Suppl 5, p. 33;
8. Peterson, W. L. 1977. *Gastroenterology* 72:1112;
9. Gibinski, K. et al 1977. *Gut* 18:636.

[c] Reference (220).
[d] Six weeks' treatment.
[e] References (222, 223).
[f] Two weeks' treatment.

healing. Many ulcers remain long after symptoms have been relieved, and it is only through the systematic use of endoscopy that it was realized that as many ulcers as revealed in these studies remained unhealed.

Recurrence of ulcer in various experimental series within a month of stopping treatment at 2, 4, or 6 weeks ranges from 53 to 67%, with no difference between placebo and control. The reasons for the relapses are not clear, since there is no difference in acid output before and after cimetidine (230) and no escape, at least with 6 weeks of cimetidine (231). The question is especially intriguing in the placebo group, as it was in the patients studied by us in an earlier study (226). There are several reported instances of perforation of DU after cimetidine, implying a rebound with increased ulcerogenesis or virulence of the ulcer disease (225). One would be inclined to the view that these occurred in unhealed but asymptomatic DU.

Wormsley (224) points out that while it may be comparatively easy to heal a duodenal ulcer, the problem is to keep it healed. The need for long-term follow-up became apparent in a study published a number of years ago (226) in which chronic ulcers remained asymptomatic in 85% of patients for over 6 months on a placebo while participating in a double-blind study which included fortnightly visits to the physician. By 9 months over 60% were still asymptomatic and it was only after 12 months that the natural history of peptic ulcer reasserted itself. Two reports on the prevention of relapse by cimetidine used in healed duodenal ulcer report a relapse of 24 to 27% by 6 months compared to placebo in which there was an 80–87% relapse by 3 to 6 months (227–229). Many who relapsed had no pain but were shown to have an ulcer by endoscopy (228). Various maintenance regimens have been suggested, from full dosage to one dose at night. Further efficacy and safety data now being acquired in several ongoing studies are needed to answer the question of appropriate long-term maintenance therapy which may be an alternative to highly selective vagotomy, though the latter is more effective and has the advantage of permanence, and a low morbidity and mortality rate.

Hypersecretory States

Since cimetidine suppresses secretion stimulated by either histamine or gastrin, its long-term use in gastric hypersecretory states—Zollinger-Ellison syndrome (ZES) (gastrin excess) and systemic mastocytosis or basophil leukemia (histamine excess)—is logical and offers a reasonable alternative to total gastrectomy, the only effective treatment so far for ZES. In some cases the doses of cimetidine required may exceed those used in duodenal ulcer (up to 2 g/day), but if that is not enough, an anticholinergic may be usefully added. Neither surgery nor cimetidine reduces mortality due to progression of the tumor which has to be treated on its own merits. The

clinical experience in 61 collected cases of ZES and 14 with other causes for hypersecretion, treated for up to 3 years, has been recently reviewed by McCarthy (232). Many symptoms in systemic mastocytosis persist despite combined H-1 and H-2-antagonist treatment including itching, rash, and diarrhea. This may indicate histamine actions which are not H-1 or H-2; or more likely the continued release of other biologically active amines.

Gastric Ulcer

In gastric ulcer (GU), also classified pathophysiologically as an acid/peptic disorder, the results with cimetidine have been marginal. In double-blind trials involving almost 400 patients with benign gastric ulcer, healing was assessed by endoscopy after 2 to 6 weeks of treatment with doses from 0.8 to 1.2 g/day, and compared in some studies to antacids taken as needed and in others to placebo (233). Though cimetidine-treated subjects consumed less antacid, healing with cimetidine was not statistically better within the period of the study. Because the various studies were each composed of small numbers, and the amount of antacid intake was not controlled, no firm conclusion can be reached. Nevertheless in the six studies cited by Freston (233), only 66% of 236 gastric ulcers treated with cimetidine (with or without antacids) were healed endoscopically with 4–6 weeks of treatment compared to 50% of 163 treated with antacid or placebo—numbers not very different from the duodenal ulcer studies cited above. There are indications that antacid therapy promotes the healing of gastric ulcer and thus their use as placebo can confuse interpretation (233). Moreover, gastric ulcer is not a homogeneous disorder; some GUs are caused by or aggravated by analgesic abuse with or without alcohol; some are rendered chronic by gastric circulatory impairment, some are complications of duodenal ulcer and have to contend with gastric acid hypersecretion, and many occur in patients with other severe diseases. The natural history of gastric ulcer is not well enough delineated yet to allow easy interpretation of treatment. Moreover, even malignant ulcers can become asymptomatic and heal on cimetidine (234). Follow-up of all healed GU by endoscopy is essential. In a preliminary report cimetidine maintenance appears effective in preventing GU relapse (235).

Reflux Esophagitis

Reflux esophagitis is another condition belonging to the group of acid/peptic diseases in which the results with cimetidine have been disappointing. Cimetidine does not affect LES pressure and its only effect could be through reduction in acid. Within the 8-week study period, those treated with cimetidine had fewer symptoms and consumed less antacid (236), but there was no difference in endoscopically judged esophagitis with 45% improved

on cimetidine and 37% on placebo. Of some considerable interest was the parallel improvement in symptoms with placebo as well as the relapse in symptoms after stopping placebo (236).

It is obviously not enough only to reduce acid output in treating esophagitis or gastric ulcer, though acid reduction is still the prime physiologic objective in duodenal ulcer and Zollinger-Ellison syndrome, but less certainly so in erosive gastritis. What we have learned is that our understanding of pathogenesis and pathophysiology of acid/peptic diseases is still fragmentary.

Acute Erosive Gastritis

Acute erosive gastritis is the principal cause for major gastrointestinal bleeding in seriously ill or stressed patients with various traumas, sepsis, shock, or burns. There are studies in progress on the prophylactic use of cimetidine in some of these states. What has been reported of the use of gastric neutralization by antacids suggests that some therapeutic benefit might be expected (237, 238). Such studies as are published (239) provide no controlled data on the effectiveness of cimetidine. In a prospective but unblinded study (240) cimetidine significantly reduced the incidence of bleeding in fulminant hepatic failure—only 1 of 26 patients given cimetidine bled, compared with 13 of 24 controls. Further properly designed double-blind studies in the prevention and treatment of bleeding from acute erosive gastritis are needed before any conclusions can be drawn.

Since H-2 blockers act either by antagonizing the effects of histamine on blood vessels or by eliminating acid secretion, one could predict that acute gastric mucosal damage from say anoxia or sepsis, or from some physical agent such as heat or alcohol may not be preventable by these agents.

Thus in various animal models acute gastric erosions are prevented by H-2 antagonists in some cases. For example, ulcers in rats due to aspirin and other analgesics have been prevented by metiamide (241) or cimetidine (242), as have ulcers due to histamine and to stress of various types (243). However, cimetidine was unable to prevent reserpine- or serotonin-induced ulcers or ulceration in pylorus ligation (241).

The mechanisms of production of acute erosive gastritis are still unclear and the use of cimetidine in their prevention in clinical practice at this time is premature.

Other Applications

Cimetidine has been used to prevent the acid destruction of therapeutic pancreatic enzymes given orally in the treatment of chronic pancreatitis (244, 245).

Side Effects

Careful clinical and laboratory observation after a 3-year period of 3000 patients treated with cimetidine revealed very few significant side effects, the principal ones being rare gynecomastia.

Gynecomastia has developed in a number of patients, mostly with Zollinger-Ellison syndrome, treated with cimetidine (232) and also occurs in this syndrome, usually the multiple endocrine adenoma variety, without cimetidine. Gynecomastia in those cases is not always associated with serum prolactin elevation, and chronic cimetidine administration does not increase either normal or elevated prolactin levels (215). Gynecomastia and galactorrhea are seen with a large number of drugs, which are pharmacologically or chemically unrelated to the H-2 antagonists. No common pathway has yet been elucidated. When it is, such a link would provide an important understanding of central neurohormonal mechanisms.

Average serum creatinine rises within one day of cimetidine treatment and remains about 0.15 mg/dl above the placebo-treated controls and above pretreatment values (246). In 60% of those given 1 gm/day, creatinine rose by up to 0.4 mg/dl, and in 11% rose above the normal range, transiently in half of those. In the remainder it fell rapidly when cimetidine was discontinued (247). A preliminary report (248) in 9 subjects showed that creatinine clearance (GFR) fell from 87 to 59 ml/min at one day but rose to 80 and 93 ml/min at 3 and 6 weeks of therapy. There was also an early, short-lived fall in effective renal plasma flow, which with the glomerular filtration rate (GFR) fall explains early serum creatinine increases. Persisting increases in serum creatinine are probably due to increased production rather than to decreased renal function (247, 248). Blood urea concentrations are not affected.

There have been a number of isolated short reports of various possible side effects including mental confusion, bradycardia, hypotension, pancreatitis, glucose intolerance, leukopenia, myalgias, abdominal pain, and ileus. Almost all occurred or were observed in patients who were either having other potent drugs or serious illnesses, stresses, or infection. Small numbers of patients have developed mild elevation of SGOT but only one instance of cholestasis has been reported (249).

Consideration of the toxicological (250) and preclinical data (61) as well as the clinical experience to date suggest that cimetidine is a safe drug. However, the wide distribution of H-2 receptors and their involvement with many organs and functions should keep us alert to some unanticipated, possibly subtle, effects and interactions.

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