SEROTONIN AS A MAST CELL PRODUCT

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The occurrence of serotonin (43, 334, 493, 536), as well as heparin and histamine (42, 473, 476), in mast cells has been established. Although Parratt and West, 1956, (536) and the investigators cited above show that serotonin occurs in mast cells, the significance of the mast cell as a source of serotonin is not clear at this time. One of the disturbing factors is that there are strong indications that 5-hydroxytryptophan, the immediate percursor of serotonin, occurs in practically all tissues of the body (77) where it may be decarboxylated to form serotonin within the cells (77, 587). Also, Brodie, 1957, points out that administration of 5-hydroxytryptophan will be followed by appearance of serotonin in all tissues in the body (77).

The results of work with a dog and a mouse transplantable mast cell tumor both support and contradict the finding that there is a correlation between the occurrence of serotonin and the mast cell population in rat skin (43). The mastocytoma of mice contained both serotonin and histamine in large amounts; in the mastocytoma of dogs the serotonin level was not affected, but the histamine concentration was increased (536). However, the activity of serotonin, as indicated by strips of rat colon in extracts, has been found to parallel the mast cell population in the skin and in concentrations of peritoneal fluid from rats (43). Contrarily, it has been reported that Erspamer, 1954, was unable to correlate the distribution of serotonin with mast cell content in rat tissues (474). The ratio of serotonin to histamine in mast cells from peritoneal fluid and skin of rats ranged between 1:16 and 1:26 when estimated by two different methods (493). Nevertheless, it is uncertain whether the available results of investigations to date warrant the general acceptance of the statement that there is a likelihood that "5-hydroxytryptamine is the edema-producing agent released by substances which damage mast cells" (493) in rats.

GENERAL CONSIDERATIONS

Rapport and co-workers (461) reported the isolation of a crystalline, vasoconstrictor substance from beef serum and proposed the name "serotonin" for it in 1948, to indicate its source and physiologic functions, and Rapport, 1949, found that serotonin is a complex of equimolecular parts of sulfuric acid, creatinine, and 5-hydroxyindole base (422). Although use of this term has since become widespread, results of the biological methods by which serotonin is often identified in animal tissues are sometimes bewildering to the reviewer. Selye (520), after reviewing the divergent literature, apparently considers "beta thrombovasine",

"vasoconstrictine" and "vasotonine" of various authors as being probably identical with Freund's, 1920, 1921, clot fluid, "Spätgift". One significant point about the concept of "serotonin" and the other 4 terms is that each term indicates a substance having a vasoconstricting action, which is the characteristic vascular effect generally attributed to serotonin by most investigators. Some investigators, however, not only relate serotonin to "Spätgift" in a general way, as a vasoconstrictor, but point out that "serotonin is a clot retraction principle" and is possibly the only dialyzable factor in platelets which is capable of causing retraction of the clot (187).

The generally accepted definition and synonomy of the hormone (633), serotonin, brings out the following points: "Serotonin. 5-Hydroxytrptamine. 5-Hydroxy-3-(β-aminoethyl) indole. Vasoconstrictor found in sera of mammals . . ." (389). Serotonin is also called thrombocytin (588), enteramine (171, 207), when obtained from invertebrates (171) or from the gastrointestinal enterochromaffin cells from the mucosa of vertebrates (171).

There are several kinds or preparations and sources of serotonin, such as bufotenin (dimethyl serotonin obtained from cohoba (2)); trimethyl serotonin, a quartenary, positively charged derivative of serotonin which was identified in cohoba seeds by Horning (2); N-methylserotonin, which by a second methylation becomes N-dimethylserotonin or bufotenin (180); a water-soluble 2,5-dimethylserotonin (525), serotonin creatinine sulfate (122, 360), 5-hydroxytryptamine picrate (171); enteramine, obtained from organs of certain invertebrates, especially the common octopus, Octopus vulgaris, and skin of the disc-tongued toad, Discoglossus pictus (171), and as an unmethylated precursor of Bufo marinus venom (558) and from argentaffine or enterochromaffin (whence the name "enteramine") cells from the gastro-intestine of vertebrates (171) and other sources. It has been suggested that many (171), possibly most, of the preparations of serotonin have similar action. However, enteramine obtained from the posterior salivary glands of the common octopus is not desirable for certain types of experimental work. In addition to serotonin it contains octopamine (1-norsynephrine) and tyramine, both of which are markedly diuretic in action since they produce systemic hypertension and constrict the efferent glomerular arterioles in the kidney (173), while serotonin normally constricts the afferent glomerular arterioles (170) and is, therefore, antidiuretic in its action (173).

Release of Serotonin

It is highly probable that serotonin may be found to have important relations to enzymic activities, for it has recently been reported to have antioxidant effects, especially in inhibiting the formation of lipid peroxidase in tissues (45).

The release of serotonin parallels that of histamine in certain ways. Both sero-

tonin and histamine are released from mast cells by histamine-releasing agents (493), both may be released from structures or cells within or associated with which mast cells are either very sparse or totally absent, and both serotonin and histamine may be released by the same or by various non-related agents. It has been suggested (474) and shown (493) that histamine-releasing agents, especially those that release histamine from mast cells, such as ovomucoid, compound 48/80 dextran, and extract of testis, disrupt the mast cells and also release both serotonin and histamine from these cells in rats. However, Brodie and co-workers, 1955, showed that reserpine readily releases serotonin deposited in the brain of mice and rabbits (122), and others of the same group (248, 333, 529) have verified and extended these findings.

It is apparent that the serotonin content of central nervous tissue is not related to its mast cell content since mast cells do not occur within the central nervous system of any species (474), and the histamine content of central nervous tissue is very low, "not exceeding a few μg/g tissue" (608), with only 0.05 μg/g in the spinal cord (615), while the serotonin content is relatively high in the brain of normal rabbits (0.55 μg/g) (77), 200 to 250 $\mu\mu$g/g wet weight in the brain of rats (611), and was increased enormously in dogs, at least "ten times the normal level", by intravenous injection of its precursor, 5-hydroxytryptophan (60 mg/k) (591), and up to 20 fold in rabbits (587) and in the brain and periphery of human patients (633).

Work with mast cell tumors in mice and dogs and with carcinoids (tumors derived from chromaffin cells of the gastrointestinal mucosa) presents sources of increased serotonin and, usually, of histamine. Transplantation of an ascitic form of solid mast cell tumor increased the total serotonin content about 14 times and the total histamine content about 22 times in mice; a transplantable mast cell tumor in dogs developed a marked increase in histamine but the serotonin content was not affected (536). It has also been pointed out that although chromaffinomas of the intestine "contain large amounts of serotonin" a few of these tumors may be found having only small amounts of histamine (536).

Although one can hardly suppress his curiosity, it is too early in the recognized life of serotonin as a potent edema-producing agent (493) to determine which of the various agents known to release serotonin also release histamine. It has, however, been stated that compound 48/80, dextran, ovomucoid, and extract of testes disrupt mast cells and release both serotonin and histamine from these cells, and that serotonin subcutaneously injected into rats' feet caused marked edema without damaging the mast cells (493).

Reserpine administered as a single large dose (5 mg/kg) to laboratory animals caused nearly complete release of serotonin from the brain, blood platelets, and intestinal tract (248). However, serotonin in the intestine is more resistant to

release by reserpine than that in the blood platelets or brain. Reserpine (0.015 mg/k) administered daily for 3 months caused a progressive decline of serotonin in the platelets and, to a less degree, in the brain, but failed to cause any significant change in the level of serotonin in the intestine of rabbits (248). Administration of 1.0 mg doses of reserpine daily for 10 days to 3 hypertensive people had a cumulative effect as shown by its causing a 95 per cent reduction in serotonin content of blood platelets. A progressive decline in serotonin content of platelets was observed in rabbits receiving 0.015 mg/kg daily, but serotonin levels in the brain were reduced to a lesser degree, while the serotonin level of the intestine was not significantly changed (248). It has also been pointed out that although reserpine readily releases serotonin from blood platelets of rabbits in vivo and in vitro, "neither histamine nor protein is liberated from platelets"; consequently, "no general change in permeability is involved" (529). This observation is partly supported by Humphrey and Jaques, 1956, who found that antigen-antibody combination and possibly several other agents release histamine and, presumably, serotonin from platelets without altering the form or structure of the platelets in any way detectable under a phase-contrast microscope (595).

Zucker and Borelli (644) found that serotonin preformed in blood platelets can be completely liberated "without disintegration, agglutination or cohesion" of the washed platelets as related to the process of blood clotting produced by a variety of factors. Bigelow (52) also reports the liberation of platelet serotonin without visible injury to the platelets. Other investigators report that intraperitoneal injection of reserpine phosphate caused release of platelet serotonin without disruption of the platelets (530). Plasma containing calcium appears to be essential for the release of either serotonin or histamine from blood platelets. Humphrey, 1956, using washed platelets from the buffy coat of centrifuged rabbit blood concentrated in "a suitable suspending medium without plasma", found that addition of the proteolytic enzyme trypsin released histamine from the platelets, but that no histamine was released when a histamine liberator, thalassin or compound 48/80, was added to the suspension. These results indicated to him that the presence of plasma is essential for release of histamine from rabbit platelets by histamine liberators (595). Later, employing a more decisive approach, Humphrey and Jaques, 1956, showed that not only plasma but also calcium is necessary for the release of either serotonin or histamine from rabbit platelets. When the washed platelets, prepared as in the previous experiments, were mixed with antibody (which had been purified by salt fractionation) followed by antigen, precipitate was formed in abundance, but neither serotonin nor histamine was released. When plasma and calcium were incorporated in the suspension of platelets the addition of antigen and antibody released both serotonin and histamine (595).

The use of compound 48/80 to liberate histamine from platelets invites discussion, for compound 48/80 is considered by certain investigators, if not generally, as being a "fairly specific histamine liberator" for mast cells (474) and is held by Perry, 1955, as being "completely inactive" in releasing histamine from platelets (595). Perry, 1956, also states that the antigen-antibody complex is known to release histamine from platelets regularly and he goes even further by suggesting that investigators consider compound 48/80 specific for release of histamine from mast cells (595).

The amount of serotonin in normal blood has been determined for man and certain mammals and is expressed in terms of gammas of serotonin in one milliliter of whole blood: For the rabbit, 4.00 γ/ml; beef, 1.7; dog, 0.25; rat, 0.20; guinea pig, 0.15; and man 0.10 (590).

Inhibition of Serotonin

There is a surprisingly large number and range of agents which may destroy serotonin or antagonize certain of its actions. The mention of a few of these agents and their mode of action may reflect some light on the relationship of serotonin to capillary permeability changes. However, few of these agents appear to be specific for serotonin, as has been repeatedly pointed out (483), and others exhibit preferential antagonism of certain activities of serotonin. A good example of this relationship is given by Woolley (632) who emphatically points out that many antagonists of the spastogenic effects of serotonin on smooth muscle do not have any mental effects. Cerletti (94) also cautions that many antagonists of the spastogenic effect of serotonin on excised smooth muscle are practically ineffective in living animals. Welsh (613) suggests that serotonin is essential in certain invertebrates to mediate nerve action and that nerve action is abolished by those agents which block the action of serotonin.

Free serotonin is rapidly degradated by one or more amine oxidases. This rapid utilization may help to explain the absence of serotonin in many structures, especially in those structures in which its precursor, 5-hydroxytryptophan or tryptophan is present in the absence of serotonin. Other investigators (360) suggest that serotonin intravenously injected into human subjects is trapped, transported, and released by blood platelets and that it may be absorbed and later slowly released by tissues.

The fact that 5 normal dogs after receiving serotonin creatinine sulfate (10.0 μg/kg/min) by intravenous infusion for 3 hours showed no effects of the serotonin, such as hypotension and bradycardia, supports the tenet plasma serotonin is rapidly metabolized, probably by monoamine oxidase, as in the brain (77) or in the oxidative deamination of parenterally administered serotonin, to form an intermediate of 5-hydroxyindoleacetic acid (591). Earlier works merely indicate that serotonin is rapidly inactivated by amine oxidase (193).

Alteration in the functional activity of serotonin in the brain may result in psychiatric and behavioral changes in laboratory animals and man (632). Likewise, Gaddum, 1953, has shown that an excess of serotonin will specifically inhibit its own action. For example, an excess of serotonin produces insensitivity of the uterus of rats to smaller although ordinarily physiologically active amounts of this hormone (632).

Antihistaminic Drugs

Several antihistaminics, including benadryl, phenergan, and thenfadil, reduced the pressor but not the depressor action of serotonin in dogs (423), but were more effective on the response to histamine in cats (424). Diphenhydramine and tripelennamine blocked the induction of spastogenic action of serotonin, as well as the effects of histamine, in preparations of isolated guinea pig ileum (462). Erspamer (168) found that a rather impressive number of antihistaminic agents exert varying degrees of inhibition of the uterus-stimulating and antidiurectic effects of serotonin ("enteramine"). He states that pyribenzamine seemed to be the most active; benadryl, neohetramine, and phenergan, next in activity; antistin, the least active of the antihistaminics he tested. From these experiments he (168) concluded that the inhibiting action of these agents was in many respects inferior to that of certain sympatholytic drugs, such as dibenamine and dihydroergotamine, and that the effects of the antihistaminics on serotonin were not related to their effects on histamine, the autonomic nervous system, or directly on smooth muscle.

It has been suggested that the antagonistic action of dibenamine on the antidiuretic effects of serotonin and the inability of dibenamine to abolish or reverse the moderate and inconstant pressor effect of serotonin on anesthetized dogs result from competition between serotonin and dibenamine for an existing substrate (170).

Analogs and Antimetabolites

A number of antimetabolites which are structural analogs of serotonin, sympathomimetic, and sympatholytic drugs (169) antagonize serotonin, and a surprisingly large number of the antimetabolites inhibit or block adrenergic and/or antidiuretic action of this hormone (169, 632, 634) The characteristic effect of analogs is the result of their competing with serotonin for its normal receptor (632, 633), but they may have multiple effects in cells (452). 1-benzyl-1, 25-dimethylserotonin (BAS), a specific antimetabolite of serotonin, has the special advantage of blocking certain of the peripheral effects of this hormone and at the same time favoring the increase of serotonin in the brain in response to administration of 5-hydroxytryptophan in mice (638). Another water-soluble, rather active antimetabolite of serotonin, 2,5-dimethylserotonin, effectively antagonized the spastogenic action on isolated uterus and artery rings and the pressor action of

serotonin in dogs (525). Woolley (632) holds that there are 3 principal classes of the naturally occurring antimetabolites of serotonin. The harmula alkaloids, represented by harmine; a second class represented by reserpine and yohimbine; and the ergot alkaloids, which include lysergic acid diethylamide (LSD) and ergotamine.

Most of the known antimetabolites are active only on isolated preparations of organs or tissues and either are incapable of antagonizing serotonin in living animals or have a low potency (637). However, some of the methylserotonins, especially 2,5-dimethyl serotonin, are potent antiserotonins in vivo in dogs and on arteries and uteri in vitro (637).

Reserpine

Reserpine (Rau-sed, Serpasil), one of the 14 alkaloids obtained from Rauwolfia serpentina (426), apparently has two effects which inhibit the action of serotonin. It depletes by releasing the stored, and blocks storage (78, 333) of this hormone. Reserpine is thought to produce tranquility by blocking the binding sites of serotonin. Therefore it is concluded that free serotonin is necessary for the mediation of the sedative effect of reserpine (132). Reserpine releases serotonin stored in at least 17 sites in the brain of the dog (591), in the brain of other species, in the intestine, blood platelets, and elsewhere (248, 529, 530). Reserpine prevents storage of serotonin by incapacitation or blocking of the serotonin-binding sites in the brain and blood platelets (132, 248, 591) and causes blood platelets to lose their store of serotonin by disruption of the platelets (333, 530). It has been suggested that reserpine lowers blood pressure and body temperature through its central action in relation to the concentration of serotonin, rather than of reserpine, in the brain (132). However, it should be noted that the mode of action of reserpine is not through hypnosis, for it stimulates activity of the activating system and "evokes the alert electrographic pattern" (477), and that phenidylate (ritalin) is strongly analeptic in cases of reserpine-induced depression (188).

Premedication with reserpine prevented the neurotropic effects of intra-arterially injected serotonin in dogs and prevented intracerebral edema following injection of serotonin into the cerebrum of mice (82). Intravenous injection of reserpine has a hypotensive effect. The work of Cronheim and Grouzis (122) shows that in urethane-anesthetized dogs, premedicated by intravenous administration of reserpine (1 mg/kg) 24 hours before infusion of serotonin creatinine sulfate (10.0 mg/kg/min) at the rate of 0.5 ml/minute, resulted in a fall of about 62 (from about 108) to 46 mm Hg in blood pressure and about 25 heart beats per minute. Bilateral vagotomy showed that integrity of the vagus nerves was not essential in this reaction. Since serotonin infusion had no observable effect on 5 normal dogs, these investigators hold that the supposed depressant effect of serotonin on the heart

and blood pressure should be attributed to the direct effects of the reserpine which were made possible by the presence of the infused, free serotonin.

It has been suggested that the sedative and cardiovascular effects of reserpine are dependent upon the presence of free serotonin (122) and that the pharmacologic manifestation of reserpine on the brain may be either a consequence of, or merely concurrent with, changes in the brain serotonin content (77). Reserpine is one of the most potent releasers of serotonin; yohimbine, harmine, and certain other naturally occurring structural analogs of serotonin antagonize the action of this hormone on smooth muscle by competition (632).

Lysergic Acid Diethylamide

Cerletti (94) shows that there is a formidable number of derivatives and compounds of lysergic acid which show activities similar, although varying in degree, to lysergic acid diethylamide (LSD, LSD-25), other compounds which are comparatively inactive, and still others which are isomeric forms and, consequently, may occur in a variety of steric configurations. The result is that there is often confusion of terminology and of experimental and clinical results obtained. The designation most often encountered in the literature is "lysergic acid diethylamide (LSD)" or simply "lysergic acid" or LSD and, occasionally, LSD-25. Cerletti (94) employs "LSD" as a code, or abbreviation, for lysergic acid diethylamide in the title of his work.

The brom derivative of LSD (BOL, 2-brom-d-lysergic acid diethylamide) antagonized the stimulant effects of serotonin on smooth muscle in vitro very effectively and, in larger doses, suppressed serotonin-induced pressor-depressor responses in rats, but in general its systemic effects on dogs and cats were not so effective (500).

LSD, a hallucinagenic indole (587, 591) and naturally occurring analog of serotonin (632), has both serotonin-like and antiserotonin properties (632). LSD antagonizes the effects of serotonin in smooth muscle (632) and of administered serotonin on the central brain (77), and is used in neuropsychiatry to produce experimental mental states resembling schizophrenia (dementia praecox) (105, 146).

It appears that lysergic acid diethylamide is specific in its inhibition of serotonin (189). Although Brodie, et al., 1955, state that the results of their work indicate that LSD blocks serotonin, Costa, 1956, reports that weak serotonin-produced uterine contractions are increased, rather than reduced or suppressed, by LSD, but that reserpine inhibited these contractions (260). LSD strongly antagonizes the vasoconstrictive effect of serotonin; as little as 1.0 μg of LSD inhibited the action of 2.0 to 10.0 μg of serotonin on vessels in the isolated perfused kidney of rats, but it increased the vasoconstrictive effect of epinephrine (94). This series

of experiments shows that although LSD inhibits the vasoconstrictive action of serotonin it enhances this property in epinephrine.

Serotonin caused melanophores in the skin of a fish, Lebistes reticulatus, to contract and become spheroidal, but addition of LSD (25 μg/ml) greatly expanded the melanophores and caused them to send out multiple processes (94).

The action of LSD apparently may be contingent upon multiple factors or conditions, for Marrazzi, 1957, states that LSD and serotonin, as well as several other drugs, produced inhibition of cerebral synapses in cats (77). LSD-25 has a high potency in producing symptoms simulating certain of the aspects of naturally occurring schizophrenia (367). It is also interesting in this connection that LSD produced reduction in cerebral cortical adenosine triphosphate, while chlorpromazine produced an increase in this energy-rich phosphate in the brain, especially in the hypothalamic tissue (260). Tolerance to LSD-25 may develop extraordinarily rapidly, especially if heavy daily dosage (100.0 μg) is given to human patients. Thus, LSD-25 becomes "its own best antidote, or 'autodote' " (1).

The turnover of LSD is apparently very rapid, for Cerletti (94), by injecting mice intravenously with 35 mg/kg (total dose about 700.0 μg) of LSD-25 and checking various tissues at 10-minute intervals for serotonin inhibition, determined that during the first two hours of the experiment the half life time of the LSD-25 was 37 minutes. This is much more rapid than the turnover of labeled serotonin, which had a half life of 1 to 2 hours in the brain and 10 to 12 hours in the intestine (591). The foregoing experiments indicate that the production of LSD is at least twice as rapid as that of serotonin.

LSD is rapidly eliminated from the tissues and blood of an animal's body by being excreted chiefly in the bile, but small amounts (about 2%) may be eliminated in the urine or feces or by the lungs (94).

Miscellaneous Agents

Among the various agents which antagonize the action of serotonin may be mentioned the following substances: Yohimbine particularly and many of the ergot alkaloids are antagonistic to serotonin (170, 423, 524) as an antimetabolite of serotonin (632). Certain structural analogs of serotonin are antagonistic (632, 635). Monoamine oxidase, which in turn is inhibited by iproniazid, destroys serotonin rapidly (100). Amine oxidase rapidly inactivates serotonin (193), and probably many other substances also antagonize the action of this hormone. Also, Blaschko and Hellmann (61) found that pieces of tissues containing amine oxidase, including rat brain, guinea pig diaphragm, renal cortex (especially the proximal convoluted tubules) and liver, developed a precipitate which stained them dark brown when serotonin or tryptamine was added and the cultures incubated.

Local anesthetic drugs antagonize the stimulating effect of serotonin on isolated

cardiac and smooth muscle, including the auricles of rabbits, ileum of rabbits and guinea pigs, tracheae of cats, and uterus of rats (535). Gaddum and co-workers, 1954, found that in guinea pigs cocain effectively inhibited serotonin-produced contraction of the ileum but did not affect uterine contraction in rats (94).

Deficiency of pyridoxyal phosphate, a derivative of vitamin B_6, may inhibit the formation of both serotonin and histamine since this substance plays an important part in all amino acid decarboxylations (591). Serotonin is formed by decarboxylation of 5-hydroxytryptophan by the enzyme 5-hydroxytryptophan decarboxylase (502, 334) and histamine is likewise formed from histidine by histidine decarboxylase (431, 504, 615). Chickens maintained from hatching to 6 weeks of age on a diet low (about 1–2 % of optimum) in pyridoxine had an average of about 25.0 per cent of the normal amount of serotonin in the brain, intestine, blood, and liver (591).

Distribution of Serotonin

The significance of the distribution of serotonin in the body is more closely related to its potential production within tissues than to the actual occurrence of the hormone. Apparently, the presence in a structure of 5-hydroxy-L-tryptophan (192) or of the amino acid tryptophan (587), may be far more important than the presence of serotonin itself. There are at least 2 valid reasons for offering this suggestion. Free 5-hydroxytryptamine is rapidly destroyed, apparently by metabolism catalyzed by monoamine oxidase (100, 591) and possibly by other agents (193, 591). Serotonin is made available at local sites chiefly by synthesis from the amino acid tryptophan, via 5-hydroxytryptophan (579, 588, 591). The 5-hydroxytryptophan is converted into 5-hydroxytryptamine (serotonin) by action of a specific enzyme which is generally held to be 5-hydroxytryptophan decarboxylase (334, 587, 588, 591).

Serotonin, often in the form of a precursor (172), has been found widely distributed in nearly all of the structures, tissues, or cells in mammals and man, in at least certain structures in invertebrates (170, 171, 588), and in plants and bacteria (591). Variations in rate and quantity of serotonin production have been found in various structures and in the same structure at different times in the same inbred animals (591). For instance, it has been shown that in 17 regions of the brain of the dog the serotonin content varied from 0.17 to 2.1 μg/g (591). Another group of investigators (9) report finding daily changes in serotonin content of the brain and slightly higher values in the brain of female than of male ZBC mice.

Serotonin was isolated and identified in beef blood plasma (461). Probably for this reason blood plasma was formerly believed to be the source of serotonin (339), but it is now known to be widely distributed (591), while blood platelets are considered the chief source of serum serotonin (457, 530, 646). Since serotonin is

readily metabolized (100, 579, 591), its absence in a structure, tissue, or cell is insignificant, especially if its immediate precursor, 5-hydroxytryptophan, and the enzymes which synthesize serotonin from this substance are present. Most animal tissues contain "huge quantities" of an enzyme which "is highly specific for 5-hydroxy-L-tryptophan" decarboxylating it to serotonin (591), but this decarboxylase has no action on the amino acid tryptophan (591).

Relation of Synthesis to Distribution

The resistance of the blood-brain barrier to absorption of serotonin by the brain (77, 591), its ready permeability to orally administered 5-hydroxytryptophan (78, 587, 591), and the resulting increase in brain serotonin (78, 587) show conclusively that the distribution of serotonin may be strikingly related to the site of its synthesis.

Serotonin is formed in mast cells of rats (43, 334) and in certain structures in the body by the enzyme 5-hydroxytryptophan decarboxylase from 5-hydroxytryptophan (207, 334, 587, 589, 591) and probably by all somatic cells by converting absorbed 5-hydroxytryptophan, or tryptophan via 5-hydroxytryptophan (587), to serotonin (77, 213, 587), especially following administration of 5-hydroxytryptophan (77, 589). Activity of this serotonin-forming enzyme, 5-hydroxytryptophan decarboxylase, is strong in the gastrointestinal tract, kidneys, and liver (207, 589), but it is feeble in bone marrow, blood platelets, and spleen; it is fairly strnog in certain areas of the brain and sympathetic ganglia in mammals (207). Sympathetic ganglia in situ and homogenates of the excised ganglia of normal mammals have been shown to have a relatively high capacity for synthesizing serotonin, but all attempts to find free or preformed serotonin in these structures were unsuccessful (206). Certain other structures, notably the kidney of hogs, which is a commercial source of this enzyme, have been found to contain little or no serotonin, but to be relatively rich in 5-hydroxytryptophan decarboxylase activity (588). 5-hydroxytryptophan decarboxylase "occurs exclusively in the nonparticulate fraction of ultracentrifuged cells" (207). The distribution of the enzyme need not parallel that of extractable serotonin, but it may do so (207). The work of Walaszek and Abood (611) showed that most of the serotonin occurring in the brain of normal rats is bound to the mitochondria, but that the binding of serotonin to mitochondria is prevented by phenylether and to some extent by dinitrophenol.

When 5-hydroxytryptophan was administered to normal rabbits, serotonin not only increased in the structures where it usually occurs, such as the brain, blood platelets, and intestine, but also in structures where it is not usually found, such as the heart, kidneys, liver, and uterus (587). Similar effects were obtained by administration of this substrate labelled with C^{14} to rabbits, in which the serotonin in the depots of the body became so highly labelled as to suggest an increase in serotonin within the structures (587). Since it is held that administra-

tion of 5-hydroxytryptophan is followed by formation of serotonin in all tissues of the body (77), it apparently would be logical to assume that those structures in which this hormone is not usually found, such as the heart, kidneys, liver, and uterus (587), metabolize serotonin rapidly, as suggested by Brodie, 1957 (632), and consequently would be expected to have a fairly high activity of 5-hydroxytryptophan decarboxylase, as has been shown is true for the kidneys and liver (207, 589, 591). A more nearly direct approach is shown by the work of Udenfriend and Titus (589) in which serotonin was labelled by administering C^{14}-tryptophan. Their results show that the half life of the resulting C^{14}-labelled serotonin was less than 2 days in the platelets and much less than 2 days in the stomach and intestine. Later work indicates that the half life of serotonin in the brain is only 1 to 2 hours; in the intestine it is about 10 to 12 hours (591).

Recorded Sites of Occurrence

In reviewing the literature on the distribution of serotonin one can hardly avoid often being in doubt of the validity of the investigator's claim to have differentiated between the occurrence of serotonin and of histamine since similar tests are often employed to demonstrate the presence of both substances. The biological methods commonly employed for determining the presence or absence of serotonin in a tissue are usually unavoidably inadequate, while the quantitative procedures are, for the most part, so hampered by the shortcomings of the qualitative methods that the final results have little other than relative value. The first difficulty encountered is that, apparently as with histamine, injury to a tissue may result in a loss of serotonin comparable to the nature and extent the tissue is injured. Thus, it has been shown in iproniazid-treated rabbits that when brain or intestine, which are rich in monoamine oxidase activity, was tested it was found that the serotonin content was rapidly decreased following homogenization of the tissue (269). Curiously enough, it has also been found that if mice are pretreated with iproniazid, which has been shown to favor serotonin production by inhibiting monoamine oxidase activity in the metabolism of serotonin (591), no effect on the rate of serotonin metabolism by the whole animal could be detected. However, homogenized tissues from these mice failed to destroy serotonin, while the monoamine oxidase activity in slices of the tissues was not inhibited (591). Since it has been shown that in the brain, iproniazid inhibits activity of monoamine oxidase, which apparently catalizes the metabolism of serotonin, it is surprising that the monoamine oxidase in the homogenized brain or intestine was unable to destroy serotonin but was not inhibited in slices of the same tissues. A plausible explanation of these results is that although in vivo effects of iproniazid in inhibiting activity of monoamine oxidase can readily be demonstrated, it is not as effective as might be indicated by data obtained by use of homogenates would imply (591).

Serotonin has a fairly wide occurrence in the structures of man and individuals

of several species of mammals and lower forms. There is also the possibility that serotonin or its precursor forms may be found widely distributed in lower vertebrates, invertebrates, and various forms of plant and animal life.

The gastrointestine, particularly the argentaffine cells (171), blood platelets (122), mast cells of rats (43, 334, 493), and certain areas of the brain (591) contain considerable quantities of serotonin. Serotonin also occurs in the lungs (591), in normal urine (585), occasionally in the spleen (423) and blood plasma, where its source is the platelets (457, 646), in sympathetic ganglia (206), in the posterior salivary glands of the common octopus, but not in Octopus macropus (172), in the skin of a toad, Discoglossus pictus (172), and in the venom of another toad, Bufo marinus (588). The presence of 5-hydroxyindole compounds has been reported in plants and in bacteria (591).

The inability of investigators to find serotonin in a particular organism or tissue may be related to activity of antagonistic agents rather than to actual absence, as is suggested by the reported half life of labelled serotonin and one of its antagonists. The half life of lysergic acid diethylamide is about 37 minutes (94) and that of serotonin in the brain is about 1 to 2 hours, while the half life of serotonin in the intestine is at least 10 to 12 hours (591). This difference in half life of serotonin in two structures, each of which normally has a high serotonin content (94, 591, 632), is interpreted as indicating that serotonin is apparently formed more rapidly in the brain than in the intestine (591). Whether this rapid increase in production of serotonin in the brain is a response to the rapid destruction of this hormone or the rapid destruction is related to the rapid production apparently is an unanswered question.

Stomach and Intestine

The largest amount of serotonin found in any part of the body occurs in the gastrointestine, but its function is not understood (591). Neither, apparently, is its source in the gastrointestine definitely known. Erspamer, 1953, found that the serotonin content varied greatly in different regions of the intestine in different individuals of a single species as well as in different species of mammals and other vertebrates (423). Some investigators (171, 172) apparently believed that from a physiological, if not quantitative, point of view the argentaffine cells, or the mucosa (269), in the stomach and intestine are the most important source of gastrointestinal serotonin. The argentaffine cells of the stomach and intestine occur singly and are scattered between the zymogenic cells and the basement membrane and rarely occur in the villi but are scattered singly between the cells lining the crypts of Lieberkühn. Argentaffine cells are never abundant in the small intestine, but are most numerous in the vermiform appendix in man (374). For these reasons it seems strange indeed that these argentaffine cells should supply

enough serotonin to warrant the conclusion that the gastrointestine is the richest source of this hormone in the body (591). Likewise, there appears to be no explanation for serotonin in the intestine being more resistant to release by reserpine than that in the blood platelets or brain of rabbits (248).

The human appendix has the densest population of argentaffine cells found in the gastrointestine and these cells average 5 to 10 in each crypt of Lieberkühn (374). Since carcinoids arise from argentaffine (Kultschitzky, enterochromaffine) cells (626) it is not surprising that some of these characteristically yellowish tumors should have an unusually high serotonin content, particularly among those arising in the veriform appendix. Langemann and Kägi (336), Udenfriend, 1957 (591), and others call attention to the fact that patients with malignant carcinoid have hyperserotonemia. However, Udenfriend also points out that not all patients with carcinoid have hyperserotonemia, for these individuals may have a blood serotonin level ranging from small to excessive amounts (591). A carcinoid found in the appendix of a woman had the extremely high serotonin content of 952 μg/g of fresh tissue; while normal appendiceal tissue had a value of only 1.0 μg/g. It was estimated that the capacity of this carcinoid for forming serotonin was about 35 times that of the normal human appendix (208).

Central Nervous System

Although much attention has been paid to the serotonin content of the brain (94, 632), the total amount of serotonin in the brain is believed to be only "a fraction of a per cent" of that in the body (591). Nevertheless, because of its neuropharmacological implications, probably more work has been done on relations of serotonin to the brain than to the remainder of the entire body.

It has been shown, by employing a method of testing based on fluorescence, that the serotonin content of different areas in the brain of the dog varies considerably. Of the 22 morphophysiological areas tested in these dogs, no serotonin could be detected in 5; the serotonin content in the 17 other areas varied from 0.09 μg/g (cerebellum) to 2.1 μg/g (amygdala) (591). These results indicate the high degree of inaccuracy which may be expected in assays of samples of brain taken at random or from unidentified areas of the brain of various animals or man.

Administration of the amine oxidase inhibitor, iproniazid (50 mg/k), to rats or rabbits produces a large increase of serotonin in the brain in a short time, since metabolism of the serotonin is inhibited as a result of the inactivation of monoamine oxidase. However, it was found in determining the serotonin values in the brain of these animals that in intact slices of the tissues, monoamine oxidase was not inhibited, but that this enzyme was totally inhibited in the same tissue after it had been homogenized (591).

It was found by differential centrifugation that 60 to 75 per cent of all the

serotonin occurring in the brain of the rat is bound to mitochondria and that the remaining 25 to 40 per cent is scattered among the supernatant fractions and nuclear debris (611). However, other investigators report that differential centrifugation of homogenate of rabbit brain failed to show that serotonin has a particular affinity for any of the cell fractions (269).

Both of these observations may be correct for the particular species being used, or unrecognized technical or other factors may have played a significant part in the results obtained. For instance, it has been found that the serotonin content of tissues in general (269), specifically of rabbit brain (269), rapidly diminishes after homogenization. Also, it has been found that phenylethyl prevents binding of serotonin to intact mitochondria (611), that monoamine oxidase rapidly metabolizes this hormone (591), and that there are other agents which rapidly deplete tissue serotonin (269, 591, 611, 632). A point to be remembered is that probably none of the serotonin-blocking agents is specific for serotonin (483).

Blood Platelets

It has been pointed out that little is known about either the amount or distribution of serotonin in the blood (591), but Rand and Reid (457) and Zucker and Rapport (646) hold that the blood platelet is the source of plasma serotonin. They estimated the amount of serotonin in platelets as being 1×10^{-9} μg/platelet for man and 1.7×10^{-9} μg/platelet for cattle. Rand and Reid (646) found, by differential centrifugation of citrated beef blood, that an extract from plasma containing platelets was active on isolated rat uterus or guinea pig intestine, but that when the platelets were removed before extraction of the plasma the extract was practically inactive whether or not it contained erythrocytes.

Other investigators (52, 423) have shown that removal of the platelets from normal blood serum clearly reduced its vasoconstrictor potency. The presence of heparin in platelet-rich plasma inhibited its vasoconstrictor activity, but after fragmenting the platelets by freezing to -70 C and thawing 3 times, the vasoconstrictor activity of the heparinized platelet-rich plasma was greatly enhanced (52). Thrombocytopenia is commonly accompanied by reduced plasma serotonin activity (52, 423). In a group of 9 thrombocytopenic subjects having a platelet count less than 100,000/ml all had diminished plasma serotonin activity (52); 3 thrombocythemic patients with 2–4 million platelets/ml also had decreased serotonin activity (52). These 3 patients had multiple complications which might account for the reduction in serotonin activity. The results of these experiments and observations convinced the investigators that the platelet is the source of serum serotonin but did not eliminate the possibility of other factors being involved (52). This adds interest to the suggestion that the principle found in platelets and blood serum causes increased blood pressure in cats by provoking a dis-

charge of epinephrine (520), for it is held that usually serotonin is primarily a depressor in cats (422).

Blood platelets from rabbits and mice apparently contain appreciable quantities of both serotonin (122, 248, 529, 530) and histamine (60, 595). However, as stated by Dale, 1956, blood platelets of the horse contain no histamine at all (60).

There appears to be some difference in opinions concerning the question of how serotonin gets into the blood platelets. Two investigators (645) found that human and canine platelets in 0.2 to 4.0 μg/ml concentration of synthetic serotonin for 5 or 10 minutes at room temperature absorbed some of the serotonin. Experiments in which platelet-rich canine or human plasma or platelets in whole blood were used produced variable, mostly negative, results due to disappearance of the serotonin in the cultures. They (645) found that washing the platelets prevented disappearance of the serotonin in vitro in 4 of 9 experiments using canine platelets and in all 5 using washed human platelets. These investigators (645) also hold that most, if not all, of the serotonin in human platelet-rich plasma could be recovered from the platelets. They apparently correlated the ability, or inability, of platelets to absorb serotonin with morphological appearance rather than with the possible presence or absence of enzymes, such as monoamine oxidase, which is credited with the ability to catalyze the metabolism of free serotonin rapidly (423, 591).

Administration of C^{14}-labelled tryptophan, which was incorporated into the serotonin, indicated that 5-hydroxytryptamine is stored in the platelet during its formation and that the serotonin remains in an inactive state within the platelet until it disintegrates and releases the hormone into the plasma where it is rapidly inactivated (100, 590). It is reported that the amount and rate of serotonin released from blood platelets is related to the extent and rate of disintegration of the platelets (230). However, other investigators observed complete release of platelet serotonin without detectable alteration in the form or structure of the corpuscles (595) and without causing the platelets to cohere, agglutinate, or disintegrate (644) or show any injury (52). Also, washing blood platelets with an isotonic salt solution does not free the contained serotonin (78). However, it is held that the blood platelet does not form serotonin from 5-hydroxytryptophan, but that the serotonin is synthesized at the site and stored during formation of the platelet (590). Thus, by inference, it appears that the actual synthesis of platelet serotonin normally takes place in precursor cells of the platelets in bone marrow, which would probably be the megakaryocytes. This is very interesting since rabbit platelets, which contain appreciable amounts of both serotonin and histamine, decarboxylate C^{14}-histamine in stable condition (506). Thus, in latitude of distribution, serotonin shows a strong tendency to parallel histamine.

The serotonin of blood platelets apparently is more sensitive to chronic administration of reserpine than the brain and much more sensitive than the intestine in

rabbits (248). A single large dose of reserpine (5.0 mg/k) caused release of nearly all of the serotonin in blood platelets, brain, and intestine in laboratory animals; chronic daily administration of light doses (1.0 mg/k) over a period of 10 days freed about 95 per cent of the platelet serotonin in 3 hypertensive patients (248). Daily administration of reserpine (0.015 mg/k) caused progressive reduction of platelet serotonin in rabbits (248).

Pharmacophysiologic Activity

Pharmacologically, or in vitro, serotonin has a generally spastogenic effect on smooth muscle (77, 94, 193, 424, 462, 483, 520, 528, 535, 591, 633). The spastogenic effect on excised smooth muscle is further discussed under tests for serotonin and under serotonin compared with histamine.

The primary physiological, or in vivo, effect of serotonin, either endogenous or exogenous, is that of a pressor agent (171, 172, 213, 422, 461, 466, 520, 635). It appears, in general, that the pressor action of serotonin is directly the result of its spastogenic effect on the muscular wall of arteries, for this pressor effect was abolished by feeding dogs an antiserotonin, 2-methyl-3-ethyl-5-nitroindole (a structural analog of serotonin), before intravenously injecting the serotonin (635). However, there is the possibility that neural intervention may be involved, at least in certain instances. This idea of neural intervention is supported by the finding that intravascular injection of serotonin caused nonmedullated afferent vagal nerve fibers to discharge, apparently by stimulating the thoracic and/or abdominal origins of these fibers (141). Serotonin is reported as being a very strong synaptic inhibitor, is 25 to 30 times as potent as adrenalin, and may eventually be shown to be the chief neurohumoral inhibitor of synaptic transmission (367). So important is serotonin in mental activity that it has been suggested that upset in the regulation of this amine may be responsible for illness arising in the brain (367).

Variable and Various Effects

Administration of serotonin is often followed by various, sometimes unexpected, results on structures containing smooth muscle. In general this may be partly explained by the fact that the dosage of serotonin alters the neurotropic effect of this hormone so that instead of a simple incremental change a biphasic effect is produced. For example, injection of low dosage of serotonin into the internal carotid artery causes spastic paralysis of a transient nature, while high dosage produces flaccid paralysis without causing the usual cerebral edema, and both types of paralysis are inhibited by reserpine (82). This neural relation is somewhat furthered by Page (423) who favors the tenet that serotonin plays a part in nerve metabolism, and he suggests that this hormone may have an important role in

the mechanism of traumatic and hemorrhagic shock and in myocardial infarction. Welsh, 1948, considering the effect of serotonin on the heart of Venus mercenaria in being able practically to duplicate the effects produced by stimulating the regulatory nerves, suggests that one of the normal functions of this hormone may be to regulate the excitatory nerves of this marine clam's heart (423).

Page and McCubbin (424) point out that the response of arterial pressure in man and animals to serotonin results from several variables within the individual and that various species may respond differently. Hypertensive people and dogs have similar responses to serotonin, but their responses differ from those of rabbits and cats. In dogs serotonin is primarily a pressor, but in cats it is primarily a depressant (422). Another point is made by various investigators (426) who hold that whether serotonin dilates or constricts peripheral blood vessels depends to a great extend upon dosage: minute doses produce vasodilation; larger doses produce vasoconstriction.

Serotonin affects a rather wide range of physiological and other processes. Pretreatment with this hormone significantly increased the incidence of survival in rats subjected to lethal dosage of X rays (228). There is evidence that serotonin plays a part in regulating the excretion of water and electrolytes, particularly since it has been shown that increased serotonin decreased excretion of sodium in dogs (57). Serotonin has been shown to inhibit the uptake of endogenous oxygen in vitro by brain homogenates from iproniazid-treated mice (100), to play an important part in regulating blood pressure and temperature (132) and to mediate the actions of reserpine (77, 132, 591, 632). This hormone also increases epinephrine in cats (466).

Serotonin creatinine sulfate (SCS, 10–20 μg) invariably produced a fall in both cortical oxygen tension and in systemic blood pressure in cats, although it is also stated that this hormone is a potent stimulant of smooth muscle in peripheral blood vessels; 5.0 to 10.0 μg of SCS depressed electrically evoked potentials from the cerebral cortex (139). Intravenous injection of SCS produced immediate hemostasis in peripheral wounds in experimental animals and had similar effects on a group of eviscerated and on several heparinized rats. This hemostasis was of short duration but could be prolonged by reinjection of SCS. Instead of SCS being antagonistic to histamine, the toxicity of the two drugs was found to be additive (114).

Vasomotor Relations

The earlier work with serotonin, as well as most of that which has been recorded to date, indicates that the primary relation of serotonin to the blood vascular system is that of a pressor agent. However, some investigators hold that under certain conditions serotonin causes reduction in blood pressure. Thus, it is very

difficult to evaluate the vasomotor effects of serotonin, for both pressor and depressant effects are recognized in the seemingly controversial literature. The entire situation when summed up generally indicates that a preponderance of investigators and writers consider serotonin as being primarily a pressor agent, but they may also concede a certain extent of depressive action. At least 2 investigators point out that the physiological intervention and significance of serotonin in local vasoconstriction in other than intrarenal vessels have not been proved satisfactorily (171). Other investigators suggest that serotonin is, under certain conditions at least, an edema-producing agent (493). Another investigator was unable to find any direct correlation between "increased capillary fragility" and low level of serum serotonin, although he observed that these two conditions were often associated in man (52).

Pressor Effects

Most of the numerous papers, notes, and abstracts leave the reviewers no occasion to doubt that the investigator in each instance holds that the substance he was using, which he believed was serotonin, is a vasoconstrictor, or pressor, agent. Others, however, intimate that dosage determines whether serotonin is a vasoconstrictor or a vasodilator. Certain investigators hold that serotonin causes increased capillary permeability; others hold that this hormone, when freed by histamine-releasing substances, including dextran, compound 48/80, and ovomucin, which damage mast cells, is the agent which produced edema in rats (493). However, it is stated that this edema is mediated by the combination of serotonin and histamine or of closely related substances (493).

Serotonin powerfully constricted coronary and carotid arteries in swine (542), had an initially variable effect on the systemic arteries, but always reduced the mean systemic arterial pressure after about 3 minutes of continuous infusion (20–150 μg/kg/min) in dogs. In 11 experiments under these conditions, the mean pulmonary pressure increased 300 per cent, but the mean systemic arterial pressure decreased 28 per cent, while the cardiac output rose 60 per cent in the dogs (494). The pressor action of 5-hydroxytryptamine, when assayed in dogs, is 3 times as potent as 7-hydroxytryptamine (422). It was found that serotonin (2.0–8.0 μg/kg, intravenously) is at least 10 times as potent in stimulating respiration in dogs as tryptamine (142) and that it is a pressor of both systemic and pulmonary arterioles (466) in dogs.

Hypotensive Effects

Although serotonin is preeminently a pressor agent it may cause variously reduced blood pressure. Intravenous injection of 10 to 200 μg of serotonin caused successively initial fall and a rise followed by a more prolonged fall in systemic

arterial pressure in chloralosed cats. This effect was not altered by atropine, spinal section, or vagotomy (465). Silva (531) reports only hypotensive effects of intravenous injection of serotonin in toads.

Intravenous injection of 50 to 100 μg/kg of serotonin always caused an abrupt fall in blood pressure, respiratory arrest, and other symptoms in cats. Ganglionic block reversed the blood pressure response but prolonged the period of respiratory arrest. Further work on these cats indicated that in this animal serotonin produced a von Bezold-Jarisch reflex by affecting the peripheral autonomic sensory endings (508). Other investigators obtained similar results in chloralosed cats by rapid venous injection of 5-hydroxytryptamine creatinine sulfate, but in addition to the profound reflex cardiopulmonary change, which included the Bezold-Jarish reflex, pulmonary vasoconstriction, as indicated by increased right ventricular pressure and bronchoconstriction, was noted (111). It has also been found that small amounts (2.0–10.0 μg) of serotonin injected into the region of the carotid sinus produced a fall in blood pressure and an increase in respiration, which was usually preceded by apnea of short duration, in cats. Section of the nerve to the sinus abolished both the vascular and respiratory responses, but apnea remained. Similar injections into the regions of the aortic bodies had parallel effects on the vascular and respiratory systems which, likewise, were abolished by vagotomy. These responses to the local administration of serotonin are explained by the investigators in terms of the respiratory stimulation being due to chemoreceptors and the fall in blood pressure to the baroreceptors (211).

Antidiuretic Activity

It is generally conceded that serotonin inhibits diuresis in man, rats, and various other mammals (173, 175); however, investigators are not in accord as to its mode of action. Two main approaches to an explanation of the mode of action of serotonin in effecting antidiuresis are in vogue. Briefly, in one approach the vasoconstrictor effect of serotonin on the afferent glomerular arterioles is stressed; in the other its effect on the water reabsorption mechanism of the renal tubules is stressed. The available information suggests the probability that both approaches play a part with afferent arteriolar constriction playing the major role. The extremely high reabsorption values for glomerular filtrate as it passes through the renal tubules reported by various investigators for normal man and animals indicate the difficulty, if not impracticability, of determining the effect of administered serotonin on tubular reabsorption in normal animals and man. For instance, it has been estimated that normally 90 per cent of the water in glomerular filtrate is reabsorbed by the renal tubules in the frog (41) and that this value reaches 99 per cent in man (160).

A normal human adult produces about 180 liters of glomerular filtrate per day,

of which only about 1.5 liters ("about 1.0%") per day is excreted from the body as urine (160). The small amount of glomerular water (about 1.0%) normally excreted in man (160) suggests that the potent antidiuretic effect of neurohypophysial extract, which is generally believed to act directly upon the renal tubules to increase their reabsorption of glomerular filtrate (41), actually effects antidiuresis chiefly by constricting the efferent glomerular arterioles (41).

Erspamer and Ottolenghi (174) were so impressed with the antidiuretic action of serotonin, extracted with acetone from the posterior salivary glands of Octopus vulgaris, on the rat that, as a working hypothesis, they adopted the tenet that serotonin regulates the function of the kidney. Certain other investigators (55, 57, 127, 499) are not convinced that serotonin plays an especially significant part in regulation of the renal output by controlling the glomerular arterioles. Sala and Castegnaro (499) report that small doses (0.1–0.3 mg/kg) of serotonin injected either subcutaneously or intravenously acted as an antidiuretic without stimulating smooth muscle in hydrated dogs. Chiefly from this effect, they concluded that serotonin reduced the flow of urine by increasing reabsorption of water as the urine passed down the renal tubules. If this were the case, the specific gravity of the urine of the serotonin-treated dogs should be altered. Dasgupta (127) found that pretreatment with chlorpromazine (a vasodilator) protected hydrated rats from the antidiuretic action of serotonin. From this work he concluded that the antagonistic effect of chlorpromazine on serotonin-induced antidiuresis may be explained in terms of its effect as a vasodilator or, possibly, by its effects on the water reabsorption mechanism of the renal tubules.

A point of interest is that in all the works reviewed on the antidiuretic effects of serotonin, we found no indication that the investigator had considered the possibility that insufficient intake or utilization of protein may have been a contributing factor. It has been shown that a protein-deficient diet causes a progressive increase in antidiuretic activity in rats (55).

Serotonin Compared with Histamine

The discovery that serotonin occurs within and is synthesized by mast cells (43, 334, 493), that mast cells also contain histamine (42, 402, 474, 475, 476, 617) and that serotonin is not formed from 5-hydroxytryptophan by platelets, but is probably transferred to the platelet during its formative period (590) whence it may be released (457, 475) along with histamine (43, 60, 609), further complicates the problem of differentiating serotonin and its activities from histamine and its activities. Species differences in response of a structure to serotonin may be taken as an indication that results of biological assay of the structure in question may have only relative value. For instance, it has been shown that strips of the carotid artery of cattle are very sensitive to serotonin, but similar strips of this artery from swine and dogs are so nearly insensitive to this hormone as to render the por-

cine and canine material undesirable for biological tests (423). Small amounts of serotonin or of histamine increased the coronary flow when injected into the coronary artery of the dog, while an extract of the neural hypophysis reduced it (510).

So far, it appears that the two amines are much more reliably differentiated chemically and physically than by their pharmacological activities, which appear to differ chiefly in potency if smooth muscle is used for the assay (189). Although serotonin (5-hydroxytryptamine) and histamine (5-imidazoleëthyl-amine) (389) are both amines and are both produced in nature by decarboxylation (77, 200, 504, 505, 591), they are recognized as different chemical entities and are usually accorded opposite pharmacological effects, the possibility of mistaking the effects of one for the effects of the other exists.

Tests for Serotonin

Certain investigators have employed the method of a) fluorescence (77, 530, 591), b) a specific chemical method (590), c) electrophoresis (585, 588, 646), d) blood pressure (508, 632), e) motor activity of the bladder (165, 171, 193), f) gastric juice production and/or bronchiolar tone (165, 193, 284, 508), g) nictitating membrane of the cat (466), h) kidney of the cat (94, 466), i) perfused isolated rabbit ear preparations (94, 422, 461) and other procedures. However, the most commonly used method is a form of biological assay of extracts employing smooth muscle, such as rabbit's ileum (461), but usually the guinea pig's ileum (165, 198, 207, 284, 462, 591, 632), colon strips of the rat (43), uterus of rat or guinea pig (94, 171, 457, 483, 632, 637), or a muscular artery (52, 94, 169, 457, 466, 632, 634, 637). The isolated heart of a marine clam, Venus mercenaria, is recommended as being very sensitive to serotonin (585) and has been successfully used by others (423, 491, 613); the trachea of cats and the auricles of rabbits have also been used (535).

The biological methods employed by some investigators for the identification of serotonin apparently fail to differentiate sharply the action of serotonin from that of histamine, since some of these methods, especially those employing uterus or intestine, commonly have been used to detect the presence of histamine (47, 341, 547). Even though serotonin regularly has pronounced spasmogenic action on certain prepared, isolated smooth muscle structures, such as segments of carotid artery (52, 636), uterus of guinea pigs, mice, or rats (189, 201, 466, 636), intestine of guinea pigs (466, 528), the colon of rats (43), and heart of Venus mercenaria (206, 585), this reaction of smooth and cardiac muscle is far from being specific for serotonin. For example, acetyl choline 1:5 million, histamine 1:5 million, or barium chloride 1:500,000 in Locke-Ringer solution is each spasmogenic for isolated guinea pig uterus or ileum (528).

The uterus of mice sensitized with egg albumin contracts in vitro when eggwhite

is added (189). However, it is held that isolated strips of normal or sensitized uterus is 1,000 times more sensitive to serotonin than it is to histamine (189, 311). In this connection it is interesting to note that injection of mice with H. pertussis cells produced increased sensitivity to both serotonin and histamine (311, 404, 405).

Erspamer's, 1953, method of using the atropinized uterus of spayed rats after administration of strongly physiologic doses of estrogenic hormones affords test material which is very sensitive to serotonin (in dilutions up to 1:200 million) and is negligibly sensitive to histamine (423), and appears to offer a reliable means for differentiating the spasmogenic action of serotonin from that of histamine. However, as has been pointed out for other techniques (591), the possibility exists that the effects of related substances, such a certain analogs, may be indistinguishable from the effects of serotonin.

Another interesting point pertaining to the specificity of the effects of serotonin is that although apparently not all antihistamines are capable of blocking the spastogenic effects of serotonin on smooth muscle, diphenhydramine and tripelennamine do prevent the induction of spasm in preparations of isolated guinea pig ileum by acetyl choline and histamine as well as by serotonin (462). However, attention should be directed to the finding that administration of antihistaminic drugs failed to inhibit anaphylaxis of isolated uteri strips, or in the intact mouse (189).

Several factors probably affect the results obtained by using smooth muscle, but the physiological state of the tissue being used is probably the one most often overlooked. Erspamer (170) states that the uterus of rats in estrus apparently is the best test object for the presence or assay of serotonin; others (632) advocate pretreatment of rats with estrogens to insure uterine response. Various investigators (483) have shown that the sensitivity of the uterus of the rat to serotonin is high during estrus and in pregnancy, but diminishes during diestrus, immediately following partuition, and after ovariectomy; Woolley (632) states that "the uterus will not respond to serotonin except during estrus". These objections are apparently overcome by Twarog and Page (585) who recommend use of the isolated heart of Venus mercenaria, a marine clam, as providing a selective and highly sensitive means of assaying serotonin activity.

Immersion of a section of guinea pig ileum in a strong solution of tryptamine, 5-hydroxytryptamine, or substance P causes contraction in the piece of intestine, but this contraction ceases in a few minutes in spite of the continued presence of a potent amount of the excitor in the solution. After the piece of intestine has been desensitized by the excess of either tryptamine or 5-hydroxytryptamine it is insensitive to both substances, but remains sensitive to other stimulating substances (198). This reaction is interpreted as indicating that the stimulating effect of tryp-

tamine and of 5-hydroxytryptamine is mediated by one type of receptor in the intestine and that some other substance, such as histamine, causes contraction of the ileum by stimulating other receptors. Nevertheless, there apparently is no adequate method of bioassay by which intestinal contraction caused by serotonin can be differentiated from that caused by histamine or certain other agents.

Metabolism of Serotonin

Sjoerdsma and co-workers, 1955, found that the enzyme monoamine oxidase apparently catalyzes the metabolism of serotonin (591). Other work shows that serotonin is rapidly metabolized by monoamine oxidase when the hormone is liberated in reasonable amounts (77) or administered parenterally (589, 590, 591). That histamine is similarly destroyed by the enzyme histaminase is generally conceded, with few exceptions (16), but whether or to what extent diamine oxidase and various other factors are involved is still controversial (295, 504, 569, 641). Schayer (504) recognizes 3 kinds of mammalian enzymes which metabolize histamine in physiological amounts. These are an acetylating enzyme, diamine oxidase, and 'histamine-metabolizing enzyme II', which is probably a composite of an oxidative and a methylating enzyme (504). These enzymes have varying degrees of efficiency in different animals (504).

Urinary Serotonin and Histamine

Since free serotonin, exogenous as well as endogenous, is rapidly metabolized (100, 589, 591) by far the major part recovered in the urine is in a degradated, inactive state, usually in the form of 5-hydroxyindoleacetic acid (589, 590, 591), primarily as a result of metabolism of the serotonin by oxidative deamination (589, 590, 591).

The kidneys and liver appear to contain significant quantities of an enzyme which is similar to, if not identical with, monoamine oxidase and catalyzes the metabolism of serotonin (591). When serotonin was aerobically incubated with homogenates of either kidney or liver, about 30 per cent of the metabolized hormone was recovered as 5-hydroyindoleacetic acid; the other 70 per cent was unidentifiable as any known compound (589). Similar results were obtained in vivo in which 20 to 30 per cent of the serotonin administered to dogs was recovered from the urine as 5-hydroxyindoleacetic acid in addition to several indoles which were not identified (589).

Since both serotonin and histamine are excreted chiefly by the kidneys, the urine content bears a fairly definite relation to the intake of these amines. This relation is much more significant for histamine than for serotonin since both free and parenterally administered serotonin are rapidly inactivated through oxidative deamination by monoamine oxidase, while very little of the parenterally administered

histamine is degradated. The result is that the amount of free urinary histamine bears a relation to the amount of free histamine administered (200). Likewise, the amount of conjugated histamine in the urine is related to the amount that was metabolized (200). However, a considerable error may be introduced into this evaluation by certain hypertensive renal-vascular conditions, especially with regard to the relation of the amount of serotonin metabolite to the intake. It has been observed that chronic glomerular nephritis or advanced renal disease of malignant hypertension reduced the amount of urinary 5-hydroxyindoleacetic acid in man (68).

Another probable source of error lies in the fact that there is a considerable amount of evidence indicating that synthesis of both serotonin and histamine is inhibited by deficiency of pyridoxine (pyridoxine phosphate, vitamin B_6). This effect is not specific for either substance, for pyridoxine appears to play an important part in decarboxylation of amino acids in general and for metabolism of epinephrine and norepinephrine (591) as well as for decarboxylation of 5-hydroxytryptophan and histidine.

Acetone extracts of urine from normal dogs and people contained 0.1 to 1.0 μg/ml of serotonin (which is comparable to the 0.1 to 0.4 μg/ml serum content of heparinized dogs), and venous infusion of serotonin increased the urine content of this substance (585). However, the normal, daily output is astonishing, for it has been estimated that normal dogs excrete about 2.0 to 3.0 mg, and human subjects about 7.0 to 10 mg, of 5-hydroxyindoleacetic acid per day (579, 589). These amounts presumably account for most of the dietary values, for daily output indicates that the turnover of serotonin in tissues is probably much larger than has been suspected (579).

The urine of dogs treated with serotonin yielded 20 to 30 per cent of the administered dose of serotonin in the form of 5-hydroxyindoleacetic acid, while the urine of those receiving 5-hydroxyindoleacetic acid yielded unchanged nearly the entire amount that was administered (589). From these values the authors calculated that in human subjects about 20 mg of serotonin was metabolized daily to produce 7 mg of 5-hydroxyindoleacetic acid daily (589).

The urine of large carnivores, including lions and tigers, had an unusually high concentration of conjugated histamine (200) which had a dietary origin, for parenterally administered histamine produces an increase in free histamine but has little effect on the level of conjugated histamine in the urine (200).

Renal Relations

The part played by the kidneys in the synthesis and/or metabolism of serotonin and histamine in different mammals is obscure. Apparently, the kidney of most mammals contains very little or no serotonin, but it has been shown that serotonin

appeared in the kidneys of normal rabbits, where it is not normally found (587, 591), after administration of 5-hydroxytryptophan (587). The results of these experiments appear to indicate that in the kidneys of the rabbit serotonin is metabolized about as rapidly as it is formed. Walton, 1956, found that the kidney of the house cat contains an appreciable amount of histaminase but no, at least no detectable, histidine decarboxylase, while the kidney of normal rabbits contains very little or no histaminase, but has a fairly strong histidine decarboxylase activity (200) and contains no measurable amount of serotonin (587). These findings indicate that the kidney of rabbits contains no histamine and no serotonin, but that it has the enzyme necessary for synthesizing histamine, while the kidney of hogs is well equipped to synthesize serotonin and inactivate histamine, for it contains appreciable quantities of 5-hydroxytryptophan decarboxylase (588) and is one of the best sources of histaminase (381, 591). The kidney of hogs not only contains the enzyme necessary for synthesizing serotonin (588), but contains it in sufficient quantity to be a commercial source of 5-hydroxytryptophan decarboxylase, and McHenry and Gavin (381) described a method for obtaining a stable powder high in histaminase activity from this source. The results should be interesting if the data on the occurrence of the above substances in a wide range of mammalian kidneys were tabulated. However, Brodie's statement to the effect that serotonin is formed in all tissues of the body following administration of 5-hydroxytryptophan (77) indicates the ability of all body tissues, as well as the kidney, to form serotonin.

There is evidence that other metabolic products of serotonin occur in the urine, some of which apparently have pharmacologic properties of serotonin. Ketty calls attention to the work of Bumpus and Page, 1955, in which they isolated substances from normal human urine which they considered methylated derivatives of serotonin (419). In addition to traces of bufotenin (dimethyl serotonin) occurring in the human urine, methylation of serotonin has also been reported in plants, in certain invertebrates, and in a toad (591).

It is generally conceded that following administration of histamine-releasing agents (341) or administration of histamine (504), there is an increase in urinary histamine (200); and it has been shown that this urinary histamine is spastogenic for atropinized guinea pig ileum (341). Also, the works of McIntire, et al., 1947, Rosenthal and Tabor, 1948, and Millican, et al., 1949, show that after separation by McIntire and co-workers', 1947, method for other urinary substances, histamine is the only remaining spastogenic substance acting on atropinized ileum of the guinea pig (341).

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