EFFECT OF MAST CELL PRODUCTS ON CAPILLARY PERMEABILITY

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The physiological implications of changes in capillary permeability are profoundly significant under normal conditions as well as in "disease states" (640) or in certain well-defined pathological conditions. Proper capillary function is so very important that Szent-Györgyi (568) looks upon it "as a mechanism which, in its precision, greatly surpasses the finest Swiss watch", and he regards capillary fragility as an indication "that this mechanism is out of order". The term capillary fragility" as used by many writers includes all stages of "increased capillary permeability", but the term "increased capillary fragility" should be limited to "chemical lesions in the capillary wall, specifically in intercellular substance" (545), or to other drastic conditions, including rupture of the collecting venule of the capillary bed (339). This idea is recapitulated in the statement that an intact capillary system indicates a solvent body (66).

The work of Kramer and Kramer, 1953, indicates that multiple factors are involved in maintaining an intact capillary system (66) for they have shown that hormones of the pituitary-adrenal system play a significant part in the control of capillary resistance (623). Other investigators show that fasting profoundly increases capillary resistance and that realimentation with an isocaloric protein diet rapidly causes the capillaries to return to the state of normal permeability (623). Disturbance in the ionic balance (339), in enzymic activity (18, 20, 21, 148) and, in short, the activity of almost any disturbing agent results in change in capillary permeability.

Altering the calcium-potassium ratios, increasing the amount of potassium, or reducing the amount, or omitting, calcium in perfusion experiments caused swelling of the intercellular cement substance and a great increase in permeability of the capillaries in the living mammal; while substituting magnesium for calcium ions also caused the extracellular cement to transform into a jelly-like, eythrocyte-permeable material, and excessive amounts of calcium hardened the cement and decreased its permeability (649).

Ascorbic acid-deficiency is conducive to capillary fragility in proportion to the severity of the deficiency. The capillary bed in vitamin C-deficient guinea pigs responded to experimental trauma by formation of petechiae much more readily than in guinea pigs receiving normal amounts of ascorbic acid (339).

Zweifach (647, 648) found that merely stroking the overlying peritoneum with a microdissecting needle caused increased capillary dilation and permeability in

the exteriorized mesentery of the mouse, and it has been found that similar effects are produced by lightly applying a camels' hair brush (84).

The relations of mast cell products to changes in the permeability of capillaries apparently involve substances and their effects which are not fully understood. A substance, indistinguishable from 5-hydroxytryptamine by its chemical and biological properties, has been obtained from peritoneal mast cells of the rat (43, 493) and later shown to be formed by mast cells from 5-hydroxytryptophan (334). This substance, 5-hydroxytryptamine or serotonin, was found to be present in the skin and subcutaneous connective tissue of rats in amounts proportional to the mast cell population of these tissues (493).

Since it has been generally conceded that 5-hydroxytryptamine (serotonin, 5-hydroxy-3-(β-aminoethyl)indole) is a "vasoconstrictor found in sera of mammals" (389) it is difficult to envisage this hormone as being a substance which strongly increases capillary permeability. Nevertheless, results of the work of Benditt and his colleagues (43, 334, 493) certainly indicate that this is the case. Rowley and Benditt (493) state that the combined evidence obtained "makes it very likely that the edema-producing agent released by mast cell-damaging substances is 5-hydroxytryptamine". It thus appears from the work of Rowley and Benditt (493) that the effects of serotonin on peripheral, especially dermal, capillary permeability are similar to, perhaps even identical with, those commonly attributed to histamine.

If one disregards for the moment its synthesizing and storing functions, the part played by the mast cell in initiating and sustaining hyperemia and increased capillary permeability, by releasing histamine, heparin, probably serotonin, and other substance, is the mast cell's most significant contribution to the physiologic and metabolic processes. The work of several investigators (402, 475) strongly indicates that mast cells are a very important, if not by far the most important, source of histamine released in the skin. Other investigators have shown that there is a direct correlation between the number of mast cells and the amount of histamine in the skin (382, 402, 473, 474, 617). In one laboratory it was shown that the skin from the hands and feet of untreated rats contained 61.0 μg/g of histamine, but in rats pretreated with compound 48/80, which is nearly specific for mast cells, skin from the feet contained only 8.6 μg/g; skin from the dorsum of the normal rats contained 27.9 μg/g and in those pretreated with compound 48/80 the dorsal skin contained only 5.4 μg/g. Skin from both regions was rich in mast cells, but that from the back contained only about 75 per cent as many mast cells as that from the hands and feet (402). However, there are reasons for believing that mast cells also increase capillary permeability by secreting a substance which has a solvent effect on the intercellular cement material of the endothelium and on the adsorbed protein film covering the endothelial surface

(380). If this point can be established and the conclusions of Lewis, 1927, that markedly increased capillary permeability is dependent upon certain chemicophysical changes in the capillary wall (402) are valid, the significance of mast cells in normal and greatly increased capillary permeability will be very much enhanced.

Mast cells also function in the formation of hyaluronic acid in pericapillary connective tissue ground substance (19, 21, 22, 23, 93, 384, 565). Hyaluronic acid actively opposes the spread of fluid in the tissues (18, 21, 148, 550, 648) unless it is altered by some substance, such as pituitary gonadotropic hormones, possibly estrogens (550) or hyaluronidase (18, 20, 148, 479). Since it is indicated that hyaluronidase is produced in the connective tissue in anaphylaxis (551) there is good reason to suspect that this enzyme is also produced whenever an excess of histamine is released. Duran-Reynal's, 1947, suggestion that hyaluronidase regulates capillary permeability (13) apparently supports this view. He also points out that in addition to hyaluronidase other chemical regulators, such as hypophyseal gonadotropic hormones and possibly estrogen, play a significant part in increasing the permeability of ground substance (550). It has also been shown by various investigators that several of the bioflavonoids, including hesperidin methyl chalone, possess effective antihyaluronidase activity and that ascorbic acid potentiates bioflavonoid activity (479). Demonstration that oral administration of hesperidin methyl chalone reduces the spreading reaction of intracutaneously injected hyaluronidase (479) strongly indicates the significance of hyaluronic acid in preventing increased capillary permeability.

The dilated capillaries and edema produced by topical applications of weak solutions of histamine to the base of human finger nails (47) indicated that hyaluronidase, or some other spreading substance, altered the nature of the connective tissue ground substance, presumably by changing some of the hyaluronic acid from a gel-like to a sol-like state (148). Indeed, because of the resistance to connective tissue permeability afforded by normal hyaluronic acid, the formation of a significant edema would, at least as a rule, presuppose degradation of the hyaluronic acid in the connective tissue ground substance.

There is good reason to believe that all cells contain at least a physiological trace of histamine, and it has been shown that appreciable quantities of histamine can readily be released from certain of these cells (60, 108, 155, 186, 238, 336, 503, 619). However, the mast cell appears to be the only cell which contains a maximum amount of stored histamine and at the same time is cytologically and cytochemically adapted to the requirements for general investigation of the relations of the release of endogenous histamine to increased capillary permeability, as the works of several investigators indicate (402, 473, 474, 617).

McGovern (380) suggests that mast cells also secrete a "spreading substance"

which, by altering "the consistency of the endothelial cement lines" and endothelial surface film, is to a great extent responsible for regulating capillary permeability. He apparently believes that "histamine, heparin and the spreading substance are components of one secretion of mast cells and that *in vivo*, they do not exist individually" in the rat. It is generally conceded that histamine and heparin are stored in mast cells in an inactive, loosely bound form (382, 474), but McGovern's (380) suggestion that a spreading substance, histamine and heparin are all three components of "one secretion of mast cells" is apparently a new approach. The presence of 5-hydroxytryptamine, serotonin, a vasopressor substance, in mast cells (43, 334) presents a new angle in determining the functions of the mast cell, for this substance does not seem to harmonize with the effects of histamine, heparin, McGovern's "spreading substance" and acid mucopolysaccharides. Nevertheless, it is held that the presence of 5-hydroxytryptamine with heparin and histamine emphasizes the significance of mast cells "as participants in the reaction to injury" (43).

The view of Manwaring and his colleagues, 1923, that all anaphylactic reactions are actually secondary to "increased specific capillary permeability", which is the fundamental physiological change evoked in protein sensitization, apparently is becoming widely accepted (37). This tenet is supported by the work of Rapaport, 1941, and others who found that among allergic children having this type of capillary fragility, about half of them improved following administration of the bioflavone, vitamin P, or vitamin K (597).

Several investigators hold that the abundance of mast cells in a structure is dependent on the amount of connective tissue present (392). I wish to add to this statement our observations showing that there is also a vascular requirement, for mast cells do not become numerous in the fat of the so-called hibernating gland in the hamster until hyperemia has appeared, and then the increase in mast cells occurs in the region of the fat body where conversion of white to brown fat has set in. Also, it is well established that mast cells have a marked tendency to align themselves along, or to "cuff" or "skirt" (Heller's Mastzellenhetten) arterioles and capillaries (392, 453, 621).

Vasomotion

The amount of blood supplied to a structure is normally governed by controlling the diameter of the blood vessels supplying that structure — that is, by vasodilation and vasoconstriction. The significant point of vasomotion is that it is generally conceded to be the most important primary method by which capillary permeability changes are effected.

It is held that certain agents may effect increased capillary permeability without altering the diameter of the capillaries. These agents usually, by indirect

action, alter the physical and/or chemical nature of the endothelium, perivascular sheath and/or connective tissue ground substance. However, it appears to be paradoxical to consider the possibility of causing an appreciable alteration in any or all three of these components of the blood tissue barrier without producing changes in the diameter of the involved capillary. Some of the agents or factors usually considered in this category are pH and tonicity changes in the extra cellular fluids. Thus, it is pointed out, that in experimental work loss in capillary fluid may be caused by hypertonic solutions of albumin, glucose, sodium chloride or sucrose shrinking and separating the endothelial cells with consequent capillary leakage (649). Excessive amounts of sodium fed to hamsters were responsible for capillary changes which were indicated by "numerous petechiae in the capillary bed of the cheek pouch" (339).

The ground substance may be altered by thyroid hormone (20) which may alter its salt-water relations and the relations of hyaluronate compounds and connective tissue fibers (20, 649), and other agents. X irradiation (649), and absence or insufficiency of ascorbic acid (479, 649), hesperidin (369, 479) or other bioflavonoids affect the ground substance and induce increased capillary permeability, or actual fragility, and edema (339, 369, 479, 649). Oral administration of hesperidin methyl chalcone has been shown to diminish the spreading reaction of hyaluronidase when injected into guinea pigs (479).

Terminal Vascular Structure

The term vasomotion as used in this work is limited to that part of the terminal vascular structure, or "capillary bed" (647), having muscular sheets, bands, or fibers in the walls (59, 647). The true capillaries, the walls of which are free of muscle fibers (647), are capable of reacting only passively to vasomotion, which may cause variations from the normal tone to various degrees of dilation or constriction of the arteriolar trunk. Consequently, the volume of blood which may flow through the capillaries (except, possibly those possessing Rouget cells (329)) under conditions of normal blood pressure is controlled by the diameter of the arteriolar trunk. Thus, it appears that local volume changes in true capillaries are chiefly the direct result of increased volume, probably with no significant local change in pressure, of blood in the arterial trunk of terminal vascular structures.

The difficulty of identifying the nature of the blood vessel is often complicated by the conditions of the experiment and by physiological or pathological states. Also, the rather loose way in which investigators sometimes designate capillaries in describing results obtained often causes the reader to wonder whether the involved blood vessel is a true capillary or some other part of the terminal vascular structure. In this review we have followed, as far as is practical, Zweifach's (647)

work on in vivo dissection, function and terminology of the terminal vascular structures. Most of Zweifach's (647) work was done on blood vessels in the mesentery of the mouse. Nevertheless, his structural and functional concepts appear to be in agreement with the generally accepted pharmacological actions of substances producing known effects on peripheral capillaries, such as histamine and epinephrine (377, 547).

The terminology and sequence of structures here employed follow: The terminal vascular structures comprise the arteriole, precapillary, "arteriolovenular (a-v) bridge" (capillary bridge or "permanently open capillary") (647), true capillaries, prevenule and venule. The true capillaries arise from the arterioles, precapillaries, and a-v bridges (647), and their origins are commonly provided with a muscular or endothelial valve-like structure which is opened by dilation of the arteriolar trunk. True capillaries may empty into the venous part of the a-v bridge, prevenule and/or venule; usually are collapsed during vasoconstriction, or some may be collapsed and others contain static blood during the basal level of flow (329) but are distended with blood during dilation of the arteriolar trunk of the terminal vascular structure (647).

Effects of Arteriolar Changes

Systemic or extensive vasodilation decreased the pressure and rate of flow of the contained blood, but at the same time it may greatly increase the permeability of the walls of the precapillaries, a-v bridges and, especially, of the true capillaries, and thus permit abnormal amounts of plasma, inorganic ions, inordinate amounts of protein, corpuscles, and other circulating substances to pass out of the blood stream into the tissues (87, 619). This increase in capillary permeability is extremely important in normal growth, wound healing and maintenance, as well as pathological, processes. In pathological conditions these changes may present serious problems, for, under the influence of histamine, protein leakage may reach 5 to 6 times the normal rate of the affected capillaries (238).

Since mast cells are rich in stored histamine (402), it is significant that there is a growing tendency for investigators of changes in capillary permeability to attach increasing importance to the release of mast cell-histamine as a provocative factor in increasing vasodilation and thus increasing permeability of capillaries, especially when confined to a delimited area or region.

The consideration of vasomotion for the purpose of this review is limited chiefly to the production and control of "active hyperemia" (90), with special emphasis on "capillary hyperemia" (90). Local capillary hyperemia results chiefly from the action of an agent causing relaxation of the muscle fibers in the wall of the arteriolar trunk of the terminal vascular structures, particularly in the arteriolar and precapillary regions and, probably, in the a-v bridges. This is held to result in

increased dilation and a corresponding volume of blood in the arteriolar trunk which causes consecutive dilation as the increasing blood volume is forced through the relaxed a-v bridge and the previously inactive, or even collapsed, true capillaries.

Variously Effected Vasomotion

Vasomotion, as delimited in this review, may be produced by any one of a variety of agents which commonly operate by either stimulating or inhibiting the lamina muscularis of the larger blood vessels and/or the terminal vascular structures, the muscular bands in the wall of a-v bridges or the muscle fibers which form the valves at the origin of the true capillaries. It thus appears that active vasomotion is dependent upon the contraction of muscle tissue in the blood vessels to produce vasoconstriction and upon relaxation of this muscle tissue to permit vasodilation. There is evidence to support the idea that the vasomotor state of the arterial trunk of the terminal vascular structure not only controls the state of the true capillaries but also markedly influences the tone of the aorta and great arteries, including the coronary arteries, and the per minute output of ventricular blood (59). Since the true capillaries of mammals are devoid of muscle tissue (647) they are incapable of active constriction, but their endothelial walls are capable of exerting an appreciable degree of elasticity apparently independently of pericytes or periepithelial cells. Ponder (449) supports this idea by stating that most observers do not credit endothelial cells with contractility but attribute all active contractility to the "a-v capillaries and metarterioles" which are effective because of the smooth muscle in the walls. Thus, there is normally a fairly definite correlation between the diameter, volume of blood flow, and degree of permeability of the wall of the true capillaries and a-v bridges and, possibly, also involving the precapillaries and arterioles to a certain extent.

It has been estimated that in resting skeletal muscles about 90 per cent of the capillaries may be empty and collapsed or in stasis and the remaining 10 per cent constricted and virtually inactive, while the blood supply to the resting tissue is maintained by a certain alternation of these conditions in the capillaries, and that during physical activity blood courses through many of the previously collapsed capillaries (329).

Rouget cells, or pericytes, when present may have a function in constricting capillaries (329), but presence of these cells on mammalian capillaries has not been established (30, 240, 647). It should also be mentioned that the power of active contractility has been ascribed to endothelium in vitro by Levi, 1923, and in vivo by the Clarks and others, while some investigators stoutly maintain the inability of endothelium per se to contract (13, 449). Nagel, 1934, found that capillary endothelium offered little or no resistance to microdissection needles, and the

little resistance present was due to the connective tissue; therefore, the endothelial cells were very readily deformed by any appreciable force. Consequently, endothelial resistance to any force exerted against it is practically negligible, the connective tissue 'periepithelium' being chiefly responsible for any resistance to capillary distension (84). However, some investigators hold that the flow of blood through the capillaries can be reduced, or even stopped, by the endothelial cells becoming swollen and distending into the lumen of the capillary (84). We have observed very large cuboidal endothelial cells in certain inflamed human tissues, but not in any kind of normal tissue. It follows then, that, under normal conditions at least, the true capillaries in themselves are essentially inactive and respond primarily to the volume and pressure of blood in the muscular part of the terminal vascular structure which comprises the a-v bridge, precapillary arteriole, and arteriole.

There is, however, the probability that ionic changes and/or other factors, including Starling's, 1896, principle that increased venous pressure increases capillary transudation (160, 263), may affect capillary permeability independently of the muscular part of the terminal vascular structure. Although stimulation of the splanchnic nerve was followed by an increase in volume of an intestinal loop while it was enclosed in a plethysmograph, whether the resulting hyperemia was actually caused by stimulation of the vasodilator nerve or merely by relaxation of the intestinal muscle is debatable, for it has been shown that any change in intestinal tone is followed by a change in blood flow (599). Uvnäs (599) supports this latter tenet by pointing out that low concentrations of acetylcholine increase intestinal blood flow, while concentrations, sufficiently high to cause contraction of the muscle tissue, also reduce intestinal blood flow. Unfortunately, the fact that the intestinal mesentery is richly supplied with mast cells, which store histamine, or that the least injury or even disturbance causes release of histamine apparently was not considered. The manipulation of the intestinal loop incident to enclosing it in the plethysmograph would be expected to release a sufficient amount of histamine to account for the increased blood flow.

Recent experiments in which the fragility of the capillary bed in the cheek pouch was increased by feeding hamsters excessive amounts of sodium, adding 30 per cent of fat, and withholding choline or ascorbic acid from the diet of rats or guinea pigs and mechanically or electrically stimulating exposed mesenteric vessels showed that leakage was due to defective venules and thus demonstrated that the site of the escaped blood during increased capillary fragility was the collecting venule of the capillary bed (339).

Although it is impractical to rule out neuromuscular relations, the contradictory effects obtained with magnesium indicate capillary permeability changes. Deficiency of dietary magnesium caused vasodilation (331), while excess of administered magnesium depressed the blood vascular and respiratory systems in rats (160).

McCollum and co-workers (331) found that addition of only 1.8 parts per million of magnesium to an otherwise adequate diet prevented occurrence of the magnesium deficiency syndrome in rats.

The suggestion has been made that some of the various agents which are commonly credited with causing vasomotion act indirectly by causing release of histamine. Whether these agents act by releasing histamine and/or serotonin from mast cells or other cells should not be overlooked; neither should the generally accepted fact that almost any kind of cell injury will provoke release of histamine be overlooked. The relations of histamine and of serotonin to vasomotion are very intimately associated with capillary permeability.

Histaminergic Neural Action

The action of histamine as a vasodilator is said to parallel that of cholinergic, parasympathetic nervous stimuli, while the action of epinephrine, or its derivatives, A-40 and aludrine (293), as a vasoconstrictor is held to parallel that of adrenergic, sympathetic nervous stimuli. Vasodilation is believed to be caused by a neural mechanism (31) and apparently to spread by antidromic or axon reflex (492, 648). Nevertheless, Uvnäs (599) points out that the available experimental evidence indicates that "sympathetic vasodilator fibers are exclusively cholinergic" and are probably limited in effect to skeletal muscles and, possibly, to the coronary vessels, but that there is very little evidence indicating effectiveness of sympathetic vasodilator nerves to the skin of the dog's ear or to the intestines in this animal.

The world is indebted to Claude Bernard for the discovery in 1851 of vasoconstrictor, and later of vasodilator, innervation in the rabbit (31). However, the mechanism of neural vasodilation as it affects the capillaries is not as well understood as is vasodilation. The vasoconstrictor neurons all belong to the sympathetic nervous system, while vasodilation is accomplished chiefly by neurons from the parasympathetic, but also by fibers from the sympathetic and somatic sensory systems (31). Ample histamine occurs within the sheaths of these nerves; as much as 100 μg/g histamine dihydrochloride has been found in the sympathetic, splenic postganglionic nerves in the ox (608). However, von Euler (608) is not convinced that this histamine "serves as a mediator of nerve effects" on smooth muscle. Thus, the question of the presence of histaminergic nerves in mammals is far from being settled.

The muscularly walled arterioles are surprisingly well supplied with both vasodilator and vasoconstrictor efferent autonomic nerve fibers (235), a fact which appears to indicate that neural control of vasomotion is limited to vessels having smooth muscle in the walls (649) either forming the tunica media or occurring as thin bundles or, possibly, as single cells. Since Zweifach (647) observed muscle in the wall of arterioles, precapillary arterioles, and a-v bridges, but found contractile perivascular elements conspicuously absent in true capillaries in the

mesentery of the mouse, it appears that the smooth muscle in these structures may be subject to autonomic stimulation but that this form of stimulation probably is incapable of affecting the true capillaries directly. Nevertheless, control of the diameter of the precapillary segments of the arteriole affects the diameter of the capillaries by regulating the amount and head-pressure of the blood entering them.

The neuromuscular mechanism suggests an explanation by which non-histamine-induced hyperemia of dermal areas, such as blushing, is effected. However, the probability of "central antidromic impulses" and of " 'nicotinic' action of acetylcholine" playing a part in blushing and in certain other instances of vasodilation has been seriously considered (492). Nevertheless, von Euler (608) states that his and Astrom's experiments involving stimulation of the ileum of guinea pigs through rather long (7–8 cm) pieces of splenic nerve from the ox indicate that the transmission of neural stimuli is through release of histamine. Several other investigators also hold that a chemical mediator, such as histamine, is involved in neural stimulation (429), while others suggest that enervation affects capillary sensitivity to histamine in a manner which is not completely understood (47). If this is the case in the normal animal, it would appear that vasodilation is generally effected by release of histamine. However, other writers indicate that histamine alone or adenylic acid alone could cause capillary dilation, for histamine causes arteriolar dilation in the dog, monkey, and man, while adenylic acid, like histamine, is released by tissue damage and also causes arteriolar dilation (31). Other writers discourage this idea by holding that in vasodilation, histamine has a direct action on the true capillaries, but that it dilates arterioles "indirectly through the axon reflex" (241). Tonutti (581) suggests that hormones may condition the tissue's reactivity potential to an irritant, while Boyd (70) indicates that still others believe that although histamine dilates capillaries it contracts arterioles. This last conclusion is open to discussion, for investigators apparently agree that although perfusion of the vessels in excised structures commonly produces arteriolar contraction as opposed to dilation in intact animals (47) it probably never has an opposite vasomoter effect on capillaries, certainly not on non-muscular, or true, capillaries.

Feldberg, 1955, suggests that one effect of large dosage of histamine may be neuromuscular block, but he does not state whether or not this neural effect is related directly to increased capillary permeability. However, he holds that the muscular weakness or paralysis of rats and cats following injection of large doses of either histamine or of histamine liberators, such as compound 48/80, may be entirely accounted for by the injected or released histamine producing either a neuromuscular block or affecting the muscle directly with the result that stimulation of the motor nerve becomes ineffective (569). Feldberg, 1956, states that the

muscular weakness and paralysis seen in rats after administration of a heavy dose of compound 48/80 "is certainly due to neuromuscular block" (569). The results of these experiments in producing muscular weakness by injecting the histamine-releasing compound 48/80 are very significant in that they indicate that mast cells are the chief source of the histamine since mast cells are fairly numerous in the internal perimysium of skeletal muscle in hamsters, and compound 48/80 is considered to be almost, if not quite, specific for the release of histamine from mast cells (399, 402, 474, 476).

Dale, 1910, 1911, found that intravenous injection of histamine depressed blood pressure profoundly in monkeys, dogs, cats, and fowl and that this result was caused by the primary action of the histamine independently of "the integrity of the sympathetic nervous system" (47).

A novel approach to this general problem was made by Barany and Nordqvist, 1949, who found that nerve block caused by an histaminolytic or typical local anesthetics, such as procaine, could be removed by a histamine solution. They also found that when histamine was added to the solution containing a blocking agent, such as procaine, the property of the local anesthetic was lost (370). This antagonism between local anesthetics and histamine suggested to Martin (370) that since "all histaminolytic agents are local anesthetics" there is the probability that by use of Barany and Nordqvist's technique for nerve block it should be practical to correlate the action of local anesthetics with their antihistaminic power.

Epinephrine

Vasodilation results from intravenous infusion of epinephrine (547, 619) as well as from histamine. Epinephrine, unlike norepinephrine, "within the physiological range" has an over-all vasodilator effect and causes increased blood pressure by increasing the output of the heart (616). The spanchnic and peripheral blood vessels may be powerfully constricted following intravenous injections of epinephrine, which acts upon the muscular layer in the vascular wall in proportion to its thickness. Consequently, the arteries are more strongly contracted than the terminal arterioles (547). Local injections of epinephrine produce local vasoconstriction; while intravenous injection of epinephrine into normal animals produces a sharp, though not sustained, rise in blood pressure and an increased amplitude in heart beat, while in vagotomized dogs the blood pressure may exceed 300 mm of mercury (547).

Staub, 1946, attributed the vasodilation following intravenous administration of epinephrine to the effects of histamine liberated by the epinephrine, since he observed a decidedly increased rise in plasma histamine (619). Whelan (619) observed that there was pronounced vasodilation in the forearm, which was fol-

lowed by a sustained, increased flow subsequent to intravenous injection of epinephrine into a human subject. He attributed this sustained flow to the appearance in the forearm of "some non-histamine, dilator substance from a site of release elsewhere in the body" since he obtained no increase in plasma histamine in the forearm by injecting epinephrine into the brachial artery.

The reported variable, often contradictory, effects of epinephrine on vascular structures is not as easily explained as may be imagined, for serotonin, histamine, acetylocholine, and epinephrine each constricted the isolated carotid arteries of swine. Epinephrine not only constricted the walls of the carotid arteries but also constricted the vasa vasorum of these arteries. However, neither epinephrine nor histamine was able to cause constriction of the vasa vasorum of coronary arteries of either man or swine, but acetylocholine readily caused them to constrict (542).

Histaminic Effects

Notwithstanding the fact that there are many agents and conditions capable of causing vasomotion, the most important single point to be discussed at this time pertains to histamine-produced hyperemia and the concomitant increase in capillary permeability, which may be local or extensive, and which may involve the entire structure or body. A disturbing factor in discussing histaminic effects is that it is appearent from the work of Benditt and his colleagues (43, 334, 493) that in an undetermined number of instances effects due to activity of serotonin or to the combined effects of this substance and histamine may have been erroneously credited to histamine, or vice versa. It has unquestionably been established that histamine can cause increased capillary permeability; whether it acts directly by dilating the capillaries or indirectly by constricting the arterioles and venules or acts on all structures of the capillary bed simultaneously has not been definitely settled. Rocha e Silva (485) carries the idea much further by stating that histamine not only constricts the small arterioles and venules, but also dilates the capillaries and increases their permeability, and that histamine is the only substance which has been shown to be capable of thus effecting dilation and increase in permeability of blood capillaries. He supports this idea by pointing out that irritating, toxic, inflammatory, and other agents which induce increased "capillary activity" do so chiefly by causing release of histamine. Irrespective of whatever time may prove concerning the relative and actual values of serotonin and histamine as edema-producing agents, the earliest published work on this function of serotonin appears to be that of Rocha e Silva (485) and Benditt and his co-workers (43, 493).

It has been suggested that changes in capillary permeability may be effected without producing a readily detectable change in the capillary wall. A possible example of this effect may be attributed to changes in the protein film covering the endothelial surface (647) and in the consistency of the endothelial cement sub-

stance and surface film brought about by the "spreading substance" secreted by mast cells (380) or hyaluronidase (18, 148). Lewis', 1927, tenet that chemical and physical changes in the consistency of the capillary wall are essential for increased capillary permeability (492) strengthens this point of view.

Although histamine is a powerful vasodilator (619), there is a considerable amount of evidence indicating that it, probably aided by other agents including other mast cell products, also induces physicochemical changes in the components of the capillary wall (13, 380, 649) which, acting in conjunction with the increased volume of blood and possibly various other factors (18, 20, 21, 59, 492), is capable of profoundly increasing capillary permeability.

Histamine has been found to stimulate endothelial cells to phagocytize foreign lipoid, cholesteremic, and other materials, and it has been shown that this phagocytosis is prevented by antihistamines (13). Heinlein, 1935, holds that histamine causes endothelial cells to swell and subsequently palisade or even to become detached (13).

Various investigators hold that X irradiation increases capillary permeability, but they are not agreed on the mode of its operation in causing the increased permeability. Dahl, 1937, thinks that although there is no injury to the endothelium, irradiation injures cells in the extravascular tissues, causing them to liberate the histamine which in turn causes the increased capillary permeability; Elfskind, 1940, maintains that X irradiation causes endothelial nuclei to swell, roundup, and lose their nucleoli (13). Similar conditions often prevail in instances of pathologically increased capillary permeability. That X irradiation, especially if filters to prevent it are not used, produces capillary dilation in the skin was known to the early radiologists, who employed the "skin erythema dose" (S E D) as a base for reckoning dosage.

These observations and conclusions strongly indicate that released histamine causes capillary injury and concomitantly increased permeability, while the well-known tendency of mast cells to aggregate along small blood vessels and capillaries apparently indicates mast cells as the most likely source of this histamine. However, it is fairly evident that the mature mast cells (Type II) in the neighboring connective tissue are the source of most of this histamine rather than those adjacent to the blood vessel, which are chiefly immature (Type I) cells (472).

There is a considerable amount of evidence strongly indicating that death or injury of any cell, or even mild disturbance of some cells, will cause or evoke release of histamine. Nevertheless, it is only comparatively recently that many of the more obscure instances in which histamine is released have been associated with increased capillary dilation and permeability. For instance, erythema, or redness of the skin, has been recognized as a hyperemia for many years (147), but the more modern clinicians and investigators usually attribute this condition to

such causes as irritation or photochemical reaction. Despite the weight of evidence indicating the significance of histamine as an instigator of vasodilation and increased capillary permeability, this idea is modified or rejected in part or entirely by certain investigators.

Analysis of the over-all problem of the relation of histamine to hyperemia and increased capillary permeability is extremely complicated under normal physiological conditions and is further complicated by experimental procedures, "disease states" (640), including such conditions as factitial urticaria (492), or dermographia, and pathological conditions, because of the likelihood of multiple factors being involved.

Diverse Relations of Histamine

Histamine causes marked contraction of intestinal and uterine smooth muscle of the guinea pig (47). An isolated piece of guinea pig's uterus reacted by contracting when placed in 1:250,000,000 histamine in Ringer's solution. Histamine also caused contraction of excised pieces of uterus of the dog and rabbit, but had highly variable effects on the uterus of mice, while it usually inhibited contraction of excised pieces of rat uteri (47).

Histamine is a potent vasodilator of intact blood vessels (619) but, as described below, perfusion with it usually causes the blood vessels in excised structures to constrict. However, that histamine plays an important part in vasodilation following exposure to certain adverse conditions, including immersion of fingers or hand in cold water, temporary arrest of delimited circulation, exercise, and epinephrine infusion of the human antebrachium, "is in some doubt" (619). Nevertheless, Code (108) holds that "stimulation of gastric secretion *is* a function of histamine", and the work of others (47, 229) supports this view. Since a sustained increase in glandular secretion is effected through hyperemia, and histamine is known to be a potent agent in causing vasodilation and increased capillary permeability (108), the ability of this amine to cause increased volume and acid content of gastric juice should primarily be attributed to histamine-produced hyperemia. The fact that investigators have shown that a powerful histamine releaser, such as compound 48/80, when injected subcutaneously into dogs or intravenously into cats is followed consistently "by the secretion of large quantities of highly acid gastric juice" supports the contention that increasing secretion of acid gastric juice, by "increasing the blood supply of the gastric glands", is a function of histamine (108).

Several investigators have made a point of the distribution of mast cells in the wall, especially in the adventitia, of the aorta and great veins (564) and of their characteristic of aggregating around ("cuffing"), or aligning themselves along, small vessels and capillaries (263, 392, 472, 473, 621). The presence of mast cells,

which often form a perivascular sheath of immature, non-metachromatic mast cells (type I of Riley (472)) around muscular walled-arterioles and true capillaries (472, 473), and of numerous mature metachromatically staining mast cells (type II of Riley (472)) scattered throughout the loose connective tissue farther away from the blood vessels, appears to assure an adequate supply of histamine for unlimited, directly histamine-produced vasodilation, or for transfer of stimuli from vasodilator nerves (31).

Since, as has been stressed repeatedly in this review, mast cells are an important source of histamine, one apparently would be justified in assuming that these mast cells are an important source of the histamine, which undoubtedly plays a significant part in vasodilation in general, wherever they occur in connection with blood vessels and that this significance is related to the density of the mast cell population in the adventitia and neighboring connective tissue.

The effects of histamine and its antagonists on the normal terminal vascular structures and their functions bear a fairly definite relation to the architecture of the small blood vessels and may also involve the lymphatics. The tone and response of muscle tissue in the wall of arterioles, precapillaries, a-v bridges, and the dilation and contraction of the true capillaries are essential to maintenance of the blood supply demanded by the condition of the tissues involved (647). These conditions in normal animals vary from the basal, or resting, level of tissue activity, in which the contracted arterioles, precapillaries, and a-v bridges carry practically all the arterial blood directly to the prevenules, while the true capillaries are virtually empty and may even be collapsed, to the hyperemic state in which the arterioles and a-v bridges are dilated and the true capillaries may all be greatly distended with blood (647).

Mechanics of Capillary Response

It is extremely difficult to explain the mechanics of changes in capillary permeability since investigators are not in agreement as to the structure of the capillary wall (13, 647, 649), particularly of the endothelial membrane (13, 377, 607, 647, 649), or the significance of chemical and physical changes in the luminal adsorbed protein film and/or in the perivascular connective tissue (13, 20, 148, 220, 327, 380, 648).

Changes in capillary permeability usually result from changes not only in the capillary wall, which probably includes reticular and elastic fibers and collagen (13), but may also involve all entities forming the structure of the hematoparenchymal barrier. This may include changes in the adsorbed protein film covering the luminal surface of the endothelium (380, 647, 649), probably in the basement membrane (13) and the endothelial cells themselves (13), and the consistency (380) and porosity (13, 467, 647, 648, 649) of the endothelial intercellular cement

substance and in the pericapillary adnexa. The pericapillary adnexa, which includes elastic, fibrous, and collagenous connective tissues, part of which is organized to form the "pericapillary sheath", and the amorphous connective tissue ground substance containing hyaluronic acid (20, 148, 220, 327) and collagen (231, 316), forms probably the most important part of the blood-tissue barrier (550), the endothelial membrane serving chiefly as the "skeletal framework" of this barrier (649). This idea is carried much further by Duran-Reynals, 1947, who believes that capillary permeability is regulated by hyaluronidase, which is very important in controlling the permeability of the ground substance (148, 220, 327), while Chambers and Zweifach, 1947, apparently think that the action of hyaluronidase causes capillary fragility (13). Drinker, 1927, presumably as a result of perfusing the web of the foot with extracts of pituitary gland and horse serum, concluded that a hormone is present in frog blood which is capable of restoring and maintaining normal capillary permeability in capillaries previously made permeable to colloids (329).

Hyaluronidase evidently plays a very important, although indirect, role in controlling capillary permeability by altering the viscosity of the hyaluronic acid in the pericapillary connective tissue and its ground substance. The idea that the anti-inflammatory effect of adrenocortical hormones is mediated chiefly through the activity of these hormones in increasing capillary resistance and the consequent decrease in capillary permeability (327) sheds some light on the relation of viscosity changes in hyaluronic acid to permeability changes in the capillaries. Other work (220) showing that the anti-inflammatory action of certain adrenocortical substances affects hyaluronic acid by increasing "the hyaluronidase inhibitor levels" in the blood serum adds to transportation complications but does not militate against the concept of cortical control of hyaluronidase. Five of 36 adrenalocortical hormones (1 mg/100 g body weight/day for 3 days), including cortisone acetate, increased capillary resistance, as shown by the abdominal skin test, in rats previously accustomed to handling 50 to 60 cm Hg over that of control animals (327). In the light of results obtained by other investigators (220), this increase in capillary resistance should be attributed chiefly to the potency of cortisone and certain other adrenalocortical hormones in suppressing activity of hyaluronidase and consequent increase in viscosity of the hyaluronic acid.

Sommers (550) stresses the significance of normally intact basement membranes and connective tissue ground substance and points out that localized dissolution of basement membranes sometimes precedes parenchymal atrophy of aging organs. Although his emphasis is upon organs, it is evident that capillary permeability changes are the motivating factors.

Kisch, 1955, attaches great significance to the wall and adnexa of the capillary in regard to the complexity of its structure and relation to permeability changes

in capillaries as revealed by the electron microscope. He regularly observed an unidentified substance between the capillary wall and its sheaths. He makes various comments on the complexity of capillary structure and stresses the significance of changes occurring in the capillary wall under various conditions, especially as seen in ascorbic acid deficiency (649).

An important point in the mechanics of capillary permeability pertains to the physical state of the capillary wall which in true capillaries of the mouse's mesentery is composed of elastic endothelium that "remains the sole contractile element" (647) and in the distended state exhibits stigmata, or perforations (467, 647). Thus, since the wall of the true capillary is elastic and porous, increased blood volume in the arteriolar trunk and the related increase in capillary dilation may increase leakage of protein molecules at a rate much higher than would be suggested by the actual increase in diameter of the capillary. Vasomotion of the true capillaries in both normal and inflammatory conditions could be effected without any direct influence being applied to the true capillaries, other than the elasticity of the endothelial walls which would function only in producing a certain degree of tonus in the capillary, for any vasomotion affecting the a-v bridge-precapillary-arteriolar region of the artery would be immediately transferred as a blood pressure change in the true capillaries. Thus, inhibition of the muscular region of a terminal arteriolar structure would cause dilation and, if sustained, an increase in capillary blood pressure which would favor exudation. These relations could account for Menkin's (387) having found the available data to indicate that in inflammation or simple hyperemia, capillary dilation is accompanied by increased capillary pressure. Landis, 1934, also held that arteriolar dilation is responsible for "the rise in capillary pressure in hyperemic conditions" (387).

Various writers have pointed out that increased capillary permeability is commonly associated with dilation in a large number of capillaries, and that capillary permeability can be increased until any colloid will pass through the wall, but that some dilation may occur without any perceptible increase in permeability, while a high degree of permeability may be attained without appreciable dilation of the capillaries (329).

Experimental Permeability Changes

Changes produced experimentally in capillary permeability may be expected primarily to involve the entire terminal arteriolar structure, both the muscular part and the muscle-free part, which comprises the true capillaries.

Hyperemia is essential, but the work of Lewis, 1927, strongly indicates that, in addition to increased blood flow, it is necessary that some sort of a physicochemical ("qualitative") change take place in the capillary wall before its permeability, especially to proteins, can be markedly increased. He found that applying suction

(90 mm Hg negative pressure) to sensitized human skin (red line) and that increasing capillary pressure by interrupting venous return failed to promote whealing and that 50 mm Hg positive pressure on the sensitized skin failed to prevent formation of wheals (492).

Capillaries are extremely sensitive to environmental changes, as well as to irritation or actual injury, as is indicated by altered permeability of the walls of disturbed capillaries. The amount or extent of disturbance necessary to provoke an increase or a decrease in capillary permeability is so small that it does not need to produce a physical change in the involved capillaries. Zweifach (647, 648) found that merely stroking the peritoneum of the mesentery with a microneedle produced a pronounced increase in permeability of nearby, but untouched, capillaries in the mesentery of mice. Hyman and Chambers offer another approach by having shown that capillary permeability can be readily decreased without any detectable decrease in diameter or other physical change in the capillaries of rabbit. They attributed this decrease in permeability to a change in the endothelial cells of the capillaries and state that this condition may be induced by extremely weak solutions of adrenocortical hormone (607). Contrarily, McGovern's (380) "spreading substance", which increases capillary permeability and which he suggests is secreted by mast cells, would be expected to increase endothelial permeability without causing perceptible change in capillary diameter, by altering the consistency of the intercellular cement and endothelial covering film, provided its actions were not augmented by released histamine.

Normal Capillaries

These observations suggest that it would be advisable to consider some of the points concerning permeability changes of normal capillaries at this time. Under normal conditions maintenance permeability, which may be considered primarily as supplying the normal amount of transudate, appears to be a function of the a-v bridge, with possible contributions from the arteriole and precapillary, while the true capillaries are primarily collapsed or otherwise inactive most of the time (329, 647, 648). Under conditions of normal maintenance a higher level of permeability of controlled duration is probably induced for the purpose of permitting passage of proteins, other substances, and added amounts of serum as needed by the tissues. Conceivably, this cyclic process may be initiated by an infinitesimal amount of mast cell secretion, which may be released by dialysis rather than by cytolysis of the involved mast cells or possibly by neural stimuli.

Renkin (467) points out that the normal endothelial cell, like many other kinds of normal cells having diverse origins and functions, has a much higher degree of permeability to lipid-soluble molecules than to lipid-insoluble molecules; and he suggests that the lipid insoluble molecules may be largely restricted to pass out of the capillaries through the stomata. He (467) suggests that the freedom with which

lipid-soluble molecules, including oxygen and carbon dioxide, permeate the capillary wall may be the result of increased permeability of the endothelial cells themselves rather than involving a change in either the intercellular cement or the stigmata. This application of differential rate of dialysis through the endothelium, which is further complicated by changes that may occur in the adsorbed protein membrane covering the endothelium, the endothelial membrane itself, and/or the pericapillary connective tissue and its ground substance, affords a mechanism which is capable of drastically changing the rate of capillary dialysis and the composition of the dialysate.

Landis, 1934, has shown that injury to a capillary may increase the amount of escaping fluid as much as 7 times the normal amount (377). This leakage is the result of vasodilation which causes dilation of the capillary pores (377, 467, 647, 648). Estimates based on the known size of particles which passed through gave maximum values around 38 Angstrom units for the diameter of the pores in normal capillaries and up to 200 Angstrom units diameter of the pores in dilated capillaries resulting from injury (377).

It should be pointed out at this time that the presence of capillary stomata is not universally accepted, for some investigators hold that capillary walls do not have actual stomata or any type of preformed openings designed to permit passage of materials into the intercapillary areas (235, 329); others believe that stomata are only temporarily formed in the cement substance and basement membrane by liquefaction; some doubt the presence of a basement membrane in any blood vessel (13, 329).

The ground substance of the connective tissue in which the capillaries are embedded normally has a gell-like or slimy, viscous consistency (20, 148), but when the capillary is stimulated with microneedles the endothelium loses its elasticity, becomes sticky, and the connective tissue ground substance becomes increasingly liquid, thus greatly favoring the spread of exudate into the tissues. This process occurs in the mesentery of the mouse, cat, and frog (648). Other investigators have demonstrated a similar reaction in exteriorized mesentery of the frog (329), rat, dog, and cat (648).

The blood vessels of ascorbic acid-deficient guinea pigs formed petechiae during experimental trauma much more readily than those in normal animals. In at least 90 per cent of the instances, the escape of the formed blood elements was through the collecting venules in the capillary field; most often through a 'tricornered' tear, but in some instances through the increased porosity of the venular wall (339).

Mechanical Irritation

Extremely delimited areas of irritation or injury (10–15 μ) are known to release histamine and to produce capillary dilation with increased capillary permeability (647, 648). Zweifach (648) showed in a film that gentle irritation, produced by

tapping the wall of a capillary with a microneedle, caused dilation of the capillary with such marked increase in the diameter of the so-called stigmata, or capillary pores (377), that they consistently trapped erythrocytes. In one instance the film shows a capillary with an erythrocyte "being extruded through a tiny opening and pinched into two parts". Since any injury may be expected to release endogenous histamine, this would be the logical explanation of the increased capillary permeability, but Zweifach (648) was unable to obtain any evidence "to establish unequivocally the participation of particular substances, such as histamine, leukotaxine, etc." in these vascular reactions.

Zweifach (648), by injecting graphite, showed that the surface of endothelial cells normally is not sticky, and he observed no tendency for platelets to adhere to the walls of arterioles or to each other in otherwise normal mice. However, irritation with microneedles, presumably by releasing histamine, heparin, and, possibly, McGovern's (380) "spreading substance" from mast cells, initiated vascular dilation and the stickiness with the result that carbon particles, as well as platelets and leukocytes, adhered to the endothelium. Even the slightest injury, such as that caused by gently stroking the mesothelium with microneedles without touching the capillary, produced stickiness within the capillary just proximad to the site of irritation, while more severe irritation of the vessel caused stickiness distad to the site of the injury. When the immediate vicinity of a terminal arteriole was intensely stimulated mechanically by injury or gently rubbing with the microneedles for 30 to 40 seconds, blood platelets accumulated on the endothelium and "adhered to one another forming long strings or chains" within the arteriole at the site of irritation (648).

Exogenous Histamine

Intradermal injection, topical application or other means of exposing tissues to histamine may provoke capillary reaction and, usually, increased permeability of the walls of the involved capillaries. Investigators in 1910 and 1911 showed that histamine injected intravenously into anesthetized fowl, cats, dogs, and monkeys profoundly reduced blood pressure (47). Dale and co-workers, 1910, 1918, found that vasoconstriction resulted when excised structures of the cat were perfused with histamine, but if erythrocytes or epinephrine was added to the heparin solution before perfusion, vasodilation was produced in these structures. Histamine perfusion of these structures in the intact, control cats also caused vasodilation (47). Florey and Carlton, 1926, injected histamine into the saphenous vein of anesthetized cats and observed dilation of mesenteric capillaries and venules and opening up of collapsed mesenteric capillaries. Removal of a piece of the mesentery was followed by constriction of its venules. When pituitrin was applied to the omentum having capillaries fully dilated by the histamine, the capillaries definitely

constricted (47). Similar effects of histamine were observed by Rich, 1921, who found that injection of histamine produced local dilation of small arterioles, capillaries, and venules in the mesentery of anesthetized cats. He also observed "new capillaries" open up in the omentum as a result of the injected histamine (47).

Topical application of weak solutions of histamine has been shown to be very effective in causing vasodilation and increased permeability. Carrier, 1922, demonstrated dilation of the capillaries in normal human subjects with accelerated capillary flow accompanied by edema following applications of histamine diluted 1:1000, 1:5,000, and 1:10,000 to the base of the finger nail (47). Feldberg, 1927, and Flatow, 1929, applied histamine to the rabbit's ear and observed dilation and opening up of new capillaries (47).

Endogenous Histamine

Rocha e Silva, 1953, states that many observers have shown that in sensitized animals antigen injury provokes platelet response in capillaries similar to that following microtrauma and that this reaction apparently is connected with liberation of histamine and heparin from hepatic cells in the dog (648). Rocha e Silva's connecting the above effects of microtrauma and antigen injury with liberation of histamine appears to be very logical, but does not preclude the possibility of adenylic acid, which is released by tissue injury and causes arteriolar dilation (31), playing a part. However, with an abundance of mast cells within the adjacent connective tissue and the presence of blood platelets, which Dale, 1956, holds contain great amounts of histamine in the rabbit, but none in the horse (60), it would hardly be necessary to look to the liver as the source of the active histamine and heparin. Speirs (551) extends and in part supports Rocha e Silva's tenet by pointing out that antigen introduced into sensitized animals, especially when it produces anaphylactic reactions, may provoke release of several substances, including heparin, histamine, hyaluronidase, possibly choline, and other active substances, to which many of the observed symptoms may be attributed.

Lewis and his colleagues, 1927, neatly showed that the triple response and whealing are directly dependent on increased capillary permeability. These investigators found that if, after arresting the circulation by compression, the mechanical stimulus was applied to the skin, whealing failed to develop as long as the circulation was prevented, but as soon as the blood was allowed to flow, the triple response immediately appeared (492).

Reference has repeatedly been made in this review to various types of experiments which show that injury, irritation, or almost any form of disturbance of living tissue will provoke release of histamine, capillary dilation, and increased capillary permeability in laboratory animals and man. However, the fact that in many ways endogenous and exogenous histamine produce similar or even identical

results, as in so-called serous inflammation (13) and whealing (492), raises a doubt as to the practicability of trying to consider exogenous and endogenous histamine separately. This distinction usually is readily made in experimental work, but when it is applied to insect bites and stings or to contact with poisonous or allergic plants or other agents, it is often difficult to determine whether the offensive histamine was introduced into the tissues or released within the tissues by the introduced substance, such as formic acid in bee stings. The demonstration of considerable amounts of histamine in nettles, lambs quarter, tomatoes, spinach (0.5 mg/g in growing seeds, up to 1.34 mg/g in flowers of over-wintered plants) and other plants (186) may add to this confusion.

Inflammatory Processes

The universal presence of increased capillary permeability in inflammed tissues and in those undergoing amyloid degeneration is attributed by Lewis, 1927, to the presence of histamine and/or its related H-substance (329). Incidentally, Lewis' H-substance is now known to be histamine (492). That histamine is capable of increasing capillary permeability is well established, and it has been shown that serotonin released from mast cells is very potent as an edema-producing agent (330).

There are certain factors which militate against presenting clearcut, indubitable evidence to show to what extent mast cells are involved as a source of the histamine, serotonin, and/or other substances concerned with hyperemia, increased capillary permeability, local tissue reaction, and consequent changes occurring in inflammatory processes. Nevertheless, there is ample proof that histamine, either endogenous or exogenous, will provoke hyperemia and increased capillary permeability; that these two phenomena play a significant part in inflammatory processes and that mast cells contain relatively large quantities of releasable histamine and are almost universally present in the connective tissues of normal structures (402, 617) and commonly occur at the site of local inflammation (361, 377). It has repeatedly been shown that intradermal injection of a minute (1 to 1 or 2 million parts (492)) concentration of histamine speedily produces the triple response (1.5–3 minutes (492)) and the 4 cardinal signs of inflammation (237, 492). Nevertheless, Ungar, 1953, holds that this reaction does not prove that histamine is the only mediator of the inflammatory reaction (285), but it might be attributed to "a more fundamental process" of which histamine release could be merely incidental (595).

Several concepts of the relation of connective tissue, including its active fibroblasts, mast cell-content, and ground substance, to the onset and support of inflammatory processes lend significance to the importance of the part played by hyaluronic acid in particular and to the products of mucopolysaccharide metabo-

lism in general in these processes. The opinion has been expressed that loose connective tissue is a primary site of inflammation (256), the chief site of mast cell formation (392, 472) and, following even the least unfavorable type of stimulation, very likely is instrumental in causing the mast cells to release their granules as a measure of protection (256).

Increasing interest is being shown in the part played by hyaluronic acid, which is held to be derived from mast cells (23), in maintaining normal capillary permeability by degradation of this mucopolysaccharide. Recent work shows that the mode of action of cortisone and certain other antiphlogistic adrenalocortical hormones is to produce increased capillary resistance (327) which is effected chiefly by suppressing the activity of hyaluronidase (220). These and other observations on the vasomotor effects of histamine and serotonin and the significance of mast cells as the probable source of these substances certainly warrant further consideration.

Capillary Dilation

Celsus (25 B. C.–45 A. D.) clearly recognized the four cardinal signs of inflammation (357) and, in the absence of any knowledge of capillaries, listed them as "rubor, calor, tumor, and dolor", a terminology and sequence of events which time has not altered (357, 361, 377). Both rubor (erythema) and calor (heat) are due to hyperemia; tumor (swelling) and dolor (pain) are the result of increased capillary permeability (357, 361, 377) and resultant pressure (492).

The physiological changes which local circulation undergoes in an inflamed area were recognized and stressed by Cohnheim, Samuel, and Virchow. Samuel in 1873 recorded his belief that changes in the walls of these blood vessels gave origin to the exudate which forms the fluid in exudative edema (387). However, Cohnheim, 1866 and later, paved the way for further experimental interpretation of inflammatory processes (387) and edematous relations.

Ehrich (158) after briefly summarizing the theories on the mode of origin of inflammation from humeral to vascular and phagocytic concepts, supports the theory that inflammation may be regarded as "disturbance in homeostasis" provoked, at least in part, by tissue injury and release of histamine. Lewis', 1924, 1927, results support Ehrich's (158) conclusions by strongly indicating that erythema following X irradiation is caused by release of histamine within the skin; Ellinger, 1928, 1930, holds that ultraviolet and X irradiations cause an increase in histamine in the skin by killing some cells and by decomposing histidine photochemically (317). Ehrich, 1953, also states that Röessle holds that instead of the vascular reaction being "an essential part of inflammation" it may be considered as an "auxilliary mechanism" having the function of accelerating removal of the cause of the inflammation (285).

Although Röessle's explanation is quite tenable, hyperemia and increased capil-

lary permeability will probably remain the most significant characteristic for recognition of inflammatory processes. Ungar (594) in his plea for some measure of agreement on the definition of inflammation, stresses the idea that primarily inflammation is a vascular response, while Dorland (140) states that inflammation is characterized "histologically by hyperemia, stasis, changes in the blood and walls of the small vessels, and by various exudations".

Mast Cell Relations

A number of pathologists have recorded the presence of mast cells in inflammation and state that they may be especially numerous during chronic inflammation (377). Many investigators have noted that the density of mast cell population is directly related to the proximity of small blood vessels and that this relation is commonly demonstrated by aggregations of mast cells around small vessels (392, 472, 476). Whether this arrangement is a form of reciprocity in which the mast cells receive needed substances from the blood stream and the blood stream receives heparin, histamine, and/or other substances from the mast cells is interesting speculation but, apparently, has not been given very much serious consideration.

It has been observed that prolonged inflammatory conditions which are favorable for increasing the numbers ("infiltration") of lymphocytes and plasmacytes are also favorable for increasing the number of mast cells. Further observations on exudates suggested that whether the edema fluid will be favorable for mastocytogenesis and the transformation of small lymphocytes into plasmacytes depends primarily upon its protein content. The protein content of the extravascular fluid is most commonly related to conditions favoring passage of the large protein molecules through capillary walls into a situation which detains the plasma protein, commonly by formation of a fibrin network, but allows a part of the plasma to pass on. These requirements are met in prolonged inflammation with the added advantage of the presence of abundant, similar materials released from cells, as in delimited necrosis, under similar circumstances of stasis. Thus, transudates or edema fluid formed by stasis, such as in cardiac or renal edema, in which the fluid has the lowest protein content of all edema fluids (70) and, consequently, low specific gravity (377), is not favorable for either mastocytogenesis or plasmacytogenesis.

The fixing and staining procedures used routinely by pathologists and many other students of inflammatory processes usually destroy the mast cell granules (344, 392, 492) and thus obliterate the most reliable characteristic for identifying them. The relations of these cells to inflammatory processes have been neglected to a surprising extent. Another point is that, although some investigators recognized an increase in the number of mast cells and tissue damage, which was at-

tributed to "repeated episodes of necrosis", in chronic inflammatory processes (377) mast cells were often considered merely as a type of "infiltrating cell" and as having an unknown purpose (361, 377).

Stemmler, 1921, observed that the normal population of mast cells is reduced in acute inflammation, as well as in granulation tissue, but that the number increases "wherever mature tissue is being formed" (344). This observation supports the contention that early in acute inflammatory processes the resident mast cell population is decimated in response to the demand for, or otherwise provoked release of, histamine and that no new mast cells are formed until a sufficiently favorable exudate is provided, as is explained below.

Halpern (237) states that all the phenomena produced by injection of egg white "are borrowed by the typical inflammatory lesion". This statement is very significant in support of the idea that mast cells play an important part in inflammation, for injection of egg white or ovomucin, especially into rats, provokes lysis of mast cells and liberates quantities of histamine by so doing (42, 238, 486, 503).

The observation that the mast cell population is reduced in acute inflammation (344, 361, 377), but increased in chronic inflammation, in which there is commonly an appreciable amount of tissue damage caused chiefly by "repeated episodes of necrosis" or alternating degenerative and proliferative changes (377), especially in allergic or rheumatic reactions (620), may be somewhat clarified by the following explanation. The initiating agent depletes the resident mast cells of the normal tissue, thus releasing histamine, which is speedily followed by the sequence of hyperemia, increased capillary permeability, protein leakage, marked edema, and stasis, which stages are generally recognized and have been confirmed by us as being conducive to mastocytogenesis, as well as "invasion" by other exudate cells. As chronicity develops, vascularity and edema progressively decrease, while mast cells are observed to have increased in numbers (377). Apparently, the condition of stasis and early necrosis stimulates progenitor cell activity to salvage certain components from the exudate and store them as granules and in so doing these progenitor cells develop into mast cells. As the hyperemia, edema, and demand for histamine regress, the supply and increment of mast cells remains in excess of the demands made for histamine by the repeated episodes of proliferation and necrosis.

Histamine in Allergy

Histamine unquestionably plays an important part in initiation, or as a concomitant, of all allergic reactions, but its mode of action as related to other factors is controversial. The significance of the mast cell in allergenic reactions is chiefly that it is a rich and readily available source of histamine, especially in the skin, where these cells doubtless play a very significant role in dermographism and

general urticarial demonstrations. Several investigators have shown that mast cells are probably the chief source of the histamine which is generally conceded to be directly responsible for initiating local hyperemia resulting in formation of the welts, hives, wheals, et cetera, which may be diagnosed as urticaria in one or more of its many forms.

Initiation of Hypersensitivity

Failure to control release, inactivation, or sudden release of histamine apparently constitutes the most important factor in allergic or hypersensitive reactions and anaphylaxis. Dragstedt in 1945 reviewed the literature on the evidence for and against histamine being related to anaphylaxis and concluded that histamine plays a significant part in anaphylactic reactions, but that the mechanism of its release is not understood (597). A number of writers subscribe to the idea that the cause of acute anaphylaxis is "the sudden liberation of histamine or histamine-like substances from the tissues as a result of the 'shocking' dose of antigen" (625). Schachter showed conclusively in 1953 that release of histamine "is a significant factor in the toxicology of acute anaphylactic reaction" in the rabbit (468). The suggestion that histamine is involved in most, if not all, reactions of substances provoking hyperergic inflammations is supported by Rocha e Silva's (484) statement that the contraction of guinea pig ileum produced by a preparation of rat anaphylatoxin "is also due to release of histamine from the isolated organ". Schild (507) sets forth data to support his tenet that release of histamine plays about the same role in human allergic asthma as it does in anaphylaxis of guinea pigs. Contrarily, Code held in 1944 that histamine is not the fundamental factor in allergic reactions and in anaphylaxis and that liberation of histamine is merely incidental to cell damage, which is of primary importance in instigating these reactions (252). Eleven years later he (107) amplified this tenet somewhat by stating that, instead of the white cell elements containing most of the histamine, the major portion of it occurs in the serum which facilitates its activity. Urbach and Gottlieb (597) feel the assumption that the substances which are usually accorded the role of instigator, such as acetocholine and histamine, are not the cause but the result of antigen-antibody reactions. Speirs (551) holds that the eosinophilia which follows antigen-antibody reactions apparently is not caused by histamine, heparin, hyaluronidase, or choline. Urbach and Gottlieb (597) point out that per se neither blood nor tissue eosinophilia is conclusive evidence that an allergy exists. They (597) add that allergies may be a result of increased stimulation of parasympathetic nerves and point to the fact that parasympathetic-stimulating drugs "favor allergization or tend to prolong an existing hypersensitiveness". Also, a diet low in ascorbic acid has been considered to be conducive to allergies in both man and mammals (597). Histamine is probably not the substance responsible

for shock, even in animals injected with H-substance (41), and probably is not the primary factor in traumatic shock (252). Dragstedt, 1945, expresses the consensus by stating that although histamine is a definite factor in anaphylaxis, no one appears to understand the mechanism which releases it (597).

Allergic Response

Perhaps the most plausible concept of anaphylaxis is that suggested by Urbach and Gottlieb (597). They, citing the works of Code, 1944, Wendt, 1939, and others, reject the explanation that anaphylaxis is "the result of a simple histamine intoxication" as being inadequate and suggest that anaphylaxis is the result of a series of interactions of a number of biologically active substances of different types of tissue products such as choline, epinephrine, histamine, and others, which affect the chemical regulation of the autonomic effector organs and the autonomic nerves (597).

It is supposed, chiefly upon indirect or circumstantial evidence, that Lewis' "triple response" (characterized by a red line, flare, and wheal), insect bites, irritants, and various other forms of local damage to the skin, liberate histamine (41). Lewis, 1927, held that his triple response "is identical with the reaction resulting from intradermal injection of histamine" which causes local dilation of capillaries and arterioles with escape of protein-rich fluid (597); Rothman (492) points out that there is now available sufficient evidence to show that Lewis' "H-substance is actually histamine". Riley (473) aptly attributes the ease with which this "triple response" may be elicited in urticaria pigmentosa skin lesions in man to the fact that lesions of this kind constitute a type of "shock organ" which is "rich in mast cells" and thus capable of releasing a quantity of histamine upon the least provocation. Contrarily, Perry (440) holds that the histamine responsible for the triple response does not come from mast cells. This statement would be rather difficult to prove or disprove experimentally, but in the light of the known mast cell content of histamine in human and other skin (18, 186, 402), it is open to considerable skepticism.

There is probably a definite disturbance in the water balance and in certain enzymic cycles during the course of allergic diseases, for there are inconsistent and noncharacteristic alterations in the chemical components of the blood, particularly with regard to amino acids, calcium, cholesterol, chlorides, magnesium, phosphorus, and potassium content (597). Rusk and his collaborators, 1939, found that the serum potassium values were definitely higher in urticaria (23.4 mg/100 ml), in acute asthmatic attacks (24.4 mg/100 ml) and in the asymptomatic period in bronchial asthma (23.6 mg/100 ml) than in healthy human subjects (19.5 mg/100 ml). Although epinephrine produced relief in these patients, it did not significantly alter the serum potassium level (597). Various investigators have found the blood

histamine level higher in asthmatics than in normal individuals (614), but as Rose, 1954, points out, the release of histamine is not the sole cause of asthmatic symptoms (614).

Histamine in Shock

The part played by histamine in several types of shock is not clearly demonstrated, and especially in man the course of shock is not constant, but may be strikingly diversified (485). In certain human cases lung emphysema, as in guinea pigs, liver congestion, which is common in dogs, or venous congestion caused by dilation of the right heart, as in the rabbit, may be pronounced conditions in anaphylaxis (485). Since shock is a condition of acute peripheral circulatory failure (140), there are grounds for suspecting that histamine is either associated with the cause of shock in certain types or with the effects of shock in those types not otherwise explained. Thus, histamine may be associated with, but possibly is not the cause of, primary shock, while it is conceivable that factors other than neural or histaminic may be responsible in certain types of shock. Briefly, whenever a sufficient amount of blood plasma is lost from the circulation, usually by pooling, hemorrhage, or transudation, shock supervenes (140).

Halpern (238) states that intraperitoneal administration of a histamine liberator (dextran (30 mg/100 g)) to adrenalectomized rats provoked severe dyspnea, prostration with acute vascular collapse, and death of all the animals within 20 minutes; ovomucoid (1 mg N/100 g) produced similar symptoms, but the rats lived a maximum of 2 hours. Intraveous injection of these histamine liberators greatly increased their toxicity. Halpern (238) concluded that the basic and major disturbance produced by administration of dextran or ovomucoid is "damage of the small blood vessels, which is reflected by an increase in capillary permeability" resulting in formation of a characteristic edema having a high protein content and a severe hemoconcentration. He (238) further indicated that histaminic action was involved by finding that edema and almost all the symptoms caused by dextran can be prevented in intact rats by injection of the synthetic antihistamine promethazine, or phenergan. Bennati and Patetta (44) found that benadryl protected animals against lethal histamine shock but not against peptone shock.

Glenn, Gilbert, and Drinker, 1943, found that experimental burns of the foot provoked escape into the tissues of quantities of plasma which approximated a third of the total volume of blood (377). Such conditions of shock certainly indicate the current concept of histaminic activity and probably involve heparin as well. However, the work of Rowley and Benditt (493) strongly indicates that serotonin plays an important part as a causative agent in cases of profound edema, especially if mast cell damage is involved as would be expected in extensive skin burns. In the case of the experimental burns of the foot, cutaneous and subcutaneous mast

cells would be expected to release relatively large quantities of histamine and heparin. Incidentally, the fact that decreased coagulability of the blood is one of the functional effects of shock (377), suggests increased release of heparin, a fact which has been verified in dogs anesthetized with dial, vagotomized, and injected intravenously with peptone (27).

Histamine shock is held to differ from anaphylactic shock in the absence of the reduced body temperature, and the increased blood coagulation time, both of which are characteristic symptoms seen in anaphalactic shock (597). A marked increase in coagulation time was observed in 4 guinea pigs killed while in profound anaphylactic shock produced by horse serum (305). Also, it is stated that arginine prevents the lethal effects of administered histamine but not of anaphylactic shock, while heparin inhibits anaphylaxis but is incapable of inhibiting histamine shock (597).

Rocha e Silva, 1947, presents another complication by pointing out that in anaphylactoid conditions fibrinolysin releases histamine and heparin from cells (520), but it is not clear whether mast cells are included or not. Selye (520) points out that the various stresses alter the water balance, chiefly by disturbing the intracellular protein-intercellular sodium relations, which is accompanied by potassium and pH changes. Acidosis of transitory nature has been observed in both animals and man following a variety of systemic stressors, including anoxia, burns, electro-shock, 'gravity shock', and 'medical shock' (520). However, nothing is said about mast cells as a source of the histamine which is known to be released in relation to some of these conditions, especially burns (377), and the resultant increased capillary permeability. Menkin (387) shows that, with few experimentally produced exceptions in dogs, similar changes take place in the inflammatory process. Other investigators (344, 361, 377) have recorded concomitant changes in local mast cell populations, but neither mast cells nor metachromasia is listed in the index of either Selye's (520) or Menkin's (387) monograph.

Mongar and Schild, 1952, point out several ways in which the effects of anaphylaxis and certain simple chemical bases are similar in releasing histamine, but that their mode of effecting the release of histamine apparently differs (507); Reuse (468) apparently holds that anaphylaxis is due to release of histamine. Parrot, 1942, and Mongar and Schild, 1955, hold that in anaphylaxis the release of histamine is a process requiring energy and that this process may be blocked by various metabolic inhibitors, including iodoacetate or lack of oxygen (507). However, chemical releasers, such as acetylamine or compound 48/80, do not require provision of energy, but are activated by iodoacetate or the lack of oxygen, as shown by minced lung of guinea pigs in vitro (507).

Wilander (621) reports that he isolated sufficient amounts of heparin from the plasma of dogs in peptone shock to account for the incoagulability of the blood in

anaphylactic or peptone shock and that protamine completely allayed the anticoagulant effect of the heparin in the dogs. He holds that during shock, the mast cells empty their granular contents into the blood, and he showed that blood clotting was not inhibited in hepatectomized dogs, but that shock plasma recovered after being passed through the isolated liver inhibited coagulation.

Antihistamine drugs operate by competing with histamine for the normal histamine-receptive sites and by this means prevent the appearance of histaminic effects (245). Such a simple explanation of histamine antagonism may hold for some, but not for all, histamine antagonists, for these substances are also histamine releasers and many of them, when used in concentrations sufficient to antagonize anaphylaxis of smooth muscle, independently produce a bronchoconstrictor action which reduces their effectiveness in treating bronchial asthma (507). Similar effects of antihistamine drugs on histamine which produced anaphylactic contraction of smooth muscle have been explained as a phase of the contraction which is not antagonized by the antihistamine (250).

Martin and his colleagues in 1949 reported that flavonoid compounds effectively inhibited histidine decarboxylase in tissue cultures. This result probably led them to suggest that the antianaphylactic effect of the flavonoid compounds used is the result of the ability of these compounds to prevent formation of histamine from histidine by inhibiting the enzyme decarboxylase (369).

Histaminopexy

Histamine fixation by experimental methods is a comparatively undeveloped field. Theoretically at least, it should be possible to inject some substance locally, intravenously or intraperitoneally, which would prevent release or inactivate liberated histamine by binding it in some way to molecules in the plasma, tissues, and/or a substance included in the injection.

The idea of histaminopexy loses some of its aspects of impossibility when viewed as a reversal of histamine release processes, in which loosely bound, inactive histamine (382, 383, 595) is activated. Whether this principle would be applicable to endogenous histamine, since exogenous histamine is not supposed to be included by the cells, is not known. Nevertheless, Laborde, Parrott, and Urquia in 1953 showed that normal human serum fixed about one third of the exogenous histamine (histamine dihydrochloride 10^{-6} and 5.0% dialysed human serum) in a solution, but that in the majority of the cases the sera from allergic patients showed no reduction in activity of the histamine by the sera as was shown by the guinea pig ileum test (430). Parrot and Laborde (430) found that the histaminopexic activity of sera was controlled to a significant extent by adrenal cortical and adenohypophyseal hormones and was reactivated by cortisone.

The statement that antihistaminic drugs operate by blocking the response of

receptors to the stimulating effect of free histamine (468) suggests that the beneficial results of these drugs are not due to their histaminopexic activity.

Blaschko (60) holds that liberated histamine exerts its biological action after passing from the circulating and tissue fluids by again being bound to "specifically histamine-sensitive patches" on the effector cells' surfaces. If this is proved to be the mode by which endogenous histamine operates in allergical reactions, then any practical means of desensitizing these histamine-sensitive cell surface patches, or to cause them to repel the invading histamine, would certainly be well worth considering for use in prophylactic or therapeutic treatment.

A rather novel idea of a contributing factor in histamine control is set forth by Parrot and Laborde (430) who describe a histaminopexic, gamma globulin-like substance which, subsequent to removal by dialysis of an antihistaminopexic, albumin-linked serum fraction (Fraction V of E. J. Cohn), reduced the histamine activity of normal human serum about 33 per cent and was at least equally effective on normal sera of the cat, dog, guinea pig (av. of 10, 39.2%), mouse, and rat (av. of 8, 38.7%). However, this histamine-fixing substance failed to bind any of the histamine in the sera from most of 51 allergic patients suffering from asthma, angioneurotic edema, chronic arthritis, eczema, duodenal or exudative and gastric ulcers, hay fever, migraine, rheumatic fever, or tuberculosis exudativa (430). Parrot showed in 1955 that adrenalectomy deprived rats of this histaminopexic substance, but that it was restored by administration of cortisone (505), and that deficiency of ascorbic acid also deprived serum of its histaminopexic action (430).

Reuse (468) holds that the beneficial effects of antihistamine in anaphylaxis are the result of these drugs inhibiting "the effects of liberated histamine on effectors", as is indicated by muscle tissue in vitro. Ungar (595) cautions that there is a possibility that proteose activation and histamine release are parallel phenomena which are due to a common cause, even though it is known that inhibition of proteolysis suppresses release of histamine (595).

Corticosteroids

At least 29 corticosteroids have been identified in extracts of the adrenal cortex, but only about 6 of these have been shown to be active (606). Elkinton and Danowski (160) show that in general adrenocortical steroids in excess disturb the body fluid balance by causing sodium retention and potassium deficits accompanied by other significant changes in the salt-water balance, sugar, ionic, and other body fluid disturbances. However, very little or no consideration is given to histamine.

ACTH, cortisone, and epinephrine (all antiphlogistic hormones of Selye (520)) are antagonistic to histamine. These substances decrease capillary permeability and also decrease formation of inflammatory exudate. However, DOC (compound S, desoxycorticosterone, desoxycortone) and DOCA (DCA, desoxycorticosterone

acetate; prophlogistic hormones of Selye), like histamine, cause capillary dilation, increased permeability, and increased exudate and thus either have no effect on, or actually favor, histaminic action. Cortisone, either administered to, or produced within, the animal following administration of ACTH is thought to be converted into hydrocortisone within the body before it becomes physiologically active (454).

ACTH (Adrenocorticotropin)

It is generally conceded that ACTH, which is an anterior hypophyseal hormone, and cortisone have nearly identical effects since ACTH acts by stimulating the adrenal cortex to produce corticosteroids, especially cortisone (221). While Conn and co-workers, 1951, have indirectly indicated that ACTH-administration produces 17-hydroxycorticosterone (Compound F) as the mediator of its action (502). Menkin (388) shows that numerous investigators have found that ACTH is as effective in suppressing increased capillary permeability in inflammation in adrenalectomized rats as in normal ones. He (388) is convinced that ACTH, by suppressing the action of exudin, acts directly in decreasing permeability of the capillaries. Menkin (388) further supports the idea of these two hormones having different effects by stating that ACTH has no effect on leukotaxin-induced diapedesis but represses the effects of exudin in producing increased capillary permeability, while cortisone has no effect on exudin but inhibits the diapedesis. ACTH in excess has been found to induce freckling and pigmentation similar to that occurring in Addison's disease, but excessive dosage of cortisone does not produce this effect (160). Other less clearcut differences in the effects of ACTH and cortisone have been reported.

Cortisone

The chief basis for the early recognition of cortisone as a "wonder drug" for treatment of various conditions involving capillary hyperenergy may be attributed to its ability to decrease capillary permeability. There are several possible means by which cortisone may decrease capillary permeability in normal as well as in histamine-induced and other edematous conditions. Romani (489) calls attention to the fact that there are numerous contradictions in the literature on the effects of cortisone on mast cells. Actually the recorded effects range all the way from producing a marked increase in number (489) to the destruction of mast cells (19, 22, 93).

Epinephrine as Potentiator

There is the possibility that immediately beneficial effects of cortisone in reducing conditions resulting from excessive amounts of histamine, "H-substance", leukotaxin, and/or similar agents which increase capillary permeability may be

due to cortisone increasing release of epinephrine, which constricts arterioles (547), and thus decreases capillary dilation and permeability by reducing the volume of blood passing through the arterioles and precapillaries. Selye (520) suggests that competition for the same aminooxidase system may account for the potentiated pressor action of epinephrine derivatives in controlling hyperemia and permeability. However, multiple factors in unknown sequence are probably involved. One of these little-appreciated factors may be 5-hydroxytryptamine ("serotonin", Spätegift of Freund, (520)) which is stored in mast cells (43, 334, 493), in blood platelets (557), and probably in other cells. Although it is claimed that human blood contains about 0.1 γ/ml of this vasoconstrictor principle (389, 557), at present it appears that very little is known about the specific relations of this substance to either inflammatory hyperemia or to the effects of either epinephrine or cortisone on capillary permeability. However, evidence obtained from more than one source "makes it very likely that 5-hydroxytryptamine is the edema-producing agent released by substances which damage mast cells" (493).

Effects of Cortisone

Certain investigators have reported that cortisone inhibits leukotaxin (387) and hyaluronidases by forming a complex heparin-lipoprotein which acts as a nonspecific antihyaluronidase. Also, with this exception, the mechanism of the antiphlogistic action of cortisone appears chiefly to involve the sulfhydryl groups (489). Moderately prolonged treatment with cortisone causes various metabolic changes, but it is debatable whether it affects polymerization of hyaluronic acid. Hyaluronic acid is known to increase the resistance of ground substance to the spread of inflammation, and by this means it plays a very important part in controlling edematous effects of increased capillary permeability (20, 148). Thus, it appears that enzymic systems may play important roles in histamine-epinephrine control of motivation of arterioles and their capillaries.

Cortisone not only has a suppressing action on capillary permeability, but it also suppresses formation of new capillaries, as in wound healing (17, 275, 330), and in the process of vascularization of tumor, skin, and other grafts (17, 330). Cortisone may have a direct antimitotic effect in skin grafting, as well as the commonly recognized indirect effect, by inhibiting the process of vascularization of the graft (330). Apparently, it is safe to assume that the mode of action of cortisone in suppressing capillary growth and in suppressing capillary permeability is through its antagonism of histamine, and this process may be abetted by other substances reported to be active in increasing capillary permeability in normal and inflammatory conditions.

Cortisone, probably as the hydrochloride (454), is a potent anti-inflammatory agent, which is supposed to have multiple means of producing this effect. In fact,

cortisone appears to have at least 3 means of effecting suppression of histaminic activity. One of these is its ability to block one or more enzyme systems, but the particular enzyme system blocked is unknown (454). A number of investigators hold that histamine is produced by decarboxylation of histidine by histidine decarboxylase (157, 505, 616). Halpern (238) holds that cortisone inhibits biogenesis of histamine, the vulnerable link for which would be histidine decarboxylase. The enzyme histaminase destroys histamine by catalyzing its oxidation (335), and cortisone is held to be able to supress the inhibitor of this process. Thus, cortisone is believed to suppress histamine by interfering with its production and by aiding in its destruction. Halpern (237) adds another angle of approach by suggesting that cortisone acts by interfering with the metabolism of tissue histamine, more specifically by preventing the degradation of the "combined" form to the "free" form of histamine.

Ungar (594) holds that a number of anti-inflammatory drugs which include cortisone, act by inhibiting the fibrinolytic system in vivo as well as in vitro. Thus, he concludes that all anti-phlogistic hormones accelerate the fibrinolysin-antifibrinolysin reaction. Zweifach, 1953, holds that vasodilation with its attendant phenomena can be produced by numerous biological substances, many of which are formed by the cells. He sees no need for any proteolytic type of enzymatic reaction (594). From this it may be inferred that there are multiple points other than those in the fibrinolytic system which can be blocked by cortisone, or other anti-inflammatory substances, to prevent release of histamine and/or increased permeability of the terminal vascular bed.

Desoxycorticosterones

The variable terminology and abbreviations of the terms used by different writers make it difficult to determine just which preparation of desoxycorticosterone was used and, in some instances, the conditions under which the preparation was employed. It appears that under comparable conditions the various preparations of the desoxycorticosterones all properly belong in Selye's (529) 1949 group of prophlogistic hormones; that is, they aid or stimulate histaminic vasodilation and increased capillary permeability. The names of some of these preparations with their synonyms, as nearly as can be determined, in parentheses follow: Desoxycorticosterone (compound S (?), deoxycortone, DO, DOC) and desoxycorticosterone acetate (DCA, DOCA, a proprietary brand; deoxycortone acetate; percortin, a proprietary brand).

Desoxycorticosterone acetate (DCA) is the form of desoxycorticosterone most often employed in experimental and clinical work. In general, DCA exerts a more pronounced effect on certain species than on others. Although all rats are susceptible to the hyalinizing effects of DCA, some strains are more susceptible than others;

while the fowl and rat apparently represent the species most sensitive to its hyalinosis-producing effects (520). This species-susceptibility may be largely responsible for the seemingly contradictory results reported by certain investigators.

DCA promotes inflammation and wound healing, apparently as a result of its phlogistic reaction, and thus it stimulates proliferation of fibroblasts and encourages deposition of collagen (520). Apparently, the beneficial effects of DCA on wound healing and its aggravating effects on inflammatory processes are essentially similar to the effects of mast cell products. That is, both increase capillary permeability in order to afford an adequate supply of blood-borne substances necessary for the formation of fibroblasts and collagen and utilization in forming cicatricial tissue and in promoting sustaining tissues, such as connective tissue adnexa, neural and vascular structures, in wound healing. This point becomes more obvious when it is recalled that cortisone and ACTH inhibit inflammation and wound healing by suppressing the processes which DCA and mast cell products promote

Desoxycorticosterone diethyl acetate appears to be an exception to the general rule, for this substance is reported as being slow-acting but, unlike DOCA, it "decreases the amount of inflammatory exudate" in croton oil granuloma pouches in rats. However, it was found to be only about 20 to 30 per cent as potent as hydrocortisone (478).

Percortin, a proprietary preparation of desoxycorticosterone acetate which was available in the early 1940's, has been reported to be anti-inflammatory in action but, since explanations of this property have not been well supported, it was suggested that the antiphlogistic effects of batches of this substance may not have been pure material (388). This conclusion was further supported by the fact that the substance in crystalline form obtained from another source had "no anti-inflammatory effect" (388). However, conditions of the experiment may have been such that the expected phlogistic results were not obtained. The work of Skelton (538) in which he used antihistamines in a futile effort to antagonize the effects of DOCA on castrated, unilaterally nephrectomized, salt-treated rats apparently supports the results obtained by use of percortin.

He also reports that under the conditions of this experiment, it was found that antihistamines, phenergen, benzodionole, and trimeton, afforded no significant protection to those rats against either the angiotoxic or nephrotrophic effects of DOCA as seen in the heart, kidney, and arterioles in the pancreas.

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