Histamine and Cardiac Arrhythmias

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I. Introduction

Modification of the cardiac rhythm by histamine has been appreciated almost since the compound’s isolation from ergot by Barger and Dale in 1910. The major arrhythmogenic actions of histamine are an $\text{H}_1$-receptor-mediated slowing of atrioventricular (AV) conduction and $\text{H}_2$-receptor-mediated increases in sinus rate and ventricular automaticity. These actions were elucidated by observing the salutary effects of histamine antagonists on the arrhythmias of anaphylaxis, and by administering exogenous histamine to various cardiac preparations in the presence and absence of histamine antagonists. The ability to record transmembrane action potential(s) (TAP) from single cells has permitted the study of electrophysiological mechanisms underlying histamine-induced arrhythmias.

We will review here what is known of the specific arrhythmogenic effects of histamine upon each particular type of cardiac cell. Arrhythmias resulting from the release of histamine from the heart (and elsewhere) during anaphylaxis will be discussed, as well as the role of histamine in the genesis or modification of other arrhythmias associated with histamine release. We will also consider other arrhythmogenic effects of histamine, including effects which are indirect (e.g., ischemic arrhythmias precipitated by histamine-mediated coronary spasm), and effects of unknown mechanism (e.g., reduction of ventricular fibrillation threshold by histamine). Finally, we will touch upon the modulation of histamine’s arrhythmogenic properties by other compounds.

II. Cellular Mechanisms of Histamine-Induced Arrhythmias

Cellular events generating cardiac arrhythmias include alterations in normal automaticity, the induction of abnormal automaticity or triggered activity, and the induction of abnormal impulse conduc-
of normal automaticity. McNeill (1980) has noted these three currents can correspondingly modify the

mimicking the effect of exogenous histamine (Yamasaki et al., 1974). Furthermore, an increase in the intracellular cAMP level is associated with an increase in the number of available slow channels (Sperelakis and Vogel, 1982), consistent with the observed effect of histamine upon actively depolarizing sinoatrial tissues and its enhancement by increasing [Ca++]o. A slow inward current (i), carried through these slow channels by Ca++ (and Na+), is one of three currents which normally determine the rate of diastolic depolarization in sinoatrial node cells (see Opie, 1984); modification of any one of these three currents can correspondingly modify the sinus rate. Thus, the usual action of histamine on sinus rate would be interpreted as an enhancement of normal automaticity. McNeill (1980) has noted that other H2-mediated cardiac effects (e.g., increased contractility, increased coronary flow; see Table 2, section VIII) are always accompanied by stimulation of adenylyl cyclase and a subsequent increase in cAMP. Nonetheless, a firm causal relationship between this nucleotide and the chronotropic response to histamine remains to be established.

II.B. Arrhythmogenic Effects of Histamine on Atrial Fibers

Apart from the pacemaker cells of the sinoatrial node (see section II.A), normal human atrial tissue is known to contain at least two other types of fibers: atrial contractile and automatic fibers. Both normally exhibit the relatively high maximum diastolic potential (−80 mV) and rapid upstroke velocity (greater than 200 V/sec) characteristic of cells with fast Na+ channels (Hordof et al., 1976). In addition, automatic fibers undergo spontaneous phase 4 depolarization (Gelband, 1972). When we recorded TAP from automatic fibers obtained from human right atrial appendages, we found histamine to augment the spontaneous rate via increases in both the slope of phase 4 and the threshold potential, and to increase the TAP amplitude. The effect of histamine on spontaneous rate was preventable by cimetidine and verapamil, but not by propranolol, suggesting that, as appears to be the case for sinoatrial tissue, histamine mediates its effects on right atrial automatic fibers through a specific H2-receptor, which, in turn, augments the slow inward current. An additional arrhythmogenic effect of histamine, the induction of delayed afterdepolarizations with the subsequent development of triggered activity (Wit and Rosen, 1983), was also prevented by cimetidine or verapamil. Finally, quiescent fibers stabilized at low resting membrane potentials (positive to −60 mV) could be induced to spontaneous rhythmic activity by histamine; this effect too was reversible by verapamil or cimetidine (Levi et al., 1981 and 1982b).

Histamine can also restore the action potential response to electrical pacing in atrial fibers depolarized by elevated [K+]o (Inui and Imamura, 1976; Kecskemeti, 1978, 1981). Increasing concentrations of histamine will increase the amplitude and duration of these slow action potentials; this effect is attenuated by H2-antagonists, reproduced by H2 agonists, and unaffected by H1-receptor agonists, at least in fibers from right atria (Inoue et al., 1979). Observations in the guinea pig (Kecskemeti, 1978) and rabbit (Kecskemeti, 1981) indicate that a similar response to histamine by left atrial fibers may be H1- rather than H2-mediated, in accordance with evidence that H1-receptors mediate the positive inotropic response of the left atrium to histamine, whereas the inotropic response of the right atrium is H2-mediated (Verma and McNeill, 1977). These H1-responses of left atrial TAP are unaffected by β-blockade, sensitive to Ca++ channel antagonism by compound D-600, and enhanced by increasing [Ca++]o (Kecskemeti, 1978, 1981). Thus, whereas increased Ca++ influx via slow channels appears to be the final pathway for both the H1-mediated restoration of slow responses in left atrial fibers and the similar H2 effect in right atrial fibers, the mechanism by which Ca++ influx is augmented in the left atrial fibers is unclear. (For the right atrial fibers, the H2-mediated, cAMP-dependent mechanism described for the sinoatrial nodal fibers in section II.A is presumed to be active.)

Other histamine-induced changes in TAP configuration of automatic atrial fibers include an increase in the maximum diastolic potential, especially at
concentrations of histamine greater than $10^{-5}$ M (Levi et al., 1981). In addition, TAP duration at any given spontaneous rate has been shown to be longer in the presence of histamine than in its absence, whereas slow channel blockade by verapamil or compound D-600 causes a shortening of TAP duration that is reversible by histamine (Ignat'eva, 1978).

In summary, histamine produces the following effects on the TAP configuration of automatic atrial fibers: hyperpolarization, enhancement of diastolic depolarization, an increased (more negative) threshold potential, augmentation of both the amplitude and duration of the TAP, and the development of delayed afterdepolarizations with the ability to initiate triggered activity. These effects are achieved by an enhancement of the slow inward current, mediated by H2-receptors in the automatic fibers of the right atrium and by H1-receptors in those of the left. Clinically, arrhythmias such as atrial premature contractions, paroxysmal (automatic) atrial tachycardia, and multifocal atrial tachycardia might be expected on the basis of histamine-induced enhancement of diastolic depolarization or triggered activity.

II.C. Arrhythmogenic Effects of Histamine on the AV Node

The most prominent effect of histamine on the AV node is a slowing of conduction which is preventable by H1-antagonists and reproducible with specific H2-agonists (Flacke et al., 1967; Levi, 1972; Levi and Kuye, 1974; Levi et al., 1975). The slowing of AV conduction due to H2-receptor stimulation is greater than would be expected on the basis of the H2-mediated increase in sinus rate; hearts electrically paced in the presence of histamine show a longer P-R interval than hearts paced at the same rate in the absence of histamine (Levi, 1972).

In addition, histamine release is occasionally associated with the development of accelerated junctional rhythms (Capurro and Levi, 1975), suggesting that histamine may also enhance AV node automaticity. Indeed, Hageman et al. (1979) have described acceleration of an AV node pacemaker by selective infusion of the specific H2-receptor agonist 4-methylhistamine into the AV node artery of dogs in which sinus rhythm had been previously suppressed. The increase in rate, as well as a decrease in TAP duration, occurs despite treatment of the preparation with propranolol (Ledda et al., 1967). More recent observations on electrically driven Purkinje fibers of the Japanese monkey also document a histamine-induced decrease in TAP duration which can be blocked by cimetidine; the resting membrane potential, maximum rate of rise of phase 0, and TAP amplitude are not affected by histamine (Hattori et al., 1983). The cellular mechanism underlying the enhancement of automaticity is unclear, since slow inward current does not play a significant role in phase 4 depolarization of Purkinje fibers (Eisner et al., 1982). In addition, histamine induces oscillatory activity in sheep Purkinje fibers depolarized by high [K+]o. Although insensitive to the β1-blocker propranolol, this effect is prevented by either burimamide or verapamil (Mugelli et al., 1980) and thus is probably another instance of H2-mediated enhancement of slow inward current.

To postulate a shortening of TAP duration on the basis of an enhancement of slow inward current may seem paradoxical, since the plateau phase is maintained in large part by Ca++ (and Na+) influx through slow channels (Sperelakis and Vogel, 1982); it might be expected that an H2-induced increase in the number of available slow channels would serve to prolong the plateau phase, thus lengthening TAP duration, as in automatic atrial fibers (see section II.B). In fact, the plateau phase represents a balance between slow inward current and several slowly activating outward currents carried by K+ (Vassalle, 1982). Evidence exists that these outward currents are activated more rapidly by increases in the internal Ca++ concentration [Ca++] (Coraboeuf, 1982). Thus, a histamine-induced augmentation of slow inward current during the long plateau phase of the Purkinje fiber may hasten the onset of repolarization by allowing [Ca+++] to rise more rapidly to the level critical for complete activation of the outward K+ currents.
Regarding normally polarized working ventricular cells, substantial agreement exists that histamine has little effect upon either the resting membrane potential or the maximum rate of rise of phase 0 (DeMello, 1976; Senges et al., 1976, 1977; Ledda et al., 1977; Eckel et al., 1982) and causes no change, or only a small increase, in the amplitude and overshoot of their TAP (Houki, 1973; Senges et al., 1976; Ledda et al., 1977; Arita and Saikawa, 1982; Eckel et al., 1982). On the other hand, the data concerning the effect of histamine on TAP duration of working ventricular cells are conflicting. Houki (1973), Senges et al. (1976, 1977), Ledda et al. (1977), and Lam and Katzung (1978) all report that histamine decreases TAP duration, whereas DeMello (1976), Arita and Saikawa (1982), and Eckel et al. (1982) observed an increase.

Perhaps the best explanation for these divergent results resides in the different stimulation frequencies employed in the various studies. Histamine-induced shortening of TAP has been reported when frequencies faster than 1 Hz were used [Houki (1973), 2 Hz; Ledda et al. (1977), 2.5 Hz], whereas Eckel et al. (1982) reported prolongation of TAP when they used a stimulation frequency of 0.2 Hz. Repetitive firing of cardiac muscle fibers is known to cause intracellular accumulation of Ca++ (Fozzard and Sheu, 1981). We postulate that at rapid stimulation rates, a histamine-induced enhancement of the slow inward current occurs superimposed upon a relatively increased [Ca++]i; thus, the repolarizing outward K+ currents are activated sooner after the TAP upstroke, much as we postulated earlier in explaining TAP shortening due to histamine in the Purkinje fiber. The apparent effect of histamine under these circumstances would therefore be to decrease TAP duration. At low stimulation frequencies, sufficient diastolic time exists for extrusion of [Ca++]i to normal resting levels; in this setting, an enhancement of the slow inward current can "balance" the normal time-dependent slow activation of the outward K+ currents for a longer period of time without ever achieving the critical [Ca++]i necessary for more rapid activation of those K+ currents.

Of the four studies in which a stimulation frequency of 1 Hz was used, two show TAP shortening (Senges et al., 1976 and 1977), whereas two report TAP lengthening (DeMello, 1976; Arita and Saikawa, 1982). The latter two studies employed Na+ concentrations of 137 mM in the perfusing medium, compared with 108 mM Na+ used in the former two investigations. Higher extracellular Na+ concentrations provide a greater driving force for the Na+-Ca++ exchange pump, resulting in a lower [Ca++]i (Sperelakis and Vogel, 1982), and, thus, in a longer TAP duration in response to histamine in accordance with our proposed mechanism. A carefully executed examination of working ventricular cell TAP duration as a function of stimulus frequency, over a range of histamine and Na+ concentrations, is necessary in order to confirm this hypothesis.

Additional evidence exists that histamine's effect upon working ventricular fibers is, indeed, an H2-mediated potentiation of slow inward current. Histamine has been demonstrated repeatedly to restore propagated action potentials in response to electrical stimulation of K+-depolarized fibers. The effect is enhanced by the phosphodiesterase inhibitor papaverine and by increasing [Ca++]i. Furthermore, this effect is blocked by the slow channel antagonist D-600, Mn++, the Ca++ chelator EDTA and H2-antagonists, and is insensitive to tetrodotoxin, β-blockade, and H1-agonists and antagonists (Houki, 1973; Ledda et al., 1976; Inui and Imamura, 1976; Inoue et al., 1979; Shigenobu et al., 1979; Gristwood et al., 1981, Arita and Saikawa, 1982; Hattori et al., 1983).

Two miscellaneous observations deserve inclusion here. Inoue et al. (1979) reported a decrease in the rate of rise, overshoot, and duration of TAP of normally polarized working ventricular cells in response to the H2-agonist 2-(2-pyridyl)ethylamine (PEA); furthermore, these actions were antagonized by the H2-agonist promethazine. Also noteworthy is the observation of delayed afterdepolarization in working ventricular cells exposed to 2 × 10^-5 M histamine (Senges et al., 1977).

In summary, the arrhythmogenic actions of histamine upon ventricular cells include enhancement of normal automaticity in Purkinje fibers and induction of abnormal automaticity in both Purkinje fibers and working ventricular cells. Variable, rate-dependent changes in TAP duration of working ventricular cells also occur in response to histamine. If sufficient local concentrations of histamine are present, enhanced normal automaticity could give rise to ventricular premature contractions or tachycardia, even in an otherwise normal heart. In situations in which ventricular cells have become depolarized to abnormally low resting membrane potentials, e.g., acute myocardial ischemia (Elharrar and Zipes, 1982), induction of abnormal automaticity could cause the same arrhythmias. In addition, the slow conduction associated with histamine-induced slow responses could provide the substrate for reentry. Histamine-induced enhancement of ventricular automaticity by either normal or abnormal automatic mechanisms, occurring concurrently with the prominent H1-mediated depression of AV conduction (see section II.C), is a combination of effects particularly likely to allow the emergence of ectopic ventricular pacemakers. Finally, the observation of histamine-induced delayed afterdepolarizations in working ventricular cells (Senges et al., 1977) suggests that histamine may cause ventricular tachyarrhythmias due to triggered activity (Rosen and Reder, 1981). Indeed, abrupt increases in idioventricular rate due to changes in ventricular pacemaker site, when histamine is administered to isolated guinea pig hearts with permanent AV dissociation (Levi and Zavecz, 1979), may be instances of such triggered ventricular tachyarrhythmias.
III. Cardiac Histamine: Content and Localization

As discussed in section II, histamine from any endogenous or exogenous source could induce cardiac arrhythmias if it were to reach the heart in sufficient concentrations; in addition, the demonstration of a substantial pool of releasable histamine in the mammalian myocardium suggests that pathological events involving only the heart may also be complicated by histamine-mediated arrhythmias. Table 1 compiles determinations of cardiac histamine content of various mammalian species obtained in several laboratories. Despite the different analytical techniques, there is fairly good agreement between observations made within a species; mice have been found consistently to contain very little cardiac histamine, whereas guinea pigs always possess considerable amounts. An especially striking finding is the pattern of distribution of histamine within the heart. Each group to have addressed this problem, in every species examined, has found the highest concentration of cardiac histamine cell to be in the right atrium, with smaller amounts present in the left atrium, right ventricle, and left ventricle, in decremental order (Giotti et al., 1966; Guidotti et al., 1967; Anton and Sayre, 1969; Harvey, 1978; Weichman et al., 1981). Giotti et al. (1966) have noted that this distribution parallels that of cardiac mast cells, suggesting that most cardiac histamine is mast cell histamine.

Alternatively, evidence exists for a non-mast cell pool of cardiac histamine. The ratio of myocardial histamine content to the number of granulated cardiac mast cells per unit area increases after treatment with antigen or d-tubocurarine (a known mast cell degranulator), or both (Guidotti et al., 1967). Much cardiac histamine is refractory to prolonged treatment with large doses of the powerful cardiac mast cell disruptor, compound 48/80 (Riley and West, 1955; Harvey, 1978). Furthermore, the uptake and degradation of the cardiac histamine not released by 48/80 (slightly greater than half the total) is more rapid than in any other tissue and is in stark contrast to the very slow turnover rate of histamine in mast cells (Johnson, 1970).

In addition to the evidence for the presence of an appreciable amount of non-mast cell cardiac histamine, Harvey (1978) has shown that the distribution of histamine in the rat heart parallels not only the distribution of mast cells, but also of norepinephrine. A similar conclusion regarding the guinea pig heart had previously been reached by Giotti et al. (1966). The question thus arises whether non-mast cell cardiac histamine is localized in adrenergic terminals. Indeed, it has been demonstrated that sympathetic nerve trunks contain concentrations of histamine even greater than those found in the whole heart (Ryan and Brody, 1970). Although reserpine has been reported to deplete cardiac histamine in the rat (Harvey, 1978), it appears to have no effect on cardiac histamine content of guinea pig or dog (Giotti et al., 1966; Ryan and Brody, 1970; Harvey, 1978). Sympathetic denervation of the canine heart results in a complete loss of myocardial catecholamine content without affecting cardiac histamine stores (Cooper et al., 1962). Furthermore, destruction of adrenergic terminals by 6-hydroxydopamine actually increases cardiac histamine in the rat (Harvey, 1978). Thus, cardiac histamine may not be contained in terminals of cardiac sympathetic nerves. Since recent observations point toward a physiological interaction between cardiac histamine and the response to sympathetic nerve stimulation (Gross et al., 1984a, 1984b; Gross and Levi, 1985), there may be a histaminergic "interecell" in the heart which may be of importance in the genesis or modulation of certain neurally mediated arrhythmias (see section VI).

IV. Anaphylaxis and Histamine-Mediated Arrhythmias

IV.A. Arrhythmias due to Anaphylactic Histamine Release

The clinical literature abounds with reports of cardiac dysfunction during systemic allergic reactions in humans (for an extensive compilation, see the review by Levi and Allan, 1980). Specific observations of arrhythmias occurring during anaphylaxis, but prior to the administration of sympathomimetic drugs for treatment of the anaphylactic state, are less frequent. Nevertheless, several such reports do exist, including descriptions of atrial premature contractions, supraventricular tachycardias, atrial fibrillation, heart block, bundle branch block, ventricular premature contractions, ventricular tachycardia, and asystole (Harkavy, 1969; Booth and Patterson, 1970; Durie and Peters, 1970; Petsas and Kotler, 1973; Carloss, 1976; Levine, 1976; Royston and Wilkes, 1978; Baraka and Sfeir, 1980). Arrhythmias during experimental anaphylaxis in the intact guinea pig include sinus tachycardia, junctional extrasystoles, AV block, and ventricular ectopic activity ranging from isolated premature beats to tachycardia and fibrillation (Capurro and Levi, 1975).

The concept that these changes in rate, rhythm, and impulse conduction are due primarily, if not exclusively, to released histamine, rather than to some other product of mast cells liberated during their immunological degranulation, rests upon three pieces of evidence. First, these arrhythmias are qualitatively reproducible by the administration of exogenous histamine to the isolated heart (Levi, 1972; Levi et al., 1975; Levi and Zavec, 1979). Second, the increase in sinus rate, the incidence, rapidity of onset, and duration of AV block, as well as the incidence and duration of increased ventricular automaticity, are all directly proportional to the amount of histamine released from the isolated heart during anaphylaxis. Third, and most important, antihistamines can prevent the development of these arrhythmias in the setting of either anaphyl-
TABLE 1
Cardiac Histamine Content of Various Mammalian Species*

<table>
<thead>
<tr>
<th>Species</th>
<th>Whole heart</th>
<th>Atrium</th>
<th>Ventricle</th>
<th>Method</th>
<th>References</th>
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<td>Right</td>
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<td>Right</td>
<td>Left</td>
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<tr>
<td>Mouse</td>
<td>0.29</td>
<td>0.36 ± 0.05</td>
<td>0.62 ± 0.04</td>
<td>FL</td>
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<tr>
<td></td>
<td>0.53 ± 0.07</td>
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<td>4.3-5.2</td>
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<td>2.42 ± 0.40</td>
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<td>1.51</td>
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<td>2.77 ± 0.12</td>
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<td>3.37 ± 0.33</td>
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<tr>
<td>Rat</td>
<td>9.97 ± 0.66</td>
<td>6.14 ± 0.90</td>
<td>3.84 ± 0.90</td>
<td>FL</td>
<td>7†(max)</td>
</tr>
<tr>
<td></td>
<td>4.88 ± 0.17</td>
<td>4.44 ± 0.16</td>
<td>1.84 ± 0.11</td>
<td>FL</td>
<td>7†(min)</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>4.3</td>
<td>20.2 ± 6.1</td>
<td>9.8 ± 1.3</td>
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<td>9</td>
</tr>
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<td></td>
<td>6.1 ± 0.3</td>
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<td>5.1 ± 0.6</td>
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<td>6.7 ± 0.7</td>
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<td>4.16 ± 0.21</td>
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<td>BA</td>
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<td>Rabbit</td>
<td>0.5-1.2</td>
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<tr>
<td>Dog</td>
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<td>1.51 ± 0.27</td>
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<tr>
<td>Monkey</td>
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<td>1.0</td>
<td>C</td>
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<tr>
<td>Human</td>
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<td>2.81 ± 1.04</td>
<td>0.71 ± 0.1</td>
<td>FL</td>
<td>1</td>
</tr>
</tbody>
</table>

* Values are means ± SEM and are expressed in µg/g of tissue.
† FL, fluorometric; HPLC, high pressure liquid chromatography; RE, radioenzymatic; BA, bioassay; C, colorimetric (method of Lowry et al., 1954).
† Harvey (1978) found substantial batch-to-batch variability in cardiac histamine content determined by his fluorometric assay, although values from different animals within the same batch showed good agreement; therefore, the maximum and minimum mean values for cardiac histamine content obtained during the assay of several batches of hearts are reported.
§ Mean cardiac histamine contents of two separate groups of animals.

laxis or exogenous histamine administration. H2-receptor blockers such as burimamide and cimetidine selectively inhibit the increase in sinus rate in a dose-dependent fashion and prevent ventricular and junctional ectopy; however, H2-blockers do not affect the increase in P-R interval (Capurro and Levi, 1973; Levi et al., 1975; Levi and Zavec, 1979). Conversely, H1-receptor blockers have no effect on increases in sinoatrial and ventricular automaticity induced by anaphylaxis or histamine administration, but prevent prolongation of AV conduction in either situation (Flacke et al., 1967; Levi and Kuye, 1974; Levi et al., 1975; Levi and Zavec, 1979).

IV.B. Other Hypersensitivity Mediators and Arrhythmias: Interactions with Histamine

Other mediators of acute hypersensitivity besides histamine are released from the heart during anaphylaxis, including prostaglandins (PG) and slow-reacting substance of anaphylaxis (SRS-A), the latter...
being comprised of leukotrienes C4, D4, and E4 (Allan and Levi, 1980a; Levi et al., 1982a, 1985a). The net effect of PG during anaphylaxis appears to be an attenuation of both the release and the effects of histamine (Allan and Levi, 1980a, 1980b). In contrast, leukotrienes C4 and D4 potentiate and extend the arrhythmogenic effects of released histamine (Levi and Burke, 1980; Burke et al., 1982).

The immunological release of arrhythmogenic mediators other than histamine may explain some of the quantitative variations between arrhythmias seen during anaphylaxis and those observed in response to exogenous histamine. The dose-response curve for the chronotropic effect of endogenous histamine released during anaphylaxis from the isolated heart falls to the left of the curve for exogenous histamine (Levi, 1972). Similarly, the conduction and/or idioventricular arrhythmias caused by the administration of 10 μg of histamine to an isolated heart last three times longer than those precipitated by release of approximately 1 μg histamine (Levi et al., 1980). The potentiation of the chronotropic and arrhythmogenic effects of histamine by SRS-A (Levi and Burke, 1980; Levi et al., 1980), and perhaps of other mediators of hypersensitivity released during anaphylaxis, could account for the apparent increased tachyarrhythmic potential of endogenous histamine. A similar interaction may contribute to the increased incidence and severity of the ventricular arrhythmias seen during anaphylaxis in the intact animal vs. those observed during anaphylaxis in the isolated heart (Capurro and Levi, 1975). Furthermore, these observations suggest that, in the setting of arrhythmias due to cardiac histamine release, the histamine-potentiating effects of the concomitantly released leukotrienes overwhelm the histamine-attenuating effects of the released prostaglandins. This results in more severe arrhythmias.

V. Nonimmunological Histamine Release and Arrhythmias

V.A. Arrhythmias Associated with Drug-Induced Histamine Release

Various drugs and chemicals are known to release histamine directly rather than by immunological mechanisms. Among these are a variety of clinically relevant agents such as anthracycline antibiotics used in cancer chemotherapy (Herman and Young, 1979; Bristow et al., 1980), morphine (Rosow et al., 1982), d-tubocurarine, and the corticotrophin analog C-44680-Ba all release cardiac histamine in a dose-dependent fashion, causing the sinus tachycardia, prolongation of AV conduction, and ventricular ectopy characteristic of cardiac anaphylaxis. Again, the increase in sinus rate and duration of idioventricular arrhythmias are proportional to the amount of histamine released (Levi and Allan, 1980).

Histamine stores of human cardiac tissue are also susceptible to nonimmunological release. Morphine, in concentrations of 4 × 10^{-9} to 1.5 × 10^{-6} M (less than that expected in the plasma of patients anesthetized with morphine, 1 mg/kg, iv, prior to cardiac surgery), causes the release of up to 40% of the initial histamine content of surgical specimens of human right atrial appendage (Levi et al., 1982b). Compound 48/80 has also been shown to release histamine from human cardiac tissue (Levi and Allan, 1980).

Doxorubicin (Adriamycin), an anthracycline antibiotic in wide clinical use as an antitumor agent (Sinha, 1982), causes hemodynamically significant histamine release in dogs. Serum histamine levels well in excess of 5 ng/ml, and occasionally as high as 12 ng/ml, occur within the first several minutes after an intravenous dose of doxorubicin comparable to the standard chemotherapeutic dose in humans; these elevations can persist for several hours (Herman and Young, 1979; Bristow et al., 1980). Specific release of cardiac histamine by doxorubicin has been shown in the isolated rabbit heart (Bristow et al., 1981).

Supraventricular tachycardias and other extrasystoles reminiscent of histamine-induced arrhythmias occur commonly in patients within the first few minutes to hours of an intravenous dose of doxorubicin (Bristow, 1982; Sinha, 1982), suggesting that doxorubicin-induced release of histamine from the heart and elsewhere is the cause of these arrhythmias. Indeed, blockade of H1- and H2-receptors can been observed in association with elevated plasma histamine values in several patients following the administration of anesthetic agents or plasma expanders (Lorenz et al., 1982).

Plasma histamine concentration in normal humans is less than 1 ng/ml (Beaven et al., 1982). Arrhythmias may be seen with levels greater than 1 ng/ml, but life-threatening arrhythmias, such as ventricular fibrillation, generally do not occur until plasma histamine concentration is greater than 12 ng/ml (Lorenz et al., 1982). An episode of primary ventricular fibrillation, without any preceding cardiopulmonary embarrassment, has been observed in a patient immediately following the induction of anesthesia; plasma histamine at the time of the event was 110 ng/ml (Lorenz, personal communication).

Experiments with isolated guinea pig hearts have yielded evidence that many drugs can liberate sufficient histamine from the heart itself to cause arrhythmias. Compound 48/80, d-tubocurarine, and the corticotrophin analog C-44680-Ba all release cardiac histamine in a dose-dependent fashion, causing the sinus tachycardia, prolongation of AV conduction, and ventricular ectopy characteristic of cardiac anaphylaxis. Again, the increase in sinus rate and duration of idioventricular arrhythmias are proportional to the amount of histamine released (Levi and Allan, 1980).
prevent hypotension following intravenous doxorubicin injection (Herman et al., 1978). Nonetheless, prevention of acute, doxorubicin-associated arrhythmias by pre-treatment with H1- and H2-receptor antagonists remains to be conclusively demonstrated.

In summary, drug-induced histamine release clearly occurs and has been associated with the development of arrhythmias in the laboratory. Although it cannot be stated definitively that such drug-induced histamine release causes clinically important arrhythmias in human beings, the weight of clinical and experimental data justifies a trial of H1- and H2-receptor blockers when conventional antiarrhythmic therapy fails in the treatment of life-threatening cardiac arrhythmias in a clinical setting suggestive of histamine release.

**V.B. Arrhythmias Associated with Cardiac Histamine Release during Ischemia**

As we have just discussed, the heart alone contains sufficient histamine to precipitate arrhythmias upon its release by either immunological (Levi, 1972; Capurro and Levi, 1975) or nonimmunological stimuli (Levi and Allan, 1980). Thus, local pathophysiological events affecting the heart might be expected to cause local histamine release, causing sinus tachycardia, prolongation of AV conduction, or ventricular extrasystoles. All these rhythm disturbances are common during the early stages of acute myocardial infarction, with ventricular arrhythmias occurring most frequently and being most frequently lethal (Alpert and Braunwald, 1984).

Anrep et al. (1936) demonstrated enhanced release of a histamine-like substance from the canine heart in response to hypoxia. In 1950, Harris proposed that histamine liberated from the ischemic myocardium may be a mediator of peri-infarctional ventricular ectopy. Early investigators of histamine release during myocardial ischemia or infarction measured histamine in peripheral blood samples from patients with acute myocardial infarction under poorly controlled circumstances, employing different assays and obtaining conflicting results (Kipshidze and Barigyan, 1967; Geltfer et al., 1968; Griffiths and Leung, 1971; Rai et al., 1976). One of these investigators did report a positive relationship between increased blood histamine levels and the occurrence of arrhythmias during the first 72 hours after admission to the coronary care unit (Rai et al., 1976), but could not address the source of the elevated blood histamine or the pattern of its putative release.

More recently, Podzuweit (1982) precipitated ventricular arrhythmias by local infusion of histamine into ischemic porcine hearts. Gaide et al. (1984) demonstrated that histamine elicits bursts of rapid automatic activity in spontaneously beating ventricular muscle preparations from spontaneously beating ventricular muscle preparations from 24-hour-old canine myocardial infarctions, while Cameron et al. (1985) reported that acutely or subacutely infarcted isolated guinea pig hearts are more sensitive to the arrhythmogenic effects of exogenous histamine than non-infarcted control hearts. Dai (1984) has claimed that the H2-receptor antagonist SK&F 93479 protects against ventricular fibrillation after coronary artery occlusion in dogs and rats. Although he did not measure circulating histamine concentrations, his findings nevertheless imply a role for histamine in the genesis of early ischemic ventricular arrhythmias.

The development of ventricular ectopy following coronary artery occlusion has been frequently studied in the open-chest, anesthetized dog, and is therefore well-characterized for this model. Ventricular arrhythmias occur in two phases separated by a ‘quiescent’ period of sinus rhythm. An early phase, characterized by bursts of rapid ventricular tachycardia which frequently culminate in ventricular fibrillation, occurs during the first half-hour after coronary artery occlusion. Maintenance of sinus rhythm then supervenes until 4–8 hours after occlusion, when the delayed phase begins. These delayed ventricular arrhythmias are characterized by frequent multifocal ventricular premature beats, often occurring in long runs, but usually at a somewhat slower rate and with a much lower incidence of progression to ventricular fibrillation than the ventricular tachycardia of the early phase (Lazzara et al., 1978). There is evidence that in the very early phase, the arrhythmias might be initiated by a focal automatic mechanism (Janse et al., 1980); later in the early phase, reentry in ventricular myocardium appears to be the major mechanism. In the delayed phase, one or more days after occlusion, abnormal automaticity and afterdepolarizations appear to be the major mechanisms (El-Sherif et al., 1982). In view of the H2-mediated enhancement of ventricular automaticity (Levi and Zavecz, 1979; see section II.D), histamine might be expected to be an initiator of the ventricular arrhythmias of either phase, especially if histamine were shown to be released from the ischemic myocardium. In addition, given the ability of histamine to restore ‘slow response’ propagated action potentials to K+-depolarized working ventricular and Purkinje fibers (see section II.D), and because ventricular cells in the acutely ischemic region exhibit a marked reduction in resting membrane potential, histamine would be expected to predispose to slow conduction through the acutely ischemic zone. This would provide the substrate for reentry during the period of early phase ischemic arrhythmias. Furthermore, reperfusion of ischemic myocardium is also frequently associated with the development of ventricular tachycardia and fibrillation which is initiated in the reperfused myocardium (Fujimoto et al., 1983); histamine release conceivably could play a role in the genesis of these arrhythmias as well.

We have recently demonstrated a mean 10-fold
increase in coronary sinus histamine concentration in response to occlusion of the left anterior descending coronary artery of pentobarbital-anesthetized, open-chest dogs (Wolff et al., 1984a; Levi et al., 1985b). Peak coronary sinus histamine concentrations clustered around 15 minutes after coronary occlusion, and histamine release was nearly always complete within 30 minutes of coronary occlusion, thus coinciding with the development of early phase ventricular ectopy. Indeed, ventricular fibrillation was always associated with a large burst of histamine release into the coronary sinus. Moreover, the number of ventricular premature contractions during the first 30 minutes after coronary occlusion in the absence of ventricular fibrillation correlated positively with the total histamine release, which, in turn, correlated positively with infarct size (Wolff et al., 1984a; Levi et al., 1985b).

In contrast to early phase ventricular ectopy, the emergence of delayed phase ventricular arrhythmias in animals surviving beyond the early phase was never associated with detectable coronary sinus histamine levels. Similarly, ventricular arrhythmias subsequent to reperfusion of the left anterior descending coronary artery after a 30-minute occlusion frequently occurred without the release of cardiac histamine into the coronary sinus (Wolff et al., 1984a). On the other hand, Robertson et al. (1985) found isolated guinea pig hearts to release histamine and creatine phosphokinase (CPK) with the concomitant development of ventricular arrhythmias after reperfusion of an occluded coronary artery.

The significance of the association between the severity of early phase ventricular arrhythmias and the concentration of histamine in the canine coronary sinus after coronary occlusion remains unclear. Studies using the H2-receptor blocker ranitidine in an attempt to alter this relationship have demonstrated no decrease in the incidence of ventricular fibrillation in the ranitidine-treated dogs and, in fact, suggest that it may even be increased (Wolff et al., 1984b). In view of the recent demonstration that H2-receptors mediate an attenuation of the cardiac sympathetic nerve is effected via presynaptic mechanisms, although disagreement exists regarding the subclass of histamine receptors mediating this effect (Lokhandwala, 1978; Hageman et al., 1985; see section VI), it may be that the potential benefit of blocking the arrhythmogenic ventricular H2-receptor during acute myocardial ischemia is overshadowed by the simultaneous loss of H2-mediated attenuation of sympathetic tone. Indeed, it is well known that sympathetic activity increases immediately after coronary artery occlusion and thereby contributes greatly to the development of ventricular arrhythmias in that setting (Malliani et al., 1980; Lombardi et al., 1983).

We cannot presently rule out the possibility that cardiac histamine release during acute myocardial ischemia is merely a marker of that ischemia, much like CPK release is a marker of myocytic necrosis, without functional pathophysiological import. Consistent with this view, Cros et al. (1980) contend that H2-receptors do not exist in the dog ventricle, since their group was unable to stimulate adenylate cyclase activity by histamine in a washed-particle preparation of dog ventricle. On the other hand, other investigations are consistent with the existence of H2-receptors in the canine ventricle (Flacke et al., 1967; Endoh, 1979). Indeed, the body of evidence for the arrhythmogenic potential of histamine, our strong positive correlations between the magnitude of histamine release and the severity of early ischemic ventricular arrhythmias, as well as recent implications of a physiological role for cardiac histamine (Gross et al., 1984a, 1984b; Gross and Levi, 1985; see section VI), together indicate to us that histamine released from the ischemic myocardium is not merely an "innocent bystander" in arrhythmogenesis.

VI. Histamine, Neural Mechanisms, and Cardiac Arrhythmias

The ability of autonomic neural activity to elicit cardiac arrhythmias, in both the presence and absence of acute myocardial ischemia, is widely appreciated and has been recently reviewed (Malliani et al., 1980). The cardiac sympathetic nervous supply is particularly important in the regulation of sinus rate, ventricular excitability, and ventricular fibrillation threshold; its overactivity can produce ventricular arrhythmias and sudden death (Malliani et al., 1980, Lombardi et al., 1983). Clearly, any substance capable of modifying the effect of the sympathetic nervous system on the heart is itself a modulator of cardiac rhythm.

Several reports indicate that histamine attenuates the tachycardia produced by stimulation of cardiac sympathetic nerves (Lokhandwala, 1978; Hageman et al., 1979; Kimura and Satoh, 1983; Gross et al., 1984a). Histamine-induced suppression of tachycardia evoked by stimulation of the canine right cardiac sympathetic nerve is effected via presynaptic mechanisms, although disagreement exists regarding the subclass of histamine receptors mediating this effect (Lokhandwala, 1978; Hageman et al., 1979; Kimura and Satoh, 1983). In contrast, experiments using bilateral stimulation of the sympathetic nerves in the isolated guinea pig heart favor a predominantly postfunctional, H2-mediated mechanism (Gross et al., 1984a, 1984b; Gross and Levi, 1985).

Additional investigations in the guinea pig suggest that the attenuation of the effects of sympathetic stimulation or exogenous norepinephrine by histamine has physiological as well as pharmacological significance. First, sympathetic stimulation is accompanied by a significant release of cardiac histamine into the coronary venous effluent (Gross et al., 1984a). Second, the H2-receptor antagonist tiotidine potentiates the positive chronotropic response to sympathetic nerve stimulation, suggesting that sufficient histamine to attenuate noradrenergic re-
sponses is normally released during sympathetic activity. Third, release of cardiac histamine during sympathetic nerve stimulation is markedly enhanced in the presence of a tiotidine, implying the existence of an $H_2$-mediated negative feedback loop through which histamine inhibits its own release (Gross et al., 1984a, 1984b; Gross and Levi, 1985).

These observations of a cardiac sympathetic-histamine interaction, in concert with the possible existence of a pool of cardiac histamine localized in neither mast cells nor sympathetic nerve terminals (see section III), allow the formulation of the following physioanatomic hypothesis for the function and location of cardiac histamine. Cardiac sympathetic nerve terminals containing norepinephrine synapse upon at least two types of cells, the ventricular cell (be it a working myocardial cell or a Purkinje fiber) and a histamine-containing "intercell," the histological nature of which is presently unclear. The ventricular cell and the "intercell" (which could be a mast cell, a histaminergic neuron, or some presently undefined type of cell) each contain $H_2$-receptors. In addition, the ventricular cells possess $\beta_1$-receptors, while some adrenoceptor—be it $\alpha$ or $\beta$—is also present on the intercell. Stimulation of the sympathetic neuron causes norepinephrine release from its terminal, which subsequently effects a characteristic response in the ventricular cell. At the same time, norepinephrine acts upon the intercell, causing it to release histamine. This released histamine then binds to a ventricular $H_2$-receptor which is closely coupled to a $\beta_1$-receptor and serves to attenuate the latter receptor's effect. The nature of this receptor-receptor interaction (e.g., chemical, morphological, etc.) is presently entirely speculative. The released histamine also binds to an autoinhibitor $H_2$-receptor upon the intercell itself, thus inhibiting further histamine release. Such a model is in accordance with evidence against the presence of cardiac histamine in sympathetic terminals (see section III), explains its release by sympathetic stimulation, proposes a mechanism for histamine's postjunctional attenuation of sympathetic responses in the guinea pig heart, and accounts for the enhancement of sympathetically induced cardiac histamine release in the presence of $H_2$-receptor antagonists. A slight modification of the model, locating the $H_2$-receptor on the sympathetic terminal, rather than on the ventricular cell, allows application of the model to species in which histamine appears to exert a prejunctional effect.

The discovery of a histamine-induced attenuation of cardiac responses to sympathetic discharge contributes to a better understanding of arrhythmogenesis in a setting of increased sympathetic tone. Acute myocardial ischemia is just such a situation: an increase in sympathetic activity is known to occur and to participate in the development of ischemic ventricular arrhythmias (Malliani et al., 1980; Lombardi et al., 1983). Meanwhile, cardiac histamine is released in proportion to the severity of ventricular arrhythmias (Wolff et al., 1984a; Levi et al., 1985b). An obvious postulate is that ischemic cardiac histamine release is a physiological response due solely to the increase in sympathetic tone and is greater when arrhythmias are more severe only because arrhythmias are more severe when sympathetic discharge is greater. $H_2$-receptor blockade in this setting might therefore be expected to exacerbate ventricular arrhythmias secondary to loss of the histamine-mediated attenuation of sympathetic activity, while enhancing cardiac histamine release via blockade of its autoinhibition. Preliminary data from our laboratory suggest that this may be the case (Wolff et al., 1984b; see section V.B).

In addition to its peripheral interaction with the autonomic nervous system, histamine can also influence centrally mediated arrhythmias. Intracerebrovascular (ICV) administration of aconitine causes the development of tachycardia and ventricular dysrhythmias ranging from isolated ventricular premature beats to ventricular tachycardia. Whereas pretreatment with ICV pyrilamine, cimetidine, or propranolol ($H_1$, $H_2$, and $\beta$-receptor antagonists, respectively) prevents the development of these arrhythmias in response to ICV aconitine, only pyrilamine abolishes established arrhythmias when administered after aconitine (Tayal et al., 1982). Thus, central $H_2$-histaminergic receptors may mediate cardiac arrhythmias that occur after intracerebral hemorrhage or similar intracranial insults.

VII. Other Arrhythmogenic Effects of Histamine

VII.A. Histamine-Induced Coronary Artery Spasm: An Indirect Arrhythmogenic Effect

Histamine can provoke spasm in the proximal segment of an epicardial coronary artery severe enough to cause ischemia in the downstream myocardium (Ginsburg et al., 1981). Thus, histamine must be considered a potential indirect cause of ventricular arrhythmias which occur with both coronary artery occlusion and reperfusion. Ginsburg et al. (1981) have precipitated histamine-induced coronary artery spasm in patients with normal coronaries who were pretreated with the $H_2$-antagonist cimetidine, suggesting the coronary vasospasm to be $H_1$-mediated. On the other hand, other reports document coronary artery spasm during anaphylaxis, despite the previous administration of $H_2$-antagonists (Druck et al., 1981; Weber et al., 1982).

Other evidence suggests that histamine may play a role in the pathogenesis of coronary occlusive events (and by extension, of associated arrhythmias) in atherosclerotic vessels. Using miniature swine, Shimokawa et al. (1983) angiographically demonstrated histamine-induced spasm in segments of coronary arteries which were non-obstructed angiographically, but atherosclerotic on postmortem examination. They found histamine to be more vaso-
active than ergonovine, phenylephrine, or serotonin. Coronary artery spasm due to histamine was prevented by the \( H_1 \)-blocker diphenhydramine but not by the \( H_2 \)-blocker cimetidine. Experiments with isolated rings of human coronary arteries also suggest coronary vasoconstriction to be \( H_1 \)-mediated (Ginsburg et al., 1980). Kalsner and Richards (1984) found that proximal coronary vessels from patients who had succumbed to coronary artery disease contained significantly more histamine and manifested significantly greater vasoconstriction in response to histamine than did vessels from noncardiac patients. In addition, vessel segments affected by atherosclerosis contained significantly more histamine than non-atherosclerotic segments. Another recent study has also demonstrated a supersensitive constrictor response to histamine in severely atherosclerotic human coronary segments (Ginsburg et al., 1984). Thus, in addition to the possibility that histamine mediates ischemic ventricular arrhythmias via a direct effect on a ventricular \( H_2 \)-receptor (see sections II.D and V.B) and may modulate the severity of these arrhythmias by attenuating the effects of the enhanced sympathetic discharge which ensues after coronary occlusion (see section VI), histamine may, in effect, initiate ischemic ventricular ectopy by precipitating the underlying reduction in coronary flow which is the primary etiology of these arrhythmias. Reperfusion arrhythmias following a transient episode of histamine-induced coronary spasm could

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* Summarized from Levi et al. (1982c).
† I, increase; D, decrease.
‡ A, atria; AVN, atrioventricular node; V, ventricles; LV, left ventricle.
similarly be considered to have histamine as their ultimate cause. Whereas the exact role of histamine in the pathophysiology of myocardial infarction and its attendant rhythm disturbances remains unresolved, it becomes increasingly apparent that the elucidation of this role is critical to the development of comprehensive and effective therapy for ischemic heart disease.

VII. Miscellaneous Arrhythmogenic Effects of Histamine

Histamine has been shown to cause a dose-dependent reduction in the ventricular fibrillation threshold (VFT), mediated by both H₁- and H₂-receptors. Although the exact mechanism of this effect is not known, the H₂-mediated component appears to account for the greatest part of the reduction in the VFT, suggesting that a histamine-induced elevation of myocardial cAMP may be involved (Trzeciakowski and Levi, 1982).

Digitalis compounds enhance both the prolongation of AV conduction and the increase in ventricular automaticity due to histamine (Levi and Capurro, 1975). Such histamine-induced alterations in impulse conduction and formation are also characteristic of digitalis intoxication (Hoffman and Bigger, 1985). Arrhythmias suggestive of digitalis toxicity have been described with low serum digitalis levels following cardiopulmonary bypass (Morrison and Kilipp, 1973; Rose et al., 1975), a procedure known to cause systemic histamine release (Meyer-Burgdorff et al., 1973). An interaction between histamine and cardiac glycosides may account for these observations.

Thyrotoxic guinea pigs display a peculiar increased susceptibility to the depression of AV conduction and enhancement of ventricular automaticity by histamine, while the chronotropic response to histamine remains unaltered (Lee and Levi, 1977; MacLeod and McNeill, 1981). Ventricular fibrillation can be induced by exogenous histamine in isolated hearts from thyrotoxic animals; very high doses of exogenous histamine cannot induce this response in hearts from untreated animals (Lee and Levi, 1977). In addition, in the hyperthyroid state, histamine increases the idioventricular rate almost exclusively by abruptly shifting the ventricular pacemaker site, rather than by gradually increasing the rate of the original ventricular pacemaker (Lee and Levi, 1979). These results suggest that thyroxine may facilitate histamine-induced triggered activity (see section II.D). Whether this sensitization to the effects of histamine in the hyperthyroid state is due to a thyroxine-induced increase in the number or affinity of histamine receptors or to some other mechanism is not known.

VIII. Other Cardiovascular Actions of Histamine

No review of the arrhythmogenic effects of histamine would be complete without at least a passing mention of its several other prominent cardiovascular effects. These have been treated extensively in a recent review (Levi et al., 1982c) and are summarized in Table 2.

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This review is dedicated to the cherished memory of George A. Feigen.

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INDEX TERMS: Histamine • Arrhythmias • Histamine release • Transmembrane action potentials • Histamine Hr- and Hr-receptors
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