Effects of Anesthetics on the Response of the Microcirculation to Circulating Humors

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Reports pertaining to the effects of humoral factors on the reaction of the microcirculation during anesthesia are few and not without unanswered questions. On the one hand, our knowledge of the mechanisms participating in the regulation of the microcirculation is incomplete, and on the other, “humors” or chemical messengers carried by the blood stream to distant target organs and tissues are not the only chemical factors which may affect the vascular smooth muscle receptors of the capillary bed.

Data are being accumulated which indicate that the so-called “local hormones”¹, ² or “tissue mediators”³ are of considerable importance in modifying microcirculatory dynamics. Difficulties arise from the rather scanty systematic studies on the interplay of these vasoactive humors with various anesthetic agents. Within the scope of this symposium, we should like to describe certain aspects outlined as follows: (1) a brief description of current concepts of the microcirculation to bring into better perspective the main subject of this discussion, (2) present information on the modification of microcirculatory homeostatic mechanisms by anesthetic agents, and, (3) the possible relationship of the microcirculatory reaction under anesthesia to circulating humors in the hope that this may stimulate further thought and study.

Microcirculatory Patterns—Description and Terminology

A comprehensive description of the microcirculation has been given in an earlier publication,⁴ and recently an excellent synthesis of contemporary thought and recently acquired information has appeared.⁵ Familiarity with some of the criteria currently employed in evaluating the functional adjustments of this segment of the vasculature is necessary for this discussion.

Anatomical Considerations. In essence, the microcirculation provides the morphologic and functional basis for exchange of gases, nutrients, metabolites and humoral products between the intravascular and extravascular compartments. To meet this requirement, the “nutrient vessels” or capillary systems are endowed with certain structural, physical and functional characteristics, which are the basis of their physiological activities. This is so regardless of the somewhat different micro-architecture related to specific functions of the particular tissue structure in diverse organs.

The microcirculatory pattern (fig. 1) is represented by small vessels which pervade the tissue and supply blood in accord with varying needs. The vessels are: (1) precapillary arterioles, (2) postcapillary collecting venules, which become permeable on occasion, (3) those intervening distal subdivisions of the arteriolar vessels, the metarterioles, which are endothelial tubes surrounded by a single discontinuous layer of muscle cells, and, (4) the final subdivision of the vascular apparatus, the true capillaries, which are devoid of muscle cells except, as in some, at their point of origin from the metarteriole. The strategic junctional muscular portion of the capillary bed has been designated the precapillary sphincter⁶ which directly controls blood flow into the capillary network. An important architectural feature of many vascular beds is the preferential thoroughfare channel: the precapillary arteriole, after giving off the corresponding metarterioles, continues in its course to become the main postcapillary collecting venule. This arrangement found in the mesentery⁷ striated muscle,⁸ smooth muscle and intestinal

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mucosa\(^6\) permits rapid passage of blood from artery to vein, bypassing the intervening capillary network.

**Functional Considerations.** The functional adequacy of the microcirculation can be remarkably independent of changes in perfusion pressure or total blood flow. Although the output of the heart has definite effects on the microcirculation, it has been established beyond doubt by the work of many investigators, that the distribution of the blood to tissues is controlled independently of the systemic circulation by the intrinsic action of the microscopical vessels. This relative independence results from the ability of the microvessel to respond sensitively to circulating humors, both blood-borne and of local tissue origin. An outstanding characteristic of the muscular microvessels is the gradient of reactivity to vasoactive drugs\(^7,8\) and to electrical stimulation.\(^9\) Reactivity was found to vary inversely with their diameter. Results of studies of electrical activity in single smooth muscle fibers\(^10\) also show a clear-cut gradient for duration of the spike-potential from a single shock of 200 milliseconds for the arteriolar muscle fiber, compared to 50 milliseconds for precapillary muscle. This strongly suggests that the gradient of reactivity to drugs might be due to the presence of different kinds of muscle fibers at various segments of the microcirculation. Recently, it has been disclosed,\(^11\),\(^14\) that the muscular microarterial vessel exhibits certain mechanical and physical characteristics not seen in the larger segments of the vascular tree. Briefly, these consist in a paucity of change in the diameter of vascular lumina, i.e., "apparent rigidity" over a large range of variation in internal pressure. Both of these characteristics, physical and functional, constitute important mechanisms which implement regulation of the spontaneous periodic activity of the microarterial vessels, a homeostatic entity which has been termed *vasomotion*.\(^17\)

The phenomenon of vasomotion has been aptly described as an intrinsic rhythmic response of the smooth muscle to the distending influence of the intravascular pressure of the blood coursing through that vessel.\(^3\) The larger blood vessels are almost completely under the control of centrally integrated au-

![Fig. 1. Tracing of capillary bed in rat mesoappendix: (1) Precapillary arteriole; (2) Postcapillary collecting venule; (3) Preferential thoroughfare channel; (4) Metarterioles; (5) Precapillaries leading to true endothelial capillaries.](image)

tonomic neuromotor activity for their homeostatic responses of constriction and dilation. Vasomotion of the microvessel is merely modified by this sympathetic neurogenic activity. Rhythmic change in polarization of the smooth muscle cell surface (local potential) is considered\(^18\) the basis for intrinsic automaticity. Variation in neurogenic activity, humoral vasoactive agents, and changes in the ionic environment influence this basic function and serve to modify the intrinsic tone of the effector unit in the microvessels.

**Anesthesics and the Microcirculation**

Most studies of the action of anesthetic drugs on vascular smooth muscle have been made by observing the circulation of a particular organ or tissue. In the human ear vasoconstriction (reduced optical density) occurs during induction of anesthesia with both cyclopropane and diethyl ether.\(^19\) Vasodilatation (increased density) results during emergence from cyclopropane anesthesia but not diethyl ether. In man, plethysmographic studies show that the blood flow in the extremities increases with most of the commonly used inhalation anesthetics. Cyclopropane induces a two-fold increase both in hand\(^20\) and in forearm blood flow.\(^20\) A
comparable change in forearm blood flow was noted with diethyl ether or thiopental alone, or in combination with nitrous oxide. It has been suggested that vasodilatation occurs in blood vessels both of the skin and of muscle. These and other hemodynamic changes in specific segments of the circulation during general anesthesia have been discussed recently in a comprehensive review. No clearcut definition of the microcirculatory mechanism or its modification by anesthetic drugs can be derived from these methods of study. It is not possible to determine from gross changes in flow and resistance whether the smooth muscle affected is that of the arterioles, of the capillaries, of arteriovenous anastomoses (when present), of the veins, or a combination of these vascular elements.

Direct observation of the reaction to various anesthetics, of the newly grown and of the “preformed,” naturally innervated, vasculature of the Sandison-Clark rabbit ear preparation, demonstrate the profound effect of these agents on the minute blood vessels. Arteriolar constriction is associated with “light” ether anesthesia, and dilatation during deep anesthesia. Chloroform has a similar effect. Arteriolar constriction, increased vasomotion and capillary dilatation are noted during cyclopropane administration. The advantage of the rabbit ear chamber preparation is that it allows control measurements of the vascular parameters to be made in the trained unanesthetized animal. However, the conspicuous passive capillary dilatation during periods of arteriolar constriction and enhanced vasomotion which result from the rigidity of the chamber, considerably limit its usefulness. Superimposed effects on the smooth muscle tone of vasoactive materials arising from undue capillary engorgement cannot be ruled out. Vasomotion of the precapillary sphincter and metarterioles, may readily be modified by the mere physical force of artificially created increased venous pressure.

These objections to the study by the direct visualization technique of the effect of anesthesia on mechanisms controlling microcirculatory dynamics have been amply circumvented by the now classical preparation of the dog’s omentum. More recently a similar approach has been extended to the mesoappendix of the rat in the study of the effect of a number of inhalation anesthetics including diethyl ether, cyclopropane, halothane and methoxyflurane. Protracted studies upon these vascular structures serve as a firm basis for interpretation of the modifications arising from the action of the anesthetic employed.

The vascular parameters which have served for the analysis of the effect of anesthetics on mechanism controlling microcirculation, both in the dog’s omentum and in the mesoappendix of the rat, exemplified by the latter (fig. 2), are as follows:

Reactivity to Epinephrine Applied Topically. The capacity of the metarterioles and precapillaries to react to different dilutions of epinephrine applied topically has been accepted as a relative measure of the ability of these vessels to react to a physiological stimulus. Concentrations of epinephrine employed range widely in terms of parts per million.

Vasomotion of the Metarterioles and Precapillaries. Changes in the frequency and duration of the periodic spontaneous muscular activity of these microvessels, which in effect, regulate the volume of the blood entering the true capillary network, is a single valuable index of both, the tonic status of the smooth muscle cell and of the circulatory stress undergone by the tissue, to which these vessels are subservient.

Caliber of the Precapillary Arteriole and Postcapillary Vein. Micrometric measurement of these major vessels of the vascular bed provides a quantitative index of the activity of their vasoconstrictor-vasodilator mechanisms.

Capillary-Venous Outflow. The rapidity of outflow from the capillary bed into the postcapillary collecting venules determines, in great measure, the rate at which the blood returns from the tissues to the larger vessels of the systemic circulation.

Rate of Recovery. This implies, in terms of time, the return of the mechanism of epinephrine reactivity, vasomotion, vasoconstriction and venous outflow to the initial control state observed before narcosis, upon removal of the anesthetic agent.

In the capillaries of the dog’s omentum and in the rat mesoappendix an overall enhancement of the activities studied, developed during light anesthesia with diethyl ether, cyclopro-
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propane and halothane. A two- to four-fold enhancement of spontaneous vasmotion, and increased sensitivity to topical epinephrine invariably accompanied the inhalation of concentrations of 1.8 per cent diethyl ether, 28 per cent cyclopropane and 0.8 per cent halothane. Venular outflow remained relatively unchanged during light anesthesia with these agents over a period of from 60 to 90 minutes. Increase in depth of anesthesia with all three drugs led to reduction of vascular activity. Deep anesthesia was accompanied by a waning then suppression of vasmotion, a depressed response of the microvessels to epinephrine, and slower blood flow through the dilated venules. Careful micrometric measurements (550 times magnification) of precapillary arterioles and postcapillary collecting venules showed that during light anesthesia with diethyl ether and cyclopropane there was a narrowing of the

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**Fig. 2.** Record illustrating the reaction of the mesoappendiceal microvessels before, during and after halothane anesthesia. Gas concentration determined with an Elmr-Perkin chromatograph. Note increased reactivity to topical epinephrine and enhanced vasmotion lasting beyond 45 minutes of induction.
arteriole but no change in diameter of the venular lumen. Progressive venular dilatation and slow return of the arteriole toward control size, however, occurred with deep anesthesia. With diethyl ether an earlier appearance, more protracted venular dilatation, depression of vasomotion and decreased sensitivity to epinephrine were noted, than was seen with cyclopropane anesthesia.

Vascular lumenal adjustments were somewhat different with halothane anesthesia. Although, as with diethyl ether and cyclopropane, there was an equally enhanced vasomotion and hypersensitivity of the precapillary sphincter and metarterioles, no measurable change in arteriolar lumenal diameter attended light (0.8 per cent) anesthesia with halothane. Deeper halothane narcosis was accompanied by dilatation of both precapillary and post-capillary vessels.

In contrast to the above described anesthetics, methoxyflurane, in the rat, depressed the spontaneous activity of the microcirculation from the very onset of induction. Both, spontaneous vasomotion and sensitivity to epinephrine steadily declined with progression of narcosis. Venular dilatation and slowed venular blood flow persisted after administration of oxygen alone, as with diethyl ether, for a long time (30 to 40 minutes).

In general, these studies utilizing either the omentum of the dog or the mesoappendix of the rat indicate that the functional efficiency of the microcirculation can be interfered with, in varying degree, by the different anesthetics. The pattern of activity in the peripheral circulation not only showed distinct characteristics for each of the anesthetics studied but also was significantly influenced by the depth of anesthesia.

Although the significance of these microcirculatory changes on overall hemodynamic adjustments is not known, an indication of an efficient or inefficient compensatory pattern for local tissue function has been outlined on the basis of the microcirculatory status. When progressive vasoconstriction of the small arteries and arterioles is accompanied by increased vasomotion, thus directing blood through the capillary bed via preferential channels, an efficient compensatory activity is present. Only enough blood enters a limited number of true capillaries to satisfy the basic needs of the tissues. This pattern of activity, therefore, prevents large volumes of blood from being diverted into an extensive capillary pool. This is in keeping with the 5 per cent of the total blood volume assigned to this segment of the circulation under normal resting conditions. An indication of inefficient or unfavorable compensatory patterns is the lack of constriction and ultimate dilatation of the small arteries and precapillary arterioles, and a depressed or absent vasomotion. As a result, the entire capillary bed is soon filled with blood, blood flow is sluggish, capillary outflow is poor and venous return impaired. These patterns usually are accompanied by increase in vascular permeability and fragility.

Circulating Humors and the Microcirculation

The well delineated opposing types of adjustments, first excitatory and then inhibitory, exhibited by the microvessels during “light” and deep narcosis would seem, a priori, to be readily explainable. Many of the anesthetics stimulate autonomic centers in the hypothalamus which results in increased sympathetic activity and anterior and posterior hypophyseal discharge. It must be admitted, however, that at this level of the vascular tree we have as yet no real understanding of the mechanism of action of the “primarily” released neurohumors and the “secondary” mediators arising from target organs affected by the former. This ignorance stems from the fact that we are at present unaware of the degree of modification exerted by autonomic neurogenic activity on the microcirculation, whether anesthetic drugs affect the vessel receptor directly and, most importantly, the real nature of the receptors.

Adrenal Medullary Hormones. The microcirculatory pattern observed during induction of anesthesia with chloroform, ether, or cyclopropane may safely be related to circulating neurohumors. The earlier observation that the above agents, as well as urethane, pentobarbital and morphine are associated with depletion of epinephrine from the adrenal glands and sympathetic nerve endings is buttressed by the recent quantitative determination of levels of these amines in the circulation.
It has been established both in animals, and in man that increasing plasma concentrations of norepinephrine and epinephrine occur during cyclopropane and ether anesthesia.

The decrease in tone of the vascular smooth muscle with decreased sensitivity to stimulation by epinephrine and suppressed vasomotion resulting in sluggish, plethoric flow in the microcirculation, at times of increasing levels of circulating epinephrine and norepinephrine, is, however, more difficult to explain. One may conjecture that increasing amounts of circulating catecholamines eventually result in exhaustion of the smooth muscle receptor. Secondary blood-borne smooth muscle inhibitor substances, such as ferritin, adenilic acid, lactic acid, or other locally arising tissue mediators (serotonin, histamine, bradykinin) might also be responsible for the observed shift in the microcirculatory pattern seen during prolonged and deep narcosis.

A similar hyper-reactive compensatory type of pattern, observed with light halothane, in the absence of increased circulating catecholamines, defies explanation. For the present, the pattern observed with light halothane anesthesia, of myocardial depression and arterial hypotension, is considered a function of the lack of sympathetic autonomic system effect, both central and peripheral, on the systemic circulation. The hyper-reactivity of the microcirculation noted might be the resultant of physical forces modifying the stretch receptors leading to this pattern of behavior. Further careful quantitation of the sequence of appearance of the above mentioned amines, humors and other local vasoactive substances during anesthesia may throw further light on the pattern of behavior of halothane.

Adrenal-Cortical Hormones. Reports demonstrating that diethyl ether and cyclopropane stimulate the adrenal cortex are important to an understanding of the behavior of the microcirculation during anesthesia. Lack of adrenal corticoids may lead to an unfavorable effect on the tonic constriction of the muscular microvessels. Cortisone and ACTH potentiate the effect of norepinephrine. Likewise, the adrenal cortical hormones are required for maintenance of mechanisms controlling peripheral circulation, that is, the intrinsic tone of the microvessels, reactivity to physiological stimuli, vasomotion and vasoconstriction. The reported effect of adrenal steroids and adrenal medullary hormones on salt and water metabolism has been thoroughly discussed in reference to their interaction on the behavior of the vascular cell. Shifts in the electrolytic environment of the microvessel affect the response characteristics of the microvessels and may be accompanied by change in the fluidity of the blood. Changes in coagulability of blood are clearly evident during different types of stress. The administration of several milligrams of cortisone, hydrocortisone or corticosterone to normal rats and rabbits affects the terminal vascular bed with extraordinary rapidity. Within 20 to 30 minutes, the circulating leukocytes become round spheres and no longer adhere to the venular endothelium. The usual accumulation of leukocytes as well as cellular diapedesis are almost absent following local trauma. This derangement of mechanisms controlling microcirculatory homeostasis, together with alteration in blood flow behavior brought about by the anesthetic agents, may lead to rheological problems of serious consequence.

Posterior Pituitary Hormones. Release of pituitary antidiuretic hormone has been indicated during anesthesia with several anesthetics both in the laboratory animal and in man. Attention has focused largely on disturbance of water metabolism and sodium-potassium exchange in the surgical patient.

Because of extensive clinical use in obstetrics, the question of the compatibility of oxytocins with anesthetic agents has been raised. Microcirculatory studies with some of the drugs, including synthetic oxytocin (Syntocinon), natural oxytocin (Pitocin) and synthetic vasopressin (L-s vasopressin) are hereby summarized. These drugs were given intravenously to study the effects on the meso-appendix of the rat anesthetized with 3.5 mg per 100 g. body weight of pentobarbital sodium. Natural oxytocin depressed the microvascular response to topical epinephrine at low doses (0.02 I.U. per 100 g. body weight); higher doses (0.05 to 0.1 I.U.) resulted in an initial potentiation of response followed by prolonged depression. In contrast, the injection of synthetic oxytocin resulted, at all dose
ranges studied (0.02 to 0.05 I.U.), in a consistent depression of sensitivity of the vascular smooth muscle receptor. Synthetic vasopressin, which gave a persistent potentiative action to epinephrine, was invariably accompanied by enhanced vasomotion at a lower concentration range (0.0005 to 0.005 I.U.). Complete closure of the precapillary sphincters and metarterioles for 3 to 5 minutes attended administration of higher (0.1 to 1.0 I.U.) doses, resulting in an ischemic type of flow through preferential channels. Natural oxytocins, applied topically, were also found to produce a direct constrictor response 10 times greater than synthetic oxytocin in the rat uterine 62 omental vasculature.

These data as well as those reported from studies in the rabbit ear chamber preparation 20, 63 for topical Pitressin are fragmentary and insufficient to establish any presumptive mechanism of hormonal interaction effect at this circulatory site during anesthesia.

**Estrogenic Steroids.** The integrity of the capillary wall is largely dependent upon an appropriate balance of circulating estrogenic steroids. The effect of estrogenic therapy on its withdrawal, 64–66 and the effect on blood coagulation factors 67–69 suggest that estrogenic imbalance may lead to spontaneous hemorrhagic episodes in tissue vascular beds which may be remotely analogous to menstrual bleeding. Histological studies 70 have shown that administration of conjugated estrogens (Premarin) directly affect the sol-gel equilibrium of the acid mucopolysaccharide and complex protein of the ground substance about the microvascular wall. The effects of hypothalamic implants of minimal amounts of estradiol 71–73 indicate the presence of estrogenic sensitive centers within the hypothalamus operating upon a feedback mechanism, monitored by the amount of estrogen in the circulation, and regulating the rate of release of gonadotrophic hormone. The possible change in the integrity of the microvascular wall may be of importance in the patient affected with endocrine obstetrical problems.

There is no difference in vascular response to topical epinephrine noted in the uterine omentum of the pentobarbitalized rat at various stages of estrous cycle. 74 The blood vessels of the omental structures studied are a continuation of those supplying the uterine horn in this animal, and should be representative of uterine vessels subject to the effects of this hormone. The same authors 75 noted, however, that during the menstrual cycle and normal pregnancy in the human there was a progressive reduction in the rate of blood flow in the conjunctival capillary bed leading to marked tissue ischemia. This ischemic type of flow occurred concomitantly with an increased sensitivity to epinephrine of the conjunctival arterioles and precapillaries. Microcirculatory studies carried out on conjunctival vasculature in women during toxemia of pregnancy showed an even greater sensitivity to vasoactive drugs. 76–78 If this vascular bed reflects a generalized hypersensitivity, the increase in circulating vasoactive substances promoted by stressful states may aggravate the tissue ischemia found in hypotensive or hemorrhagic states. It may indeed be an explanation of the sensitivity of the toxemic patient to development of circulatory or respiratory dysfunction.

**Histamine.** The striking effect of various anesthetic agents on the hypothalamic sympatho-adrenal system resulting in the release of catecholamines to the circulation prompts the question of possible interaction of these humors with histamine. A profound vaso-depressor effect of histamine was described in cats and dogs in earlier work which emphasized its possible cytotoxic action. 79 A dual vascular action was described both in rabbit's skin 80 and the rabbit ear chamber preparation. 63 Doses of from 0.2 to 0.5 mg. of histamine produced constriction of the larger arteries and dilatation in smaller peripheral vessels.

The suggestion 2 that histamine, acetylcholine and norepinephrine, or epinephrine perhaps, control local tissue activity by their interrelated action has recently been emphasized. 81, 82 The enzyme histidine decarboxylase can be activated in all tissues, except blood, by the injection of epinephrine, norepinephrine and other stressors. Presumably many cells, including vascular endothelium, contain small, but metabolically effective, concentrations of histamine; epinephrine and enzymatic systems within the cell keep these agents in balance. On the basis of these studies, the
suggestion has been advanced\textsuperscript{83} that the enzyme, histidine decarboxylase, may synthesize intracellular histamine at a rate determined by the need of the tissue for blood under various environmental conditions. Thus, histamine may directly participate in the modifying mechanisms regulating the microcirculation. The administration of an antihistamine (Benadryl) prior to the injection of norepinephrine or epinephrine potentiates the action of these amines in the dog and in man.\textsuperscript{84}

Although histamine has been implicated in certain allergic reactions in a number of species, it has not been possible to establish a clearly defined physiological role for this substance, despite its widespread distribution.

**Serotonin.** Serotonin, 5-hydroxytryptamine is normally relatively abundant in many tissues (enterochromaffin cells of the intestine, blood platelets, and cells of an unknown nature in the brain), and is one of the agents suspected to be a mediator of the increased vascular permeability following tissue injury.\textsuperscript{85} The cytotoxic effects of mixtures of 5-hydroxytryptamine and epinephrine on endothelium are well documented.\textsuperscript{86} Though the amine is stored in several different types of cells, administration of reserpine and other releasers (benzoquinolines, decarboxylase inhibitors, and related agents) causes a generalized lowering of serotonin levels. This phenomenon and those related to binding of serotonin to other amines have been reviewed recently in detail.\textsuperscript{87, 88} In the intestine, serotonin is believed to be responsible for local modulation of intestinal motility.\textsuperscript{89} Increased levels of serotonin in portal venous plasma have been reported following intestinal ischemia or mere intestinal manipulation.\textsuperscript{90}

Serotonin affects different facets of vascular smooth muscle behavior by a direct action. Following systemic administration, this amine produces a variable effect on blood pressure and other elements of the circulation. Its pharmacologic action is basically one of antagonism. Recent studies both in the perfused hind-limb and in the kidney of the dog suggest that serotonin acts on the vasodilator receptors thus opposing neurogenic vasoconstriction, and may actually cause vasodilation.\textsuperscript{91}

The fact that many regimens which induce resistance or tolerance to different forms of stress are accompanied by an increase in the level of serotonin in tissues, skin and intestine, suggests that the storage and release of this amine by a particular tissue may be a protective rather than deleterious process. However, the demonstration that the vascular necrotic process basic to the localized dermal epinephrine reaction (Schwartzman phenomenon) can also be seen with elevated levels of serotonin in the blood,\textsuperscript{92} calls for caution.

**Bradykinin.** The changes in pH which may result\textsuperscript{93} from accumulation of acid metabolites during anesthesia and the fact that acidification of plasma leads to formation of bradykininogen in vitro\textsuperscript{94} brings into focus the possibility of release of bradykinin during surgical anesthesia. From the time of its first description,\textsuperscript{95} subsequent identification,\textsuperscript{96} and synthesis,\textsuperscript{97} this plasma kinin has excited considerable interest. This vasodilator substance appears in the perfusate of the subcutaneous space of the human forearm\textsuperscript{98} and in fluid collected from scalded skin in the rat.\textsuperscript{99} Besides the vasodilator and smooth muscle stimulating properties,\textsuperscript{98} bradykinin causes an increase in capillary permeability and elicits pain. In man this pain is believed to be unrelated to the dermal flush and increased dermal temperature that follows its injection into the brachial artery.\textsuperscript{100} The increase in total digital volume which followed intra-arterial injection of bradykinin in unanesthetized man\textsuperscript{100} has been ascribed to an increase in “effective” blood flow to the digit due to vasodilatation of capillaries and venules, occurring concomitantly with constriction of arteriovenous channels. In an unpublished study of the vasculature in the mesoappendix of the pentobarbitalized rat both topical application (0.001 µg.) as well as intra-arterial (ileocolic) injection (0.01 µg.) of bradykinin elicited a prompt suppression of vasomotion in precapillary sphincters and metarterioles, resulting in generalized plethoric flow.\textsuperscript{101} No selective constriction of arteriolar-venular anastomoses was noted in this microcirculatory pattern. The above vascular behavior in the human digit, drawn from rheoaphysmographic tracings, may be a peculiarity of the dermal tissue structure.

The wide spectrum of activity of bradykinin is further exemplified by recent metabolic stud-
ies showing an increased respiratory rate and minute volume.\textsuperscript{102} Carbon dioxide production is increased both absolutely and relatively during infusion of 0.05 \(\mu\)g./kg./b.w. in dogs anesthetized with dial-urethane. While much remains to be learned of the vascular pharmacology of bradykinin and related polypeptides (kallidin, substance P) the above noted cardiovascular and microcirculatory effects warrant consideration during anesthesia in the patient with burns or other forms of tissue injury associated with an increased proteolytic activity.

**Summary and Conclusions**

The reaction of the microcirculation accompanying the administration of currently used anesthetics has been outlined, and the changes in microcirculatory mechanisms discussed in relation to some of the known vasoactive tissue humors. In general, the larger vessels are under neurogenic control; the microcirculation, including the precapillary arteriole, is under the control of circulating and locally produced vasoactive substances.

Most inhalation anesthetics initially enhance specific homeostatic mechanisms (epinephrine reactivity, vasomotion, integrity of the vasculature) which enable the microcirculation to assure adequate blood supply to the tissues and unimpaired cellular activity. Deep and prolonged narcosis results in an inefficient pattern of microcirculatory reaction in varying degree depending upon the agent employed.

Some of the specific humors that have been identified or proposed as regulators of vascular reactivity, and likely to be released during anesthesia, are reviewed. Vasoactive agents among others include the catecholamines, adrenal cortical hormones, posterior pituitary hormones, estrogenic steroids, histamine, serotonin, and bradykinin. Many of the vasoactive substances exist in a bound state probably in conjunction with acid mucopolysaccharide and are released by appropriate stimuli. Almost any stress including uncomplicated inhalation anesthesia may bring about the release of these bound tissue amines. Distortion and reversal of the orderly gradient of reactivity operating at the different segments of the microcirculation under normal circumstances may follow.

The theme of this short review is the current lack of systematic information of the effect of anesthesia on the reaction of the microcirculation to circulating humors. No data could be found on the microcircular pattern of adjustment in many tissue structures during anesthesia. Studies should be extended to capillary beds of these tissues under carefully controlled concentrations of anesthetics and environmental conditions, coupled with more quantitative indices as to alterations in blood flow and vascular permeability. Such studies and further determination of the sequence of appearance of vasoactive mediators should cast further light on the subject.

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