Chapter 7

Peripheral physiological and pharmacological actions of indolealkylamines

By

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With 16 Figures

I. Acute toxicity of indolealkylamines

5-Hydroxytryptamine base. Mouse, LD 50 by intravenous route: 160 mg/kg (Freyburger et al. 1952), 135 mg/kg (Higginbotham 1959); by intraperitoneal route: 280 mg/kg (Spencer and West 1961), 340 mg/kg (Fishel et al. 1962); by subcutaneous route: > 868 mg/kg (Freyburger et al. 1952). Rat, LD 50 by intravenous route: 30 mg/kg; by subcutaneous route: approximately 117 mg/kg (Freyburger et al. 1952).

Anaesthesia greatly enhances the toxicity of 5-HT. Rats anaesthetized with pentobarbital may die following intravenous doses of the substance as small as 0.1 mg/kg (Correll et al. 1952, Tapani 1963). Similar observations have been made in rabbits, guinea-pigs, hens (Correll et al. 1952), dogs (McCawley et al. 1952) and cats (Erspamer 1954b). Death is due to respiratory failure.

It is obvious that several drugs when given prior to or at the same time as 5-HT are capable of influencing consistently the acute toxicity of 5-HT itself. To quote a few examples, pretreating of mice with 1 and 1.5 mg/kg of 48/80 increases the 5-HT toxicity 5 and 30 times, respectively (Higginbotham 1959), and pretreating of mice with 6 subcutaneous doses of 2 mg/kg thyroxine again raises the toxicity of 5-HT 5 times (Spencer and West 1961).

5-Hydroxy-N,N-dibutyltryptamine HCl. Mouse, LD 50 by intraperitoneal route: 178 mg/kg (Heinzelman and Szmuszkovicz 1963).

Bufotenidine. Mouse, LD 50 by intravenous route: 1.3 mg/kg; by subcutaneous route: approximately 90 mg/kg (Ueda et al. 1957).

5-Methoxytryptamine HCl. Mouse, LD 50 by intravenous route: 60 mg/kg; by subcutaneous route: 750 mg/kg. Rat, LD 50 by subcutaneous route: 600 mg/kg (Erspamer 1952a).

5-Methoxy-N,N-diethyltryptamine HCl. Mouse, LD 50 by intraperitoneal route: 65 mg/kg (Heinzelman and Szmuszkovicz 1963).

Psilocybin. Mouse, LD 50 by intravenous route: > 250 mg/kg (Cerletti 1959).

Tryptamine. The subcutaneous LD 50 of tryptamine hydrochloride in mice kept at an environmental temperature of 28 to 30° is about 500 mg/kg, death occurring without any marked symptoms of central stimulation (Edery and Schatzberg-Porath 1960, Maxwell et al. 1961).

The intravenous administration of sublethal doses of tryptamine HCl (32 to 48 mg/kg) in male mice produces head weave, hind leg spread, arched back and fore-paw clonus (KEASLING et al. 1963). These symptoms are similar to those observed by TEDESCHI et al. (1959) in the rat following intravenous injection of 40 mg/kg tryptamine.

Tryptamine derivatives. Data on the acute toxicity of a series of tryptamine derivatives, reported in a recent review article by HEINZELMAN and SZMUSZKOVICZ (1963) are given below. LD 50 has been determined in the mouse, by intraperitoneal route.

N-methyltryptamine. HCl	200 mg/kg
N-ethyltryptamine. HCl	167 mg/kg
N-propyltryptamine. HCl	77 mg/kg
N-isopropyltryptamine. HCl	205 mg/kg
N-n-butyltryptamine. HCl	65 mg/kg
N-isobutyltryptamine. HCl	167 mg/kg
N-(1'-methyl-)propyltryptamine. HCl	167 mg/kg
N-isopentyltryptamine. HCl	100 mg/kg
N-benzyltryptamine. HCl	200 mg/kg
N-octyltryptamine. HBr	32 mg/kg
N-(2'-ethyl-)tryptamine. HCl	200 mg/kg
N,N-dimethyltryptamine. HCl	167 mg/kg
N,N-diethyltryptamine. HCl	77 mg/kg
N,N-dipropyltryptamine. HCl	56 mg/kg
5-methyltryptamine	200 mg/kg

EDERY and SCHATZBERG-PORATH (1960) found that LD 50 by subcutaneous route in the mouse is 439 mg/kg for *5-fluorotryptamine*, and 320 mg/kg for *5-fluoro-7-methyltryptamine*.

Gramine. Mouse, LD 50 by intravenous route: 44.6 ± 1.4 mg/kg (POWELL and CHEN 1945), 45.6 mg/kg (AKKERMAN et al. 1951). Rat, LD 50 by intravenous route: 62.9 ± 2.7 mg/kg (POWELL and CHEN 1945).

Gramine first stimulates the central nervous system (clonic convulsions, hyperpnoea), then depresses it. Death seems to be due to central respiratory failure (SUPNIEWSKI and SERAFINOWNA 1938).

According to SUPNIEWSKI and SERAFIN-GAJEWSKA (1938), *2-methylgramine* is 3 to 4 times more toxic than gramine.

5-Hydroxytryptophan. In the rabbit, intravenous 5-HTP causes lethal hyperpyrexia in doses of 75 mg/kg and more (HORITA and GOGERTY 1958). Rats withstand intraperitoneal doses of 200 mg/kg 5-HTP, repeated every 12 hours for periods up to 12 months, the only toxic effects produced by the amino acid being diarrhoea, failure to gain weight, and persistent cyanotic flush (DAVIDSON et al. 1957a, 1957b).

For other data on the acute toxicity of 5-HT and for data on its chronic toxicity see Chapter 13.

A number of data on the toxicity of a series of indole glyoxamides and indole acetamines are reported by HEINZELMAN and SZMUSZKOVICZ (1963).

II. Action on the systemic blood pressure

Dog. It has been ascertained that the blood pressure response of dogs to parenteral 5-HT depends on a number of known and unknown factors, such as type of anaesthesia, dose, route and rapidity of drug administration, dominant neurogenic vasoconstrictor tone, duration of experiment etc. Only rarely have different research workers obtained exactly superimposable results, and even the same investigator has often failed to elicit identical responses in different dogs, or

in the same dog at different stages of an experiment. This justifies the statement by PAGE (1952b) that "the protean character of the response seems to be the most characteristic feature of the action of the tryptamines on arterial pressure."

Rapid intravenous injection or rapid injection into the pulmonary artery (MACCANON and HORVATH 1954) of medium or high doses of 5-HT (10—200 μg/kg) produces either a frank hypertensive response with increase in the systemic vascular resistance, or polyphasic, amphibaric reactions. The rise in pressure is always moderate, rarely exceeding 40—60 mm Hg, and barely correlated with the dose (PAGE 1952a, 1952b, 1954; PAGE and MCCUBBIN 1953a; ERSPAMER 1952a, 1954; HEYMANS and VAN DEN HEUVEL-HEYMANS 1953; DOUGLAS and TOH 1953; SCHNEIDER and YONKMAN 1954; SCHNEIDER et al. 1954; SCARINCI 1955; BINET and BURSTEIN 1955; ABRAHAMS and PICKFORD 1956a; SCHMID et al.

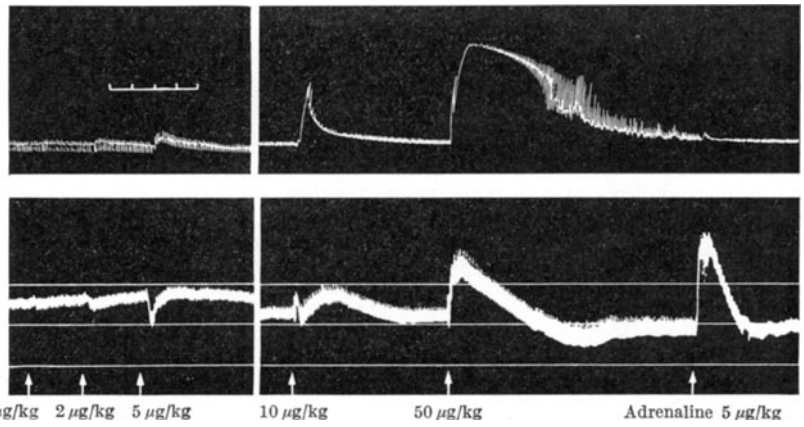


Fig. 1. Dog anaesthetized with pentobarbital. Action of different intravenous doses of 5-HT and of 5 μg/kg adrenaline on carotid blood pressure (lower tracing) and urinary bladder (upper tracing). Time in min. In this experiment low doses of 5-HT produced hypotensive responses, high doses polyphasic or hypertensive responses. Note for the urinary bladder the clear dose/response relationship. [From Fig. 11, ERSPAMER, V., R. C. sci. Farmitalia 1, 40 (1954).]

1956; HOTOVY and ROESCH 1958; JACOB and CUGURRA 1960; BRAUN and STERN 1961; WEIDMANN and CERLETTI 1961; BUÑAG and WALASZEK 1962).

Rapid intravenous injection of small doses of 5-HT (2—8 μg/kg) causes perhaps the most erratic responses: most frequently a slight fall of blood pressure, or biphasic reactions (a fall followed by a slight rise) are seen; more rarely purely hypertensive responses (PAGE 1952b, PAGE and MCCUBBIN 1953a, SCHNEIDER and YONKMAN 1954, ERSPAMER 1954, SCHMID et al. 1956) (Fig. 1).

Finally, slow infusion of 5-HT into the veins or the right atrium constantly produces a drop in mean systolic blood pressure and a decrease in systemic vascular resistance.

At an infusion rate of 8 μg/kg/min of 5-HT base into the right atrium, MAXWELL and co-workers (MAXWELL et al. 1957, 1959; CRUMPTON et al. 1959) obtained an 18% reduction in mean arterial pressure and a 21% reduction in total peripheral resistance; at the same infusion rate into the vein RUDOLPH and PAUL (1957a, 1957b) observed 28% and 55% decreases, respectively; at infusion rates of 60 to 400 μg/kg/min MCGAFF and MILNOR (1962) found decreases of the order of 22% and 38%, respectively.

Following infusion of 5-HT into the left atrium (8 μg/kg/min) the body oxygen consumption does not change, but the arteriovenous difference for oxygen

decreases (—17%), while the arterial hematocrit (+4.4%) and hemoglobin (+4.5%) present a slight increase (ROWE et al. 1963).

The hypertensive effect produced by injection of large doses of 5-HT into the femoral vein is reversed to a frank, transient hypotensive response when the amine is injected quickly into the portal vein (BERGAMASCO et al. 1956). When large doses of 5-HT (85 μg/kg of the base) are administered in anaesthetized open-chest dogs into the femoral vein, right heart, pulmonary artery, left heart, ascending aorta or common carotid arteries, it is noted that the latent period before the onset of the pressor response becomes shorter with the shift of the site of the injection towards the ascending aorta. Following injection into the descending aorta a "double-peak" pressor response is obtained (BRAUN and STERN 1961).

Intravenous injections of 5-HT repeated at brief intervals provoke pressor reactions of progressively decreasing intensity (FREYBURGER et al. 1952, ERSPAMER 1954, JACOB and MICHAUD 1962). This tachyphylaxis, however, seems to be of short duration (5—15 min) and this would explain why it was not noted by PAGE (1952b).

Concerning the influence of the type of anaesthesia on the direction of the pressure response to 5-HT, it might be important to confirm the observations of HOTOVY and ROESCH (1958) who found that, in sharp contrast to what happens in unanaesthetized dogs and in dogs anaesthetized with chloralose, rapid intravenous injections of 5-HT in dogs anaesthetized with barbiturates or thiobarbiturates produce a fall of blood pressure and a decrease of peripheral resistances.

In contrast to the intact dog, the spinal dog always responds to intravenous 5-HT with a frank hypertensive reaction which however is barely correlated to the dose and shows some tachyphylaxis (ERSPAMER 1954; PIERRE and CAHN 1956; SCHNEIDER and RINEHART 1956a, 1956b). According to PIERRE and CAHN (1956) the blood pressure of dogs having a pre-medullary brain section does not show any important change following 5-HT administration.

Ganglionic blockade with tetraethylammonium or methonium compounds seems to intensify the hypertensive reaction to 5-HT (PAGE 1952b, PAGE and MCCUBBIN 1953b, SCHNEIDER and YONKMAN 1954). According to PAGE (1952b) the same result might be obtained by transection of the spinal cord at C_6, by atropinization of the animal or by cervical vagotomy. This has not, however, been confirmed (DOUGLAS and TOH 1953, ERSPAMER 1954, FREYBURGER et al. 1952, SCHNEIDER and YONKMAN 1954, BOCK and MEIER 1963). JACOB and CUGURRA (1960) found, on the contrary, that acute vagotomy favoured the appearance of late hypotension.

Nicotine (0.01—2 mg/kg, i.v.) progressively inhibits the 5-HT "spike" (first component of the hypertensive effect). Lower doses of nicotine depress the 5-HT "dome" (second component of the hypertensive effect) and the hypertensive response caused by tryptamine, but higher doses of nicotine enhance them. There is no crossed tachyphylaxis between 5-HT and nicotine (JACOB and MICHAUD 1962).

The hypertensive effect of 5-HT is frequently weakened by sympatholytic agents (piperoxane, priscoline, yohimbine, dibenamine, dibenziline, ergotamine, hydrogenated ergot alkaloids); much more rarely it is abolished or reversed completely (ERSPAMER 1952, 1953; FREYBURGER et al. 1952; PAGE 1952b; PAGE and MCCUBBIN 1953b; SCHNEIDER and YONKMAN 1954; SCARINCI 1955). Procaine (1—10 mg/kg, i.v.) and high doses of cocaine (2—5 mg/kg, i.v.) diminish the blood pressure rise and in most experiments abolish the initial fall (SCHNEIDER and YONKMAN 1954, WEIDMANN and CERLETTI 1961, CERLETTI and WEIDMANN 1962). Low doses of cocaine, however, slightly potentiate the 5-HT effect (WEID-

MANN and CERLETTI 1961, CERLETTI and WEIDMANN 1962). Bilateral adrenalectomy during an acute experiment produced discordant results. Whereas according to SCHNEIDER et al. (1954) it did not seem to alter the cardiovascular or respiratory response to 5-HT, according to SCARINCI (1955) it caused a reduction of the pressor effect of the amine. Bilateral adrenalectomy, followed by administration for several weeks of desoxycorticosterone trimethylacetate, was found even by SCHNEIDER et al. (1954) to decrease the pressor response and to augment the depressor response to 5-HT.

Bilateral nephrectomy selectively augments the pressor actions of 5-HT and tryptamine, though less regularly and less prominently than the actions of angiotonin and renin (McCUBBIN and PAGE 1954). 1-Hydrazinophthalazine does not appear to be a constant and specific inhibitor of 5-HT (ERSPAMER 1954). 2-Methyl-3-ethyl-5-aminoindole and 2,3-dimethyl-5-aminoindole antagonize the circulatory effects of 5-HT inconstantly and partially. If indeed they are occasionally able to attenuate or abolish the hypertensive phase in the reaction to the substance, they never reduce, but sometimes seem rather to accentuate the hypotensive phase. The anti-5-HT action of the nitroindoles given orally is doubtful (PAGE and McCUBBIN 1953b). 2-Methyl-3-ethyl-5-dimethylamino-indole and 1-methyl-2-methyl-3-ethyl-5-dimethylaminoindole, given either orally or subcutaneously, are similarly incapable of protecting normal dogs from the pressor effects of 5-HT (SHAW and WOOLEY 1954).

The pressure rise provoked by 5-HT (30—50 μg/kg) is, on the contrary, potently antagonized by LSD and methysergide (UML) in doses as low as 10 to 20 μg/kg (SCHNEIDER and RINEHART 1956b, FANCHAMPS et al. 1960), and moderately by BAS, given in high doses (4—8 mg/kg) (JACOB and CUGURRA 1960). Surprisingly enough, BOL was found to exhibit weak and inconstant activity towards the cardiovascular responses to 5-HT (SALMOIRAGHI et al. 1957).

The influence of cevadine, veratridine, belladonine, bulbocapnine and harmine on the pressor action of 5-HT in the dog anaesthetized with butallylonal is variable (HOTOVY and ROESCH 1958). According to MILKOVIĆ et al. (1955) both the hypertensive and hypotensive effects of 5-HT in anaesthetized dogs and rabbits are consistently reduced by intravenous infusion of Fe^{++} salts at a rate of 1.3—1.4 mg/kg/min. Dogs premedicated with reserpine respond to infusion of 4 μg/kg/min 5-HT with a gradual additional fall of blood pressure over the reserpine-induced hypotension. Integrity of the vagi is not essential for these results (CRONHEIM and GOURZIS 1956, 1960). The hypertensive effect of 5-HT given by rapid intravenous injection is, on the contrary, either antagonized (SCHNEIDER and RINEHART 1956a, 1956b; RUTLEDGE et al. 1959; WEIDMANN and CERLETTI 1961; CERLETTI and WEIDMANN 1962) or enhanced (SCHNEIDER and RINEHART 1956a, 1956b) by reserpine pretreatment, according to experimental conditions. SCHNEIDER and RINEHART (1956b) suggest that reserpine has a dual effect on the blood pressure response to 5-HT; namely, a peripheral antagonizing effect and a central potentiating effect.

Because the vasoconstrictor effect of 5-HT in dogs anaesthetized with aprobarbital and under ganglionic blockade with chlorisondamine is inhibited by reserpine and since noradrenaline infusion in reserpine-treated animals does not restore the pressor action of 5-HT, unlike that of tyramine, WEIDMANN and CERLETTI (1961, 1962) suggest that 5-HT vasoconstriction has a certain character of its own and that 5-HT acts on a hypothetical synaptic structure at a level intermediate between the site of action of noradrenaline (direct action on the vascular smooth muscle) and tyramine (liberation of noradrenaline-like substances from the depots).

Methylphenidate administered to anaesthetized dogs markedly potentiates the blood pressure response to 5-HT. This potentiating effect, however, disappears after reserpine premedication (RUTLEDGE et al. 1959). Contrary to expectations, pretreatment with MAO-inhibitors (iproniazid, β-phenylisopropylhydrazine, harmine and others) has been found to decrease the cardiovascular effects of 5-HT. According to PAGE and MCCUBBIN (1953a, 1953b) the response to 5-HT of dogs with chronic neurogenic hypertension is strikingly different from that seen in normotensive animals. Leaving aside the inconstant appearance of moderate hypertensive peaks, the basic reaction to 5-HT of the hypertensive dog was found to be an unusually conspicuous and prolonged hypotension. In the hypertensive dog even introduction of 5-HT into the perfusion liquid of a hind leg having intact nervous connections but no vascular connections with the body produced evident vasodilatation, in contrast to the usual vasoconstriction. Atropine did not change either the intensity or direction of the pressure reaction; ganglionic blockade, on the contrary, reversed the frankly hypotensive response, making it clearly hypertensive. The above peculiar pressure changes were considerably less conspicuous in dogs with acute neurogenic hypertension, and were lacking in animals made hypertensive by noradrenaline infusion or by increase in endocranic pressure.

On the basis of experiments carried out on normotensive dogs pretreated with ganglion-blocking drugs and in dogs with neurogenic hypertension, as well as in cats and rabbits, both normal and with ganglionic blockade, PAGE and MCCUBBIN (1953a, 1953b) and PAGE (1954) consider the pressure response to 5-HT to be the result of various distinct factors: 1) intense direct vasoconstriction; 2) a reflex, possibly in the nature of the Bezold-Jarisch effect, that can be blocked by atropine; 3) transient autonomic ganglion blockade; 4) strong peripheral action that reduces or abolishes neurogenic vasoconstriction; 5) cardiac stimulation. Factors 1) and, to a lesser extent, 5) are believed to be responsible for the hypertension, factors 2) and 3) for the initial transient pressure fall and factor 4) for the more persistent secondary hypotension. PAGE and MCCUBBIN are of the opinion that inhibition of neurogenic vasoconstrictor tone is a decidedly more important phenomenon than direct vasoconstriction. They consequently believe that direction and intensity of the pressure response to 5-HT are to a great extent determined by the degree of normal resting vasoconstrictor tone. If this tone is high (dogs with chronic neurogenic hypertension) the predominant response to 5-HT is hypotension, if the tone is low (ganglionic blockade) hypertension has the advantage.

It appears that in the above interpretation of the mechanism of action of 5-HT little, if any, importance is attributed to stimulation of vasal chemoreceptor zones. HEYMANS and VAN DEN HEUVEL-HEYMANS (1953) have carried out careful experiments on this topic. Having ascertained that 5-HT has no stimulant action on the chemoreceptors of the carotid sinus and that its circulatory and respiratory effects do not depend on stimulation of afferent fibres in the carotid sinus nerves or in the cervical vago-aortic nerves, the Belgian investigators maintain that 5-HT hypertension must be due primarily to peripheral vasoconstriction and secondarily to direct stimulation of the vasomotor centers. Only following local bilateral application on the carotid sinuses would large doses of 5-HT (200 μg) cause a depression of the hypertensive reflexes originating from the carotid sinuses, with ensuing reflex hypotension.

However, these essentially negative conclusions have not been entirely accepted by others. JACOB and CUGURRA (1960) found that carotid sinus denervation partly depressed the pressor response to moderate doses of 5-HT (20—40 μg/kg,

i.v.) and favoured the appearance of late hypotension. BRAUN and STERN (1961) in their turn, observed that 5-HT (80 μg/kg, i.v.) displayed in the dog a much less pronounced pressor effect after elimination of the carotid and aortic chemoreceptors (bilateral high cervical vagotomy, crushing the carotid bodies and sectioning the carotid sinus nerves), and that shifting of the site of 5-HT injection from the femoral vein towards the ascending aorta shortened the latent period elapsing between amine administration and pressure changes.

It has been previously reported that intravenous infusion of 5-HT constantly produces a sustained pressure fall which differs from the usual amphibaric reaction to single quick injections of the amine. PAGE and MCCUBBIN (1956) suggest that when 5-HT is infused, a release of endogenous histamine may also substantially contribute, together with peripheral inhibition of neurogenic vasoconstriction, to the depressor response. This idea is not new and it has been accepted by other investigators. SCARINCI (1955b, 1955c) noted that 5-HT hypotension was inhibited in dogs, cats and rabbits by antihistaminic drugs, and similarly BUÑAG and WALASZEK (1961a) found that the sustained pressure fall produced by 5-HT in dogs premedicated with BAS-phenol was antagonized by diphenhydramine, an antihistamine agent, but remained unchanged after bilateral vagotomy.

Because 5-HT is apparently capable of eliciting a Bezold-Jarisch reflex, the question has been raised as to whether the reflex seen after veratrine administration could be mediated by 5-HT. The answer was negative (FRAHM et al. 1957).

Responses to 5-methoxytryptamine (ERSPAMER 1952a) and 7-HTP (PAGE 1952a, 1952b) are on the whole similar to those described for 5-HT. Both substances are, however, 3 to 5 times less potent than 5-HT.

4-HT (200—300 μg/kg) elicits a biphasic reaction with the major component depressor (BUÑAG and WALASZEK 1962).

5-Acetyltryptamine consistently produces hypotension both in the "open-chest" and in the "closed-chest" anaesthetized dog (BEN et al. 1962).

Bufotenine, and bufotenidine even more so, differ from 5-HT in being more regularly and potently hypertensive. Injected intravenously in doses of 0.05 to 1 mg/kg they provoke a marked rise in blood pressure, which is potentiated by cocaine and abolished or reversed by yohimbine, and still more by yohimbine plus harmalol (RAYMOND-HAMET 1941, 1942b, 1943a, 1943b, 1944; BUÑAG and WALASZEK 1962c). Sparteine shows no effect (RAYMOND-HAMET 1946). Bufotenine increases the reactivity of the circulatory system to successive injections of adrenaline, but it partly inhibits the pressure rise provoked by carotid occlusion (RAYMOND-HAMET 1942a). On the basis of the above results and of the observation that bufotenine and bufotenidine have only little constrictor effect when applied locally on the vessels, RAYMOND-HAMET (1941, 1942b, 1942c, 1943a) holds the opinion that both substances are to be listed among the nicotine-like drugs, acting on the vessels and on the blood pressure through a discharge of catecholamines.

Small doses of O-methylbufotenine induce tachycardia in dogs and increase blood pressure; large doses have the opposite effect (KANAI et al. 1962).

Concerning the effects on blood pressure of psilocybin and psilocin results are at variance. WEIDMANN et al. (1958) and CERLETTI (1959) found that intravenous administration of 50—100 μg/kg psilocybin produced in the dog a moderate but relatively long-lasting drop in the mean arterial pressure, accompanied by active decrease in kidney volume. MAXWELL et al. (1962) as well as BUÑAG and WALASZEK (1962c), on the contrary, observed that 200—500 μg/kg psilocybin produced a sustained increase in the arterial pressure (17%) and calculated vascular resist-

ances in the body. Psilocin (100—200 μg/kg) had a similarly prolonged pressor effect (BUÑAG and WALASZEK 1962c).

5-HTP given by rapid intravenous injection (30 mg/kg) produces a blood pressure fall both in normal and in reserpinized dogs, but whereas in the former pressure returns toward normal, in the latter it remains low (CRONHEIM 1960).

Tryptamine (0.1—1 mg/kg) causes a rise in systemic arterial pressure which is occasionally preceded or followed by a fall (LAIDLAW 1912, RAYMOND-HAMET 1941a, REID 1952a, PAGE 1952b, BUÑAG and WALASZAK 1962c). These effects can be seen when the vagus nerves are intact or divided. The pressor response is reduced but not completely abolished by yohimbine (2—4 mg/kg) (REID 1952a); it seems, on the contrary, definitely augmented after spinal cord transection, ganglionic blockade and pitressin administration. Piperoxane and priscoline have little or no effect (PAGE 1952b). In sharp contrast to the pressure effects of 5-HT, hypertension elicited by tryptamine is potentiated by prior treatment with MAO-inhibitors or, much more effectively, with MAO-inhibitors plus reserpine (GOLDBERG and SJOERDSMA 1959, BURFORD and WALASZEK 1960).

The response to tryptamine in neurogenic hypertensive dogs is somewhat less than in normal ones (PAGE 1952b).

N,N-dimethyltryptamine (200—500 μg/kg) displays a pressor effect similar to that described for tryptamine (BUÑAG and WALASZEK 1962c).

REID (1952a) ascribes the rise in systemic arterial pressure to direct action on the vascular smooth muscle and, subordinately, to some stimulant action on the heart, the initial pressure fall to pulmonary vasoconstriction and the secondary fall possibly to coronary vasoconstriction; BURFORD and WALASZEK (1960) and WALASZEK and BURFORD (1963) maintain that the pressor effect of tryptamine is produced partly through norepinephrine release and partly through a direct action of its own.

WOOLLEY and SHAW (1957) postulate the existence in the vascular smooth muscle of separate receptors for 5-HT and tryptamine. This is based on the observation that whereas anaesthetized dogs are protected against the pressor response to 5-HT by prior treatment with BAS-phenol, they are not protected against the pressor effects of tryptamine.

The same opinion is substantially shared by VANE et al. (see WOOLEY et al. 1962) on the basis of the observation that the pressor response to tryptamine, unlike that to 5-HT, is (a) prevented by cocaine, (b) abolished by pretreatment of the animal with reserpine, and (c) then restored by an infusion of noradrenaline.

Gramine injected into the dog under chloralose anaesthesia evokes variable responses, depending upon the dose: with 1.25—2.5 mg/kg a moderate hypertension is predominant; with 8—9 mg/kg the transient initial pressure rise is followed by prolonged hypotension. Gramine is to be listed among the minor adrenolytic drugs (RAYMOND-HAMET 1937, 1938).

Serotonamidine (5-hydroxyindoleacetamidine) is 6—7 times more potent than 5-HT as a hypertensive agent in the anaesthetized dog; however, the effect is of shorter duration. Indoleacetamidine displays approximately the same pressor activity as 5-HT. Unlike that of indoleacetamidine, hypertension produced by serotonamidine is blocked by BAS-phenol (WOOLEY and SHAW 1957).

Cat. Hypotension is the predominant pressure response to intravenous 5-HT in the intact cat (Figs. 2 and 14). More rarely, a mixed response (hypotension followed, or interrupted, by a slight pressure increase) or a frank hypertensive reaction can be seen (COMROE 1952; COMROE et al. 1953; ERSPAMER 1952a; FREYBURGER et al. 1952; GINZEL and KOTTEGODA 1954; PAGE and MCCUBBIN 1953a, 1956; REID 1952b; SCHNEIDER and YONKMAN 1953, 1954; POWELL 1955;

KOTTEGODA and MOTT 1955; WEIDMANN and CERLETTI 1955). If present, hypertension is less intense than that provoked by doses of adrenaline or noradrenaline 60 to 100 times smaller (ERSPAMER 1952, FREYBURGER et al. 1952). Simultaneously with the fall in blood pressure an abrupt and marked drop in heart rate is seen, rarely followed by a slight increase in heart rate (SCHNEIDER and YONKMAN 1954).

When correlating preganglionic splanenic outflow with pressor- and chemoreceptor inflow from the carotid sinus and aortic area of the cat, it has been found by DONTAS (1955) that intravenous injection of 4—22 μg 5-HT base produced, at the time of abrupt hypotension and bradycardia, a progressive decrease of pressoreceptor spikes and a simultaneous decrease or abolition of splanenic afferent discharge. During recovery from hypotension the splanenic activity reappeared.

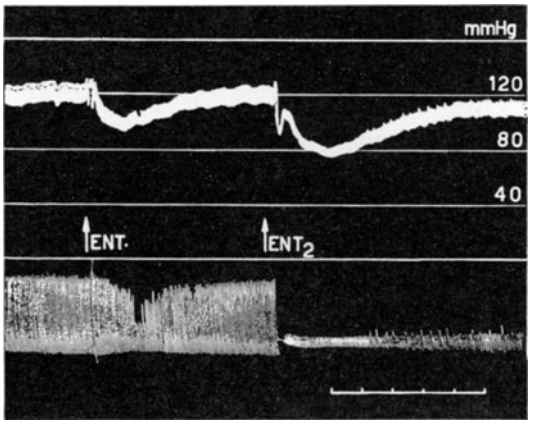


Fig. 2. Cat deeply anaesthetized with secobarbital (35 mg/kg, i.m.). Upper tracing, carotid blood pressure; lower tracing, respiration. Time in min. Blood pressure response to intravenous injection of 4 (ENT_1) and 40 μg/kg 5-HT(ENT_2) was frankly hypotensive. Respiration was strikingly depressed by the drug. [From Fig. 10, ERSPAMER, V., R. C. sci. Farmitalia **1**, 39 (1954).]

Cocaine potentiates, as a rule, the pressor response to 5-HT. Purely hypotensive reactions after the alkaloid are rare, hypertension is more sustained and with large doses of 5-HT (20—40 μg/kg) a considerable secondary pressure rise occasionally appears. This has been attributed to stimulation of the suprarenal medulla (FREYBURGER et al. 1952). Procaine 10 mg/kg and nupercaine 0.5 to 0.7 mg/kg antagonize the fall of pressure and bradycardia provoked by large doses of 5-HT (SCHNEIDER and YONKMAN 1953, 1954). Piperoxane and dibenamine generally reduce, but do not suppress, 5-HT hypertension (FREYBURGER et al. 1952). Yohimbine 1—2 mg/kg, on the contrary, does sometimes abolish it completely (PAGE and MCCUBBIN 1954, REID 1952). Cardiovascular responses to 5-HT in the cat are only slightly and irregularly antagonized by BOL and LSD (WEIDMANN and CERLETTI 1957; SALMOIRAGHI, MCCUBBIN and PAGE 1957). Pretreatment with iproniazid (2×50 mg/kg) or reserpine (2 mg/kg) fails to produce pressure changes different from those seen in untreated animals; pretreatment with 2-naphthylguanidine (100—500 μg/kg), on the contrary, causes 5-HT to elicit a rise in blood pressure instead of the usual fall (FASTIER et al. 1959). Whereas it seems well established that ganglionic blockade can abolish the normal depressor action of 5-HT and possibly reverse it to a pressor action (PAGE and MCCUBBIN 1953a, SCHNEIDER and YONKMAN 1954) there exists no agreement concerning the influence of atropine, vagal section and cooling the vagi. The statement of some research workers (COMROE et al. 1953, PAGE 1952b, SCHNEIDER and YONKMAN 1953, KOTTEGODA and MOTT 1955) that the hypotensive effect of 5-HT is largely abolished after atropine, vagotomy or cooling the vagi, and that pressor action increases, has not been confirmed (FREYBURGER et al. 1952, GINZEL and KOTTEGODA 1954, REID 1952b), or confirmed only in part by others (WEIDMANN and CERLETTI 1955).

When given intravenously to the vagotomized cat under dial anaesthesia, 5-HT (0.25—5 mg/kg) reinforces and prolongs the pressor effect of successive

doses of adrenaline (5—10 μg/kg). LECOMTE (1953) attributes this sensitization, which disappears after 30 min and cannot be obtained with tryptamine, to the presence of a phenolic hydroxy group in the 5-HT molecule, which retards the oxidation of the adrenaline injected.

In marked contrast to the cat with intact nervous system, the pithed cat and the spinal cat always respond to 5-HT with a frank hypertensive reaction (Fig. 3) which is occasionally enhanced by cocaine, and is always at least 25 to 50 times less than that produced by adrenaline (ERSPAMER 1954, FREYBURGER et al. 1952, PAGE and MCCUBBIN 1953a, SCHNEIDER and YONKMAN 1953, WEIDMANN and CERLETTI 1957). The blood pressure rise produced by 5-HT in spinal cats is due, according to WEIDMANN and CERLETTI (1957) not only to a direct constrictor effect on the vascular smooth muscle, but also to increase in the heart rate and to stimulation of the adrenal medulla. This adrenal effect of 5-HT is enhanced by iproniazid, and cannot be blocked either by hexamethonium or by LSD.

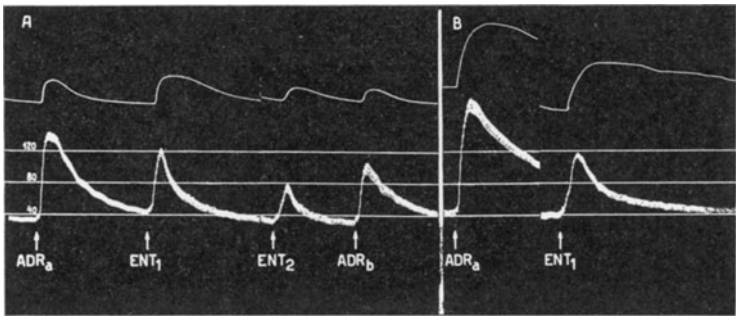


Fig. 3. Spinal cat under artificial respiration. Upper tracing, contraction of the nictitating membrane; lower tracing, carotid blood pressure. Between A and B intravenous injection of 8 mg/kg cocaine hydrochloride. In the spinal cat intravenous 5-HT was, like adrenaline, frankly hypertensive. Cocaine remarkably potentiated all the effects of adrenaline. The effect of 5-HT on the nictitating membrane was clearly reinforced by cocaine, that on the blood pressure remained practically unchanged. [From Fig. 14, ERPSAMER, V., R. C. sci. Farmitalia 1, 47 (1954).]

There is no concordance of opinion in the interpretation of the hypotension caused by 5-HT. REID (1952b) ascribes the short-lived pressure fall that occasionally precedes hypertension to a primary constriction of the pulmonary arterial bed, with ensuing reduction in the volume of blood returning to the left heart; he offers no explanation for the prolonged secondary hypotension. COMROE et al. (1953) believe that the hypotension is largely due to the associated bradycardia. PAGE and MCCUBBIN (1953a) hold that the explanation of pressure changes given for the dog applies equally to the cat. SCHNEIDER and YONKMAN (1954) consider it to be part of a complex cardiopulmonary mechanism. Finally, GINZEL and KOTTEGODA (1954) maintain that the mechanism of the pressure fall may differ depending upon the magnitude of the dose of 5-HT injected. Hypotension which follows the introduction of small doses of 5-HT seems to be due predominantly to baroreceptor stimulation and secondarily to central stimulation; pulmonary vasoconstriction would come into play only with higher doses of the substance. KOTTEGODA and MOTT (1955) are convinced that impulses producing reflex peripheral vasodilatation and reflex bradycardia are carried to the centres by afferent vagal fibres. This idea is based on the previously reported observation that hypotension is reduced or abolished by vagotomy and by cooling the vagi.

Since it is not known in what way 5-HT influences the vessels of the carotid body, the possibility of a constrictor effect giving origin to local anoxaemia cannot be ruled out (GINZEL 1958).

GINZEL and KOTTEGODA rightly emphasize the ability of 5-HT and tryptamine to produce temporary desensitization to their own actions. It is possible that some contradictory findings with these two substances and with their antagonists can be explained by this self-antagonism.

Cardiovascular responses to 5-HT in the cat are only slightly and irregularly antagonised by BOL and LSD (SALMOIRAGHI et al. 1957, WEIDMANN and CERLETTI 1957). Pretreatment with iproniazid (2×50 mg/kg) or reserpine (2 mg/kg) fails to produce pressure changes different from those seen in untreated animals; pretreatment with 2-naphthyl-guanidine (100—500 μg/kg), on the contrary, causes 5-HT to elicit a rise in blood pressure instead of the usual fall (FASTIER et al. 1959).

Numerous other tryptamine derivatives have been tested on the blood pressure of intact cats, pithed cats or cats with ganglionic blockade. The main results are as follows.

Bufotenine produces in the intact cat depression of arterial pressure or amphibaric responses (HANDOVSKY 1920, GESSNER et al. 1961, BUÑAG and WALASZEK 1962c). More rarely, predominant hypertension is seen (WEIDMANN and CERLETTI 1959). The same is true for 5-methoxytryptamine and 5-methylbufotenine. After pithing or blocking, response is frankly hypertensive. 5-Methylbufotenine raises the blood pressure of the pithed cat more potently than bufotenine; 5-methoxytryptamine, on the contrary, is less potent than 5-HT. 5-Methylbufotenine induces tachycardia in small doses but bradycardia in large doses (KAINAI et al. 1962). N-acetylation of 5-methoxytryptamine (= melatonin) destroys its activity on blood pressure (GESSNER et al. 1961).

Bufotenine O-phosphate displays in the intact cat a hypertensive action which is greater than that produced by bufotenine (WEIDMANN and CERLETTI 1959).

Intravenous administration in the intact cat of 50—100 μg/kg doses of psilocin or psilocybin is followed by a short but distinct rise in pressure, usually accompanied by relative bradycardia. This pressure rise seems more the result of centrally mediated vasoconstriction than of a direct peripheral effect, since the hypertensive response is not enhanced but rather reduced in the spinal cat (WEIDMANN and CERLETTI 1959, CERLETTI 1959).

In the intact cat, 4-HT (100 μg/kg, i.v.) produces a rise of blood pressure which is 2 to 6 times less intense but more sustained than that elicited by the same dose of 5-HT. In the spinal cat, 4-HT causes hypertension, like 5-HT, but whereas with 5-HT the pressure rise is proportional to the dose administered, with 4-HT this is not so.

5-HTP, given intravenously in doses of 2.5—5 mg/kg, elicits a moderate fall of blood pressure, which lasts 15—20 min; the same dose of 4-HTP produces a more pronounced rise of blood pressure, lasting 30—50 min (ERSPAMER et al. 1960).

Both in the intact and in the pithed cat intravenous bufotenidine (20—100 μg/kg) causes a prompt adrenaline-like rise of blood pressure. In the pithed cat it is 5 to 7 times less potent than adrenaline, but 250 times more potent than 5-HT (POWELL 1955).

Tryptamine always has the characteristics of a predominantly hypertensive drug, thus giving pressure responses similar to those described in the dog: rise in pressure which is occasionally preceded or followed by a minor fall (LAIDLAW 1912, GYERMEK 1953, REID 1952a, POWELL 1955, BUÑAG and WALASZEK 1962c). Cocaine does not potentiate tryptamine hypertension; yohimbine, ergotoxine, hydergin and, to a lesser degree, nicotine as well as diphenhydramine and other

antihistaminic agents reduce it somewhat; ganglionic blockade, atropine and curare show no remarkable effect (REID 1952, GYERMEK 1953).

Tested on the decerebrated or pithed cat, N-methyltryptamine is less hypertensive than tryptamine, and N,N-dimethyltryptamine still less so (CHEN and CHEN 1933; ERSPAMER 1952a, 1954). The trimethylammonium derivative seems, on the contrary, more active than tryptamine, possessing about $^1/_{20}$ of the pressor action of adrenaline (CHEN and CHEN 1933). Gramine causes very moderate hypertensive responses even when given in large doses (5—20 mg/kg) and sometimes hypertension is preceded by a pressure fall (POWELL and CHEN 1945, POWELL 1955).

Finally, several of the substituted β-aminoethylindazoles synthetized by AINSWORTH (1958) prove to be hypotensive in the cat. The most effective members of the series are 5-hydroxy-N,N-dimethylaminoethylindazole, 5-hydroxy-aminoethylindazole and 5-hydroxy-N-isopropylaminoethylindazole. These compounds produce a clear fall of blood pressure at doses of 0.1, 0.5 and 1 mg/kg, respectively.

Man. Single intravenous injections of 5-HT produce both in normotensive and hypertensive subjects variable responses probably dependent, to some extent, on the dose and on the manner of administration of the drug.

SPIES and STONE (1952) found that intravenous injections of 0.5—5 mg 5-HT constantly elicited a rise in both systolic and diastolic pressure independent of the initial pressure level, i.e., in normal as well as in hypotensive and hypertensive patients. After 5 to 10 minutes, the pressure returned to normal. Subsequent injections at intervals of 2 to 3 hours gave identical results.

PAGE and MCCUBBIN (1953a) obtained partly discordant results from continuous pressure recordings in 20 hypertensive patients. They believe that the most common response of hypertensive human beings to small intravenous doses of 5-HT (0.06—0.12 mg) is slight hypotension, with a negligible hypertensive component. Larger doses (0.3—1.8 mg) produce the typical response observed in dogs (brief drop followed by pressure rise and then by a more sustained drop).

The results of HOLLANDER et al. (1956, 1957) in 30 hypertensive patients were again partly at variance. These investigators observed that depressor responses occurred more often after doses of 5-HT smaller than 0.3 mg; biphasic responses (brief fall and then overshoot for 1—5 min) more frequently over 0.3 mg; and pressor responses (increase in both systolic and diastolic pressures for 1 to 6 min, eventually followed by a brief drop) towards 1 mg and more.

Predominant fall of systolic and diastolic blood pressure, sometimes preceded by a short-lived rise, was observed also by other research workers after 0.4—3 mg of intravenous 5-HT (ANNONI et al. 1955, BALDRIGHI and FERRARI 1955, REDISCH et al. 1956, BOCK et al. 1957).

Following infusion of 5-HT into a vein (HOLLANDER et al. 1957, LEMESSURIER et al. 1959) or into the main pulmonary artery (GROVER et al. 1958), at a rate of 10—1000 μg/min, systemic arterial pressure displays only minor and variable variations, while at the highest dosage levels, systemic vascular resistance decreases.

5-HT given intramuscularly in single or repeated doses of 1—4 mg does not appreciably change the systemic blood pressure or only produces unimportant delayed responses (BASSANI and FANTINI 1956, ABBATI et al. 1955, CORREALE 1957).

The blood pressure effects of 5-HT are not prevented by prior administration of hexamethonium, regitine, atropine, antihistamines or reserpine (HOLLANDER et al. 1956, 1957). When 1 mg of 5-HT is injected during pentolinium-induced hypotension, there is a short elevation followed by a marked and sustained drop

of both diastolic and systolic pressures exceeding considerably the hypotensive effect of pentolinium alone (REDISCH et al. 1956).

Possible side-effects of intravenous infusion of 5-HT in man are an increase in local venous pressure with occasional reflux of blood into the afferent vessels, burning pain along the course of the vein, which may become prominent, firm and tender; heaviness and tingling in the extremities; pressure in the head and eyes; nausea; cough, shortness of breath; abdominal cramps, and, occasionally, blurred vision, sweating, headache and excessive salivation (HOLLANDER et al. 1957, STEFANINI and MAGALINI 1956, PAGE 1957, LEMESSURIER et al. 1959). Thrombosis of the infused vein is exceptionally frequent (40% and 90%) when 5-HT is infused at a rate of 400 and 800 μg/min (LEMESSURIER et al. 1959).

Intravenous injections into human volunteers of 0.03—0.12 mg/kg bufotenine base over times ranging from 3 to 20 min produce purpling of the skin in the head and neck with slight tendency of blood pressure to increase (FABING et al.

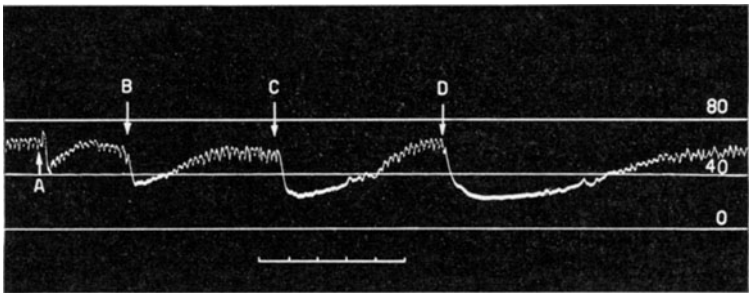


Fig. 4. Rabbit anaesthetized with urethane. Blood pressure response to intravenous injections of 15 (A), 30 (B), 70 (C) and 140 μg/kg (D) 5-HT base. Time in min. 5-HT produced pure hypotension at all dose levels, and decrease of blood pressure was proportional, both in intensity and duration, to the dose of the amine. [From Fig. 15, ERSPAMER, V., R. C. sci. Farmitalia **1**, 49 (1954).]

1956). Psilocybin, on the contrary, frequently induces hypotension and bradycardia when given parenterally to normal subjects and to mental patients in doses of 5 to 14 mg (DELAY et al. 1959).

Oral administration of N,N-dimethyltryptamine in a single dose up to 350 mg, or intravenous injection of 5—25 mg of the drug in 3 min does not display obvious cardiovascular effects (TURNER and MERLIS 1959).

Rabbit. The rabbit under urethane or pentobarbital anaesthesia reacts to crude enteramine preparations and to 5-HT with a pure hypotensive response, which is easily repeatable and satisfactorily correlated with the dose (ERSPAMER 1940b, 1940c, 1952a; PAGE and MCCUBBIN 1953a; SCHNEIDER and YONKMAN 1954). Transient slowing of the heart rate associated with cardiac irregularities is also present with uniformity (SCHNEIDER and YONKMAN 1954). Atropine, bilateral section of the vagus nerves and sympatholytic doses of dibenamine show either no effect or only a slight one on the depressor action of 5-HT (ERSPAMER 1940a, 1953a; PAGE and MCCUBBIN 1953a).

This action is, on the contrary, reduced or abolished by large intravenous doses (10—40 mg/kg) of tetrazotized diorthoanisidine (CATO and CAFRUNY 1960).

SCHNEIDER and YONKMAN were not able to confirm the statement by PAGE and MCCUBBIN that ganglionic blockade reverses the action of 5-HT from depressor to pressor.

According to LECOMTE and VAN DE BERG (1957) the blood pressure fall caused in rabbits by 5-HT is to a great extent dependent upon pulmonary vasoconstriction and consequent reduction of cardiac output.

The rabbit is less sensitive to tryptamine than either the dog or the cat. Injections of 0.2—1.8 mg/kg cause a small rise in systemic arterial pressure, which is sometimes preceded by a transient fall and followed by a further fall lasting 2 or 3 min. There is little change in pressure in the right ventricle (REID 1952a). N,N-dimethyltryptamine (125—250 μg/kg, i.v.) produces a more prolonged action than tryptamine (BUÑAG and WALASZEK 1962), whereas with bufotenine (HANDOVSKY 1920, BUÑAG and WALASZEK 1962), bufotenidine (5—100 μg/kg) (UEDA et al. 1957) and large doses of gramine (SUPNIEWSKI and SERAFINOWNA 1938) hypotension is predominant.

Psilocybin (5 mg/kg, i.v.) elicits in the waking rabbit a moderate but sustained elevation of blood pressure, accompanied by transient bradycardia (MONNIER 1959).

Guinea-pig. Intravenous injections of 0.1—0.2 mg/kg 5-HT in animals anaesthetized with pentobarbital usually elicit moderate hypertensive responses. With higher doses (0.4—0.8 mg/kg) hypertension is preceded or followed by a hypotensive phase (ERSPAMER 1952).

Rat. The intact unanaesthetized rat responds to 5-HT given by subcutaneous route in doses of 0.4 mg/kg and more with a regular pressure fall, lasting 90 to 180 min, accompanied by intense dilatation of the cutaneous vessels. Doses of less than 0.4 mg/kg are either ineffective or nearly so. 5-Methoxytryptamine is approximately 4 times less potent than 5-HT (CORREALE 1954, ERSPAMER 1952, ERSPAMER and OTTOLENGHI 1953, TAKÁCS and VAJDA 1963).

The results obtained by SALMOIRAGHI et al. (1956) in anaesthetized rats given rapid intravenous injections of 5-HT were similar. Doses of 5-HT base as low as 4—10 μg/kg produced a small transient fall in arterial pressure (von Bezold-Jarisch-like effect) succeeded by a small pressure rise, followed in turn by marked and prolonged hypotension (25—65 mm Hg for 3—4 min). Vagus section abolished the von Bezold-Jarisch-like effect; neither vagus section nor inactivation of the carotid sinus modified the prolonged depressor response. After ganglionic blockade or pithing, 5-HT elicited only large pressor responses. LSD and BOL in large doses effectively antagonized pressor-depressor responses to 5-HT in rats (SALMOIRAGHI et al. 1957).

Although confirming that the basic effect of intravenous 5-HT in rats is depressor, OUTSCHOORN and JACOB (1960) affirm that the shape of blood pressure response to the amine depends both on the dose (threshold = 0.5—1 μg/kg) and the initial level of blood pressure. The depressor effect is, in fact, less apparent or even absent at low and more pronounced at high pressure levels and the converse applies to the pressor component.

Intravenous infusion of 5-HT causes slight, transient decrease of blood pressure at infusion rates of 0.8—2.5 μg/kg/min, initial larger decrease of pressure with recovery at rates of 3—5 μg/kg/min, and finally biphasic blood pressure curve with initial fall and return to levels higher than control at rates of 5.5—8 μg/kg/min (DEL GRECO and CORCORAN 1956).

The prolonged depressor effect of 5-HT is interpreted by SALMOIRAGHI et al. (1956) as being due partly to depression of neurogenic vasoconstrictor tone and partly to a direct peripheral vasodilator effect of the amine. OUTSCHOORN and JACOB (1960) in their turn suggest that the depressor effect is both of parasympathetic and sympathetic origin, and the pressor effect of sympathetic origin, at least in part.

In contrast to 5-HT, bufotenine and psilocybin produce a pure rise in blood pressure not only in rats with ganglionic blockade but also in normal rats. In addition, the pressor response is considerably more sustained than with 5-HT. BOL is again a good antagonist (GESSNER et al. 1960).

Calf. In calves given a 3-minute intravenous infusion of 0.2 mg/kg/min 5-HT base, carotid blood pressure presents a drop of 28 ± 6.7 mm Hg (KUIDA et al. 1961).

Chicken. 5-HT and tryptamine produce a fall in blood pressure upon intravenous injection in anaesthetized chickens. The minimum effective dose of 5-HT is 1—3 μg/kg and maximal effects are elicited by 100—200 μg/kg. Tryptamine is 3—5 times less active (POWELL 1955; LECOMTE and BEAUMARIAGE 1957; NATOFF and LOCKETT 1957; BUÑAG and WALASZEK 1961 b, 1961 c; EBLE 1962).

The depressor response is not significantly affected by vagotomy, physostigmine or mecamylamine. It is, on the contrary, reversed in most instances by atropine (0.5—5 mg/kg) and either blocked or altered by antihistaminic drugs, such as parabromdylamine and diphenhydramine (BUÑAG and WALASZEK 1961 b, 1961 c). Chickens depleted of tissue histamine by repeated injection of 48/80 are found to respond to injections of 5-HT (5—100 μg/kg) or tryptamine (60 to 1000 μg/kg) with a rise in arterial pressure, instead of the usual fall. Moreover, bioassay for histamine done on urine samples taken after injection of 5-HT (50—150 μg/kg) or tryptamine (500—1500 μg/kg) shows significant increments in urine content (BUÑAG and WALASZEK 1962 b).

On the basis of these data, BUÑAG and WALASZEK suggest that histamine liberation is the major factor responsible for the depressor response to tryptamine and 5-HT in chickens, and that the latent vasopressor effect of 5-HT, which can be observed in the intact animal only when the normally stronger depressor activity of the drug has been nullified by pretreatment with atropine, antihistaminics or compound 48/80, is mainly produced by a direct peripheral vasoconstriction exerted by the 5-HT molecule *per se.*

Injections of 5-HT (0.01—0.1 μg) into the vessels of the isolated perfused chicken wing cause an intense vasoconstriction, which is directly proportional to the injected dose of the amine.

The above view that histamine release is an important factor in the fall of blood pressure caused by tryptamine is not accepted by EBLE (1962, 1963), who believes that this fall is rather the result of an acute pulmonary hypertension. In fact, systemic hypotension in the chicken is accompanied by a rise in peripheral resistance and in right ventricular pressure. Moreover, the depressive effect of tryptamine (0.1—0.3 mg/kg) is immediate and not delayed, it does not show tachyphylaxis (7 doses within 30 min) or cross tachyphylaxis with 48/80, and is not affected by cholinergic blockade with atropine or methylatropine, nor by adrenergic blockade with tolazoline or dichloroisoproterenol.

The most effective drugs for reversing the hypotensive effect of tryptamine are, according to EBLE, the MAO inhibitors tranylcypromine and β-phenylisopropylhydrazine. The pressor response thus obtained is not blocked either by cocaine or by dibenzyline.

Hypotension produced in the chicken by 5-HT and tryptamine can be blocked by lysergic acid derivatives in the following ascending order of potency: ergotamine, dihydroergotamine, LSD, BOL, ergonovine and UML (BUÑAG and WALASZEK 1962 a).

Bufotenine (50—100 μg/kg, i.v.) and 4-HT (50—100 μg/kg), like 5-HT and tryptamine, lower the chicken blood pressure; dimethyltryptamine (300 to 750 μg/kg), psilocin (50—100 μg/kg) and psilocybin (100—200 μg/kg), on the contrary, produce a prolonged pressor response (BUÑAG and WALASZEK 1962 c).

Single injections of bufotenidine lower the blood pressure. However, upon repeated injections, the depressor action of bufotenidine is reversed to pressor. Gramine (1 mg/kg) behaves essentially like a hypertensive agent (POWELL 1955).

III. Action on special vascular areas

1. Coronary vascular bed

In dogs anaesthetized with morphine and dial-urethane-nembutal, cardiac output (Fick) and coronary blood flow (NO_2 Fick) were measured before and after the mechanical infusion into the left or the right atrium of 8 μg/kg/min 5-HT base over a period of 25 min. It was found that 5-HT produced a 20 to 169% increase in coronary blood flow, a 27—62.5% decrease in coronary vascular resistance and a 31—107% increase of coronary sinus oxygen content. Thus, the decrease in myocardial oxygen extraction associated with the increase in coronary flow resulted in myocardial oxygen consumption remaining unchanged. Myocardial CO_2 excretion was maintained in a similar manner. Mechanical efficiency of the left ventricle fell by 3%. Coronary blood flow/left ventricle work ratio increased by 65% (MAXWELL et al. 1957, MAXWELL et al. 1959, CRUMPTON et al. 1959, ROWE et al. 1963).

Similar results are obtained following injection of 5-HT (1—30 μg in 1 ml saline) into the left main coronary artery. There is a prompt fall in coronary vascular resistance when the drug reaches the coronary circulation, before a change in heart rate and aortic pressure occurs. The percentage decrease in coronary vascular resistance is related to the dose administered. Myocardial oxygen consumption shows no change from control value (GRIGGS and CASE 1960).

Thus, in confirmation of the previous work of SCHOFIELD and WALKER (1953), 5-HT appears to act in the dog as a potent "benign" coronary dilator increasing the oxygen supply to the myocardium without increasing the ventricular work. These results would seem to exculpate 5-HT as a major factor in the genesis of cardiac infarct (MAXWELL et al. 1959).

In contrast to 5-HT, psilocybin (0.5 mg/kg, i.v.) does not show in the dog any true coronary vasodilator properties, and coronary vascular resistance remains unchanged (MAXWELL, KNEEBONE and ELLIOTT 1962).

In the heart-lung preparation of the rabbit 25 μg 5-HT (0.5—5 μg doses are inactive) causes a 25—60% fall of coronary flow with evident increase in coronary vascular resistance (MAGGI 1960).

Both in the isolated heart of the dog and in that of the cat, 30—300 μg 5-HT introduced into the perfusion fluid produces a clear increase in coronary flow (SCHNEIDER and YONKMAN 1954).

According to KAPILA and ARORA (1962), the intravenous injection of 5-HT (5—20 μg/kg) into dogs subjected, 18 hr previously, to a two-stage ligation of the anterior descending branch of the left coronary artery produces an immediate effect consisting of a short-lasting moderate reduction in ectopic ventricular rate and a slight increase in total heart rate, and a late effect, reaching its peak 20 hr after 5-HT administration, consisting of prolonged reduction in the total heart rate as well as in ectopic ventricular rate.

2. Pulmonary vessels

Owing to the existence of conspicuous species differences in the sensitivity of the pulmonary bed to 5-HT it seems opportune to discuss the response of this vascular area (to the amine) separately in the different animal species, starting with the dog, which has been the object of the most thorough investigation.

Dog. The first study on the haemodynamic effects of 5-HT injected into the pulmonary artery is probably that of MACCANON and HORVATH (1954) who introduced the amine (30—45 μg/kg) directly into the pulmonary artery of dogs

anaesthetized with pentobarbital. After a latency of 5—8 seconds a systemic hypertensive response was observed, lasting 2 to 5 min. No alterations in cardiac output or pulmonary blood volume, measured by the tracer dilution technique, were noted at the prehypertensive stage. At the peak of the hypertensive reaction variable responses were obtained.

Apart from these rather ambiguous results, all available evidence concordantly demonstrates that 5-HT is a potent constrictor of the pulmonary vessels in the dog.

Pulmonary vasoconstriction can be elicited by single injections into a vein, into the right atrium or into the pulmonary artery of doses of 5-HT as low as 1—5 μg/kg, or by i.v. infusion of 1—8 μg/kg/min 5-HT (NAHAS 1958, NAHAS and MACDONALD 1959, BORST et al. 1957, RUDOLPH and PAUL 1957, NOBLE and NANSON 1959, DUTEIL and AVIADO 1962).

Single injections of 1 μg/kg 5-HT into the right atrium of an intact dog produce a 37% rise in pulmonary artery-pulmonary vein pressure difference, and this effect remains unchanged after spinal section or vagotomy (NAHAS and MACDONALD 1959). Similarly, single injections of 1.5—8.5 μg 5-HT into the pulmonary artery produce a 53% increase in pulmonary vascular resistance, and injections of 20—47 μg a 62% increase. These results by ROSE and LAZARO (1958) have been confirmed by HARASAWA and RODBARD (1961) who observed that 16 μg/kg 5-HT base injected into the pulmonary artery of anaesthetized, thoracotomized dogs produced an almost immediate elevation of the pulmonary artery pressure, which was maximal (+35%) about 30 seconds after the injection and returned to control levels within 5 min.

Infusion rates as low as 8 μg/kg/min result in a 30—100% increase of pulmonary arterial pressure, and in a 55% increase in the difference of pressure between the pulmonary artery and the left atrium, with only a 16% increase in pulmonary blood flow (RUDOLPH and PAUL 1957a, 1957b; SHEPHERD et al. 1959; CRUMPTON et al. 1959). Infusion rates of 150 μg/kg/min 5-HT base produce a 300% increase in the mean pulmonary pressure, a 28% drop in systemic arterial mean pressure and a 60% rise of cardiac output. Calculated pulmonary resistances markedly increase up to 500% of control levels but, in contrast, systemic resistances decrease by 55%. Arterial oxygen saturation is usually considerably reduced during 5-HT infusion. These effects persist as long as the drug is administered (RUDOLPH and PAUL 1957a, 1957b; MCGAFF and MILNOR 1962, ROWE et al. 1963).

As a consequence of pulmonary vasoconstriction, there is a considerable decrease in the pulmonary mean transit time, as measured by the dye dilution method (from 3.92 to 2.24 seconds following i.v. infusion of 0.06—0.4 mg/kg/min 5-HT base), and an appreciable reduction in the pulmonary blood volume (from 11 to 8.7 ml/kg). According to MCGAFF and MILNOR (1960, 1962) and MILNOR et al. (1962), the magnitude of the decrease in pulmonary blood volume indicates that a relatively large part of the pulmonary vascular bed is constricted by 5-HT, and provides an example of the shifting of blood from pulmonic to systemic circuits by reciprocal changes in the distensibility of these beds.

Injection of 5-HT into the left pulmonary artery of the unanaesthetized dog produces a decrease in the volume and rate of flow in this vessel and little or no change in main pulmonary artery flow; injection into the right ventricle causes a delayed response in which flow increases moderately in both vessels (RUDOLPH et al. 1962).

Although the principal site of the increased resistance to flow through the lungs appears to be in the pulmonary arterioles (GILBERT et al. 1957, 1958; KABINS et al. 1959) or pre-capillary vessels (SHEPHERD et al. 1959), pulmonary

venules are also constricted by 5-HT, especially when given in large doses (KABINS et al. 1959, SHEPHERD et al. 1959, AVIADO 1960, BRAUN and STERN 1961).

Signs of increased arteriolar constriction are the increase in the pressure gradients between the pulmonary artery and pulmonary artery wedge pressures, as well as the reduction in the lung weight following injection of 14—100 μg 5-HT into the pulmonary artery; signs of increased venular constriction are the increase in the pressure gradients between the pulmonary artery wedge pressure and the left atrial pressure, the increase in venular pressure, as measured directly, and finally the increase in pulmonary capillary blood volume.

The rise in venular pressure following intravenous injection of 2—4 μg 5-HT base is 50—80% of the respective increase in arterial pressure (AVIADO 1960); the increase in pulmonary capillary blood volume following infusion of 100—200 μg/min of 5-HT base is 6—133% (YOUNG et al. 1962).

The increase in pulmonary vascular resistance caused by 5-HT can be reduced in the dog by augmenting the pulmonary blood flow as well as by raising the pulmonary venous pressure up to 25—30 mm Hg (RUDOLPH and AMAULD 1960).

According to BRAUN and STERN (1961) the rise in pulmonary artery and pulmonary venous pressures is due not only to a direct action of 5-HT on vascular smooth muscle but also to chemoreceptor stimulation.

This opinion is not shared by VITOLO et al. (1962) who affirm that the pulmonary vasoconstriction provoked by 5-HT is due neither to neurogenic mechanisms nor to humoral mechanisms, but only to a direct action on the pulmonary vessels.

Promethazine, BOL and LSD (0.4—0.6 mg/kg) effectively antagonize the constrictor action of 5-HT on pulmonary vessels (ROSE and LAZARO 1958). Vasoconstriction produced by continuous infusion of 5-HT is in part also antagonized by acetylcholine, histamine and adenosine-triphosphate (RUDOLPH et al. 1959).

The action of 5-HT on the pulmonary vascular area exceeds that of angiotensin (CARLIER et al. 1958), and of all other biogenic amines, including catecholamines (ROSE and LAZARO 1958, BORST et al. 1957).

Large doses of 5-HT (0.2—3 mg) injected into the dog pulmonary artery produce in 75% of the animals moderate to severe pulmonary oedema with occasional evidence of left heart failure. Without excluding the possibility of other indirect or reflex mechanisms, such as release of histamine or catecholamines, or the initiation of reflexes over the sympathetic nervous system, it seems probable that the change in capillary permeability provoked by 5-HT may be due to the direct action of 5-HT itself on the pulmonary capillary wall. On the basis of similarity of results, it is suggested by KABINS et al. (1959) that 5-HT may perhaps play a part in pulmonary oedema formation due to unilateral starch embolization.

Following intravenous injection of 10 μg 5-HT in cats and 50 μg 5-HT in dogs and rabbits, masses of whitish translucent material visibly embolize pulmonary arteries, observed by quartz-rod transillumination. From seconds to 15 min the material seems to become less rigid, breaks up, is pushed into smaller branches and passes through the capillaries (KNISELY et al. 1958).

The question whether 5-HT can initiate systemic vascular reflexes in the pulmonary vessels is answered negatively by ROSE and LAZARO (1958) on the basis of experiments carried out on an experimental preparation in which such reflexes are easily demonstrated.

The injection of 0.04—0.07 μg/kg 5-HT into the bronchial artery of the dog causes consistent bronchoconstriction accompanied by increase in bronchopulmonary flow. Blood flow in the bronchial artery is either increased or decreased (DE LETONA et al. 1961).

Cat. The intravenous injection of serum vasoconstrictor or of 5-HT (5—40 μg) into the cat causes a rise of pressure in the right ventricle and in the pulmonary artery, accompanied by a fall in the pulmonary vein. In the cat, too, this phenomenon is due to an increase in the pulmonary resistance and not to cardiac stimulation (COMROE 1952, COMROE et al. 1953, REID and RAND 1952, REID 1952b). It is not abolished by vagotomy nor by atropine, but can be in part antagonized by yohimbine (REID 1952b) and, more efficaciously, by ergotamine and LSD (GINZEL and KOTTEGODA 1953). The pressor response in the lesser circulation is lacking if 5-HT is injected into the pulmonary vein.

The action of tryptamine in the cat, dog, and rabbit is similar to that described for 5-HT (REID 1952a). According to GINZEL and KOTTEGODA (1953) 1 dose of 5-HT is equipotent, on the pulmonary vessels of the cat, to 2.4 doses of tryptamine and to 10—20 doses of adrenaline or noradrenaline.

Man. Using the technique of right heart catheterization, GROVER et al. (1958) infused 4 mg 5-HT base in 100 ml of isotonic saline directly into the main pulmonary artery of 7 patients with normal pulmonary arterial pressure. Infusion lasted 7 to 10 minutes. Mean pulmonary arterial pressure rose from 2 to 10 mm Hg, while the wedge pressure remained unchanged. The change in total pulmonary vascular resistance was variable, increasing in three cases and decreasing in three others.

HARRIS et al. (1960) infused i.v. 0.6—2.5 μg/kg/min 5-HT base into 7 patients with normal hearts and minimal healed tuberculous lesions of the lung, and injected 0.4—1.6 μg/kg 5-HT into the right atrium of 3 other patients. In only one instance was there pressure rise in the pulmonary artery after infusion and this was accompanied by a rise in brachial artery pressure. Injections into the right atrium caused sustained rise in pressure in pulmonary and brachial arteries.

Finally, STONE and NEMIR (1960) injected 5-HT (4—400 μg/kg) through the distal lumen of a catheter inserted into the pulmonary artery before and after unilateral balloon occlusion of the corresponding artery. Only minimal changes in mean pulmonary artery pressure, pulmonary capillary pressure and pulse rate were observed with no objective or subjective signs resembling those associated with pulmonary embolism.

The above results concordantly demonstrate that the pulmonary vascular bed presents in man poor sensitivity to 5-HT and that it is unlikely that 5-HT participates in the pathogenesis of the clinical picture of human pulmonary embolism.

Calf. Intravenous infusion of 5-HT into calves (0.2 mg/kg/min for 3 min) fails to alter significantly pulmonary artery pressure, pulmonary artery wedge pressure or pulmonary vascular resistance, as measured by cardiac catheterization techniques. The only statistically significant effect of the amine is to decrease cardiac output. KUIDA et al. (1961) conclude that in calves 5-HT is not an effective pulmonary vasoconstrictor agent and hence that it is unlikely that it plays a role in the pathogenesis of spontaneous pulmonary hypertension.

Sheep. Intravenous infusion of 5-HT into the sheep (25—50 μg/kg/min) produces a 20—30% rise in pulmonary pressure accompanied by a 7—30% fall in arterial oxygen saturation (HALMAGYI and COLEBATCH 1961).

3. Liver vessels

An injection of 15 μg 5-HT into the portally perfused canine liver produces a small increase in the resistance to blood flow through the liver. However, 1 mg 5-HT added to 500 ml of perfusing liquid causes no congestion. Increased re-

sistance probably occurs in the portal vessels before the hepatic artery and the portal vein join. It is concluded that it is unlikely that the cause of hepatic congestion in perfused preparations is either 5-HT or histamine (ANDREWS and BUTTERWORTH 1958).

In substantial accordance with these findings, SHOEMAKER et al. (1961) observed that in unanaesthetized dogs whose hepatic vessels had previously been catheterized, hepatic plasma flow decreased to approximately half the control value 1 to 2 min after the injection of 0.1—0.2 mg/kg 5-HT base into the femoral vein. The lowest point was reached in 1 to 1.5 min. An increase in portal venous potassium, often over 2 meq/l, occurred 1 to 2 min after the injection, followed by an increase in hepatic venous potassium. Multiplication of concentration differences by flow values showed a marked output of potassium from the non-hepatic splancnic area, 1—2 min after injection, followed by hepatic potassium output. In addition, there was a fall in arterial, portal and hepatic venous glucose levels and uptake of glucose by the non-hepatic splancnic area.

The portal pressure in the dog is raised also by the systemic intravenous injection of tryptamine. According to REID (1952) this is not due to constriction of the hepatic sphincter but appears to be a passive result of increased arterial pressure.

The action of 5-HT on the veins of the rat liver was examined by JÄNKÄLÄ and VIRTAMA (1962) with the aid of direct observation and microangiographic technique. They found that doses of 5-HT base from 0.2 to 10 mg/kg injected into the portal vein caused a conspicuous reduction of the liver volume, as shown by the decrease of the liver weight as a percentage of the total body weight (after 10 mg/kg 5-HT from 4.9 to 3.1%), and a vigorous constriction of the portal and hepatic veins. Vasoconstriction was most marked in the small venules. Pretreatment with reserpine did not prevent the venoconstrictor effect of 5-HT.

Similar results were obtained by LEVINE et al. (1964) in the isolated rat liver. Injections of 5-HT into the portal vein cannula produced a prompt decrease of hepatic blood flow and decrease was approximately proportional to the dose (threshold 12 μg 5-HT base). However, tachyphylaxis was notable in this preparation.

In human subjects the intravenous infusion of 12 μg/kg/min 5-HT base does not affect portal venous pressure significantly. The estimated hepatic blood flow is reduced by 9.2% and the splancnic resistance is raised by 13% (CHIANDUSSI et al. 1962, 1963).

4. Spleen vessels

Intravenous injection of 10—30 μg/kg 5-HT base causes a 56% decrease in the venous outflow of the *in situ* dog spleen, which lasts 7—12 min. Flow reduction is preceded by a short-lived, 25% flow increase. Direct injection of 1—20 μg 5-HT into the artery of both *in situ* and isolated perfused spleen produces similar results (RIVA SANSEVERINO and URBANO 1962).

Spleen volume is generally reduced by 5-HT, but whereas reduction of spleen volume is the sole response of the isolated perfused spleen to intraarterial 5-HT (1—20 μg), the normally irrigated *in situ* spleen sometimes responds to intravenous 5-HT (5—10 μg/kg) with an occasional volume increase, following the contraction. Lower intravenous doses of 5-HT (1 μg/kg) cause small, unpredictable changes in the spleen volume. Splenocontraction is ascribed mainly to vasoconstriction and subordinately to contraction of the smooth muscles in the spleen capsule (RIVA SANSEVERINO and URBANO 1961, 1962).

0.5—2 mg of bufotenine injected intravenously provokes, like 5-HT, a contraction of the dog spleen, which lasts longer than the pressure rise (RAYMOND-HAMET and DUFAU 1942).

5. Vessels of the placenta

ELIASSON and ÅSTRÖM (1955) and ÅSTRÖM and SAMELIUS (1957) first observed that 5-HT injected into the umbilical artery of the perfused placenta displayed a potent constrictor action which was about 10 times stronger than that of L-adrenaline, and 20 times stronger than that of L-noradrenaline. Doses of 0.3—3 μg provided moderate vasoconstriction; doses of 5—10 μg often caused complete closure of the vessels. Tryptamine was 10 to 20 less times active than 5-HT.

The action of 5-HT was enhanced by cocaine and antagonized by dihydroergotamine, LSD, tryptamine, yohimbine and chlorpromazine. Ephedrine, propanidine, iproniazid, hexamethonium, phenbenzamine, reserpine and heparin (up to 30 mg) were ineffective. Owing to lack of nervous tissue in the umbilical cord and in the placenta the above effects of 5-HT must be considered as the expression of a direct action of 5-HT on the vascular smooth muscle.

The results of ÅSTRÖM and co-workers were confirmed by others.

GAUTIERI and CIUCHTA (1962) perfused human placenta at a pressure of 50—60 mm Hg and measured venous outflow directly. The injection into the umbilical artery of 20 μg 5-HT base in 0.5 ml liquid caused an immediate decrease in the flow rate, which ranged between 19 and 61%. Vasoconstriction was maximal during the first two minutes and almost complete recovery to the preinjection level was attained in 6—8 min. There was no tachyphylaxis.

The funicular portion of the umbilical vein behaved like the umbilical artery. Here again the most potent constrictor agent was 5-HT, active at concentrations as low as 0.1—0.25 μg/ml (PANIGEL and MAYER 1959).

RODEGRA et al. (1957) and SCHMERMUND et al. (1959) suggest that 5-HT liberated from blood platelets may participate in the spontaneous closure of the umbilical artery after birth.

6. Musculo-cutaneous vessels

Careful experiments have been carried out especially in the dog and in man.

Dog. 5-HT infused into the brachial artery of the foreleg of anaesthetized dogs at a rate of 4—5 μg/min does not significantly change the total resistance of the foreleg vessels, but increases large artery and sometimes vein resistance and decreases small vessels resistance. This means that 5-HT causes pronounced constriction of large arteries and large veins with concomitant dilatation of small vessels (probably arterioles) and fall of small vessel intraluminal pressures. HADDY and co-workers (HADDY et al. 1957a, HADDY et al. 1957b, HADDY 1959) are of the opinion that 5-HT-induced segmental resistance changes occur through active mechanisms. They further suggest that a function of 5-HT may be that of influencing volume distribution of blood within various segments of the circulatory system as well as influencing water and salt distribution between intravascular and extravascular compartments.

The directionally opposite changes in segmental resistance may explain how 5-HT produces peculiar skin colour changes without predictable blood pressure variations when injected into intact animals or man.

Besides small vessel dilatation, 5-HT also produces oedema of the dog forelimb when given by prolonged infusion into the brachial artery of denervated animals. During infusion small venous pressure rises from 10 to 16 mm Hg and

weight gain of the forelimbs averages 0.4 g/min, instead of 0.1 g/min. According to HADDY (1960) these findings indicate that 5-HT produces oedema by raising capillary hydrostatic pressure.

Still owing to the opposite changes in segmental resistance it produces, 5-HT is capable of antagonizing extremes of vascular tone induced in the dog foreleg by neurogenic means. When small vessels are dilated following denervation of the foreleg, 5-HT (4 μg/min) cannot dilate them further, but continues to constrict large vessels, the net effect being constriction. When small vessels are highly constricted following bilateral vagotomy, 5-HT dilates small vessels more than it constricts large vessels, the net effect being dilatation. A similar antagonism is more difficult to demonstrate when tone is varied by humoral means (HADDY et al. 1959). The interaction of 5-HT with vasoconstrictor agents has been the object of a particularly thorough study by GORDON and co-workers (GORDON et al. 1958a, 1958b; HURWITZ et al. 1961). 5-HT (2.5—8 μg/min) in combination with noradrenaline, adrenaline, vasopressin and angiotensin was infused into the brachial artery of the denervated dog forelimb at rates which were effective locally but not effective generally. Pressures were measured at 4 sites along the length of the foreleg vascular bed while the rate of blood flow in the brachial artery was held constant. Each combination resulted in net constriction but in the case of catecholamines the constriction was less than the sum of the constrictions of the two agents administered separately owing to the antagonistic action of 5-HT and catecholamines upon small blood vessels. The venous constrictor action of 5-HT was potentiated by each of the examined pressor agents (HURWITZ et al. 1961).

Results of recent experiments by MCCUBBIN et al. (1962) on the dog perfused hind leg and the dog perfused kidney again point to the importance of neurogenic vasoconstrictor tone in determining the vascular response to 5-HT and indicate that inhibition of neurogenic vasoconstriction by 5-HT, with ensuing vasodilatation, may be mediated through the adrenergic vasodilator receptors.

In fact, when 5-HT (1—12 μg of the base) is injected into the vessels of the hind leg perfused by the dog's own circulation during stimulation of the lumbar sympathetic trunk it causes relaxation of the constricted small arteries but further constriction of the large ones, the net effect being decrease in total vascular resistance; when 5-HT is injected in the absence of stimulation it causes constriction of both large and small arteries and increase in vascular resistance. Small veins respond to stimulation and 5-HT as do small arteries. Small arteries of the mesentery react to regional nerve stimulation as do those of the hind limb.

There is no evidence of interference of 5-HT with sympathetic vasoconstrictor pathways and 5-HT does not oppose vasoconstriction due to noradrenaline or tyramine but does, in part, oppose the vasoconstriction that is due to adrenaline which acts on both adrenergic constrictor and dilator receptors. Selective blockade of adrenergic dilator receptors with dichloroisoproterenol prevents the vasodilator activity of 5-HT and eliminates the ability of the amine to depress vasoconstrictor responses to neurogenic stimulation.

MCCUBBIN and co-workers advance the working hypothesis that 5-HT affects adrenergic vasodilator receptors in a manner that causes them to have a more prominent effect when stimulated. The resultant decrease in total vascular resistance would be caused by dilatation of small arteries and veins.

RAYMOND-HAMET (1941) found that a first injection of 0.1 mg bufotenine into the dog femoral artery caused an 82% reduction in the venous outflow and that a subsequent injection of 5 mg/kg of the amine brought about a reduction

of only 30%. The substance was 100 to 500 times less vasoconstrictor than adrenaline. These results were considered to be indicative of a nicotine-like action of bufotenine on the vessels.

Man. In human subjects 5-HT infused into the brachial artery in doses of 0.4—7.5 μg/min causes a reduction of blood flow through the forearm (30% with 0.4 μg/min, 50% with 1.6 μg/min and 70% with 7.5 μg/min) as well as through the hand (75 to 90%), with a concomitant volume increase (due to oedema formation) and a marked flushing of the skin. In the forearm the fall of flow is preceded by a transient increase and, as the infusion continues, cyanosis develops gradually in the skin of the fingers. Small petechiae are occasionally observed some hours after the infusion, indicating capillary damage. Soon after beginning the infusion of 5-HT a sensation of tingling is felt in the hand and lower forearm, which decreases somewhat throughout the infusion period and subsides within a few minutes of the end of the infusion. Large doses produce severe but fleeting pain.

The above phenomena have been ascribed to dilatation of capillaries or lower-pressure capacity vessels, mainly responsible for the colour of the skin, and to constriction of arterioles or higher-pressure capacity vessels, mainly responsible for resistance to flow.

These findings and interpretations by GLOVER, WHELAN and co-workers (RODDIE et al. 1955a, 1955b; GLOVER et al. 1957, 1958) are in substantial accordance with those of other research workers.

CALÌ and LOMEO (1955, 1957a, 1957b) and CALÌ, STRANO and LOMEO (1956) found that 20—40 μg 5-HT injected into the brachial artery produced the following changes in the capillaries of the nail bed, as observed capillariscopically: remarkable reddening of the field, conspicuous dilatation of the capillaries, increase of the number of visible capillaries. On pletismographic examination, the finger volume was seen gradually to increase, up to a maximum after 10 to 20 min, and amplitude of arterial pulse to decrease consistently. Venous pressure recorded at the elbow showed a conspicuous elevation, which was of the order of 50 cm of water and persisted as long as 30 min after 50—200 μg 5-HT.

MAGALINI et al. (1956) similarly observed that 0.4 mg 5-HT base given intra-arterially caused disappearance of the radial pulse for 5 min with a short period of blanching, followed by flushing of the skin of the volar and dorsal surfaces of the hand for longer than 30 min. Pressure in the homolateral vein rose from 65 to 280 mm H_2O, whereas there was no rise of pressure in the controlateral vein.

The potent constrictor action of 5-HT on the veins upon continuous intra-arterial infusion (10 μg/min) has been confirmed by SHARPEY-SCHAFER and GINSBURG (1962).

Both BOL and sodium salicylate appear to be specific antagonists of the constrictor response of the forearm and hand blood vessels to intraarterial infusion of 5-HT, but whereas BOL displays a direct antagonistic action, sodium salicylate acts only indirectly, possibly through release of, or synergism with, some other substance, probably a hormone (GLOVER et al. 1957).

Following intravenous administration of 5-HT, changes in human forearm vessels are in many respects different from those observed after intraarterial injection of the amine. In fact, intravenous infusion of 0.5—1.2 mg 5-HT base/min causes a dilator response of the forearm vessels consisting of a huge initial transient increase in flow (3 to 4-fold, commencing within 1 to 1.5 min), followed by a smaller but sustained increase (Fig. 5). The resting level is attained 5 to 10 min after the infusion ceases. A fall in forearm flow is never seen. It has been suggested by LEMESSURIER et al. (1959) that the sustained increase in flow

probably represents a balance between the direct constrictor action of the drug and a secondary vasodilator effect.

Local venous pressure is transiently elevated by intravenous infusion of 5-HT: by 10 cm of water following 1.5 μg and by 16—18 cm of water following 15 μg given in 5 min. Pressure rise lasts 15 min. Elevation of systemic venous pressure is not obtained even with extremely large doses of 5-HT (10 mg in 15—30 min) (MAGALINI et al. 1956).

According to BOCK et al. (1957) both intravenous and intraarterial 5-HT constantly increase flow in the cutaneous vessels. Flow in muscular vessels is increased by intravenous 5-HT, in doses ranging from 0.1 to 3 mg, and by small doses of intraarterial 5-HT, but reduced by large doses of intraarterial 5-HT.

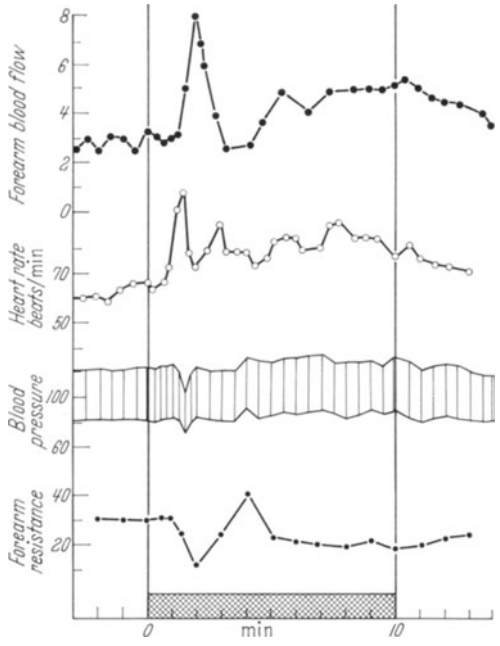


Fig. 5. The response of the forearm blood flow (●), heart rate (○), blood pressure and forearm vascular resistance (•) to 5-hydroxytryptamine creatinine sulphate administered intravenously in a dose of 2 mg/min for 10 min during the period indicated by the dotted area. The forearm resistance (mean pressure in mm Hg/forearm flow in ml/100 ml/min) is expressed in arbitrary units, blood pressure in mm Hg, heart rate in beats/min and forearm blood flow in ml/100 ml/min. [From Fig. 1, LEMESSURIER, D. H. et al., Brit. J. Pharmacol. **14**, 247 (1959).]

Local subjective symptoms of the intravenous injection are pain along the course of the infused vein and heaviness in the infused limb. There is, in addition, an abnormally high incidence of thrombosis in the vein infused with 5-HT (LEMESSURIER et al. 1959).

Intradermal injection of 5-HT in concentrations up to 20 μg/ml produces no appreciable action on the skin over the front of the forearm. Concentrations greater than this (100—2500 μg/ml) generally cause the appearance of a red reaction, lasting 15—45 min; there is neither itching nor weal formation (REID 1952b, MOLLER and RORSMAN 1959, HERXHEIMER and SCHACHTER 1959, HEITE and KLEINHANS 1962). In subjects with clearly visible and raised subcutaneous veins, doses of 5-HT as small as 1 μg cause the total disappearance of the venous network and a sharp demarcation between the area with venoconstriction and the surrounding areas (REID 1952b, DEMIS et al. 1960). The intradermal injection of tryptamine in concentrations up to 0.5% causes no blanching, but a weak red reaction around the site of the injection (REID 1952a).

Following iontophoretic application, 5-HT (3.5 mg/cm^2) produces marked erythema, slight oedema and no cyanosis. There is also conspicuous constriction of both normal and varicose veins (STÜTTGEN and SCHIPPEL 1961).

Cat. The blood vessels of the hind leg of the cat constrict moderately after the injection of 1—10 μg 5-HT into the femoral artery. The vasoconstriction, lasting over a 5 min period is frequently preceded by vasodilatation, and usually declines after repeated injections (REID 1952a). Tryptamine is 0.3—1 times as active as 5-HT; adrenaline is 10 to 500 times more active than 5-HT but the

constrictor response is of considerably shorter duration (GINZEL and KOTTEGODA 1953). Yohimbine and, more effectively, lysergic acid diethylamide antagonize 5-HT vasoconstriction (REID 1952a, GINZEL and KOTTEGODA 1953).

A more accurate and recent analysis of the effects of 5-HT on the musculocutaneous vascular area of the cat is lacking.

Guinea-pig. 5-HT produces, like adrenaline and histamine, a constriction of the vessels in the perfused hind leg of the guinea-pig. Lowering the concentration of calcium ions in the perfusion liquid causes only slight changes in the response to the three amines. This response, however, is completely inhibited by the addition to the calcium-free perfusion liquid of EDTA Na_2, which provokes a drainage of calcium from the irrigated territory (COHEN 1959, COHEN and BLANCHARD 1962).

Rat. Following intravenous or subcutaneous injection of adequate doses of 5-HT there appears, simultaneously with the changes in systemic blood pressure, a constriction of the tail artery, as evidenced by the absence of haemorrhage or shortening of bleeding time when the tail is severed. The local application of 5-HT onto the severed tail has no vasoconstrictor effect (CORRELL et al. 1952, CORREALE 1954).

5-HT is about twice as active on the intact hind leg vessels as on the abdominal aorta of the rat (STUDER and TRIPOD 1960). In rats made hypertensive through clipping of one renal artery, the vasoconstrictor action of 5-HT (0.5 μg/ml) on the perfused hind legs is the same as in control normotensive rats, but in hypertensive animals the amine counteracts oedema formation following perfusion more powerfully (TRIPOD and BEIN 1960).

When the nervous component of the vasomotor tone of the blood vessels of the innervated hind limb perfused with blood is reduced by ganglion blockade, by section of the nerves to the hind limb, or by the indirect effect of drugs, the vasoconstrictor response of the blood vessels to 5-HT (0.02 μg) is increased and perfusion pressure rises from 41.5 to 80.4 mm Hg. Similar results are obtained with adrenaline, noradrenaline, tyramine and ephedrine, but not with angiotensin or pitressin. Pretreatment with reserpine (3 mg/kg daily, for two days) reduces the mean response to 5-HT (15 mm Hg instead of 40). Results suggest that, in rats, activity in the sympathetic nervous system directly influences the reactivity of peripheral blood vessels to 5-HT and sympathomimetic drugs (LAVERTY 1962).

As in the case of the guinea-pig, the vasoconstrictor effect of 5-HT on the hind leg vessels of the rat is not affected by lowering the concentration of calcium in the perfusion liquid but is strongly reduced by drainage of calcium from the tissues produced by EDTA Na_2 (COHEN and BLANCHARD 1962).

Mouse. The effects of 5-HT on the vasculature of the mouse ear have been studied using a technique of freeze fixation which permits stereomicroscopic observation of the terminal vascular bed in a life-like state. It appears that single intravenous doses of 5-HT produce a) extravasation of parenerally administered Evans blue (after 50 or more μg 5-HT/kg), b) vasodilatation occurring directly after doses of 50—250 μg/kg or following an initial period of vasoconstriction after larger doses, and c) vasoconstriction, increasing in duration with dose (minimum 250 μg/kg). UML, 10 mg/kg, partially inhibits these effects. Local administration of 5-HT produces comparable results. Dye escape and vasoconstriction are most prominent in venules and are similar to the effects of 20 times the dose of histamine.

According to STROBEL et al. (1961) the above findings in mice provide additional evidence that concentrations of 5-HT within limits attainable from endo-

genous sources will produce the basic microcirculatory changes of early inflammation.

Rabbit ear preparation. The vessels of the rabbit's ear, prepared and perfused as described by PAGE (1942), are very sensitive to the constrictor action of 5-HT, the threshold dose being as low as 0.5—1 ng (BERTACCINI and ZAMBONI 1961). 0.15 μg of 5-HT were found by PAGE (1952) to be equivalent to about 0.025 μg of adrenaline. Similar results were obtained by GINZEL and KOTTEGODA (1953), who observed that the action of 5-HT on the ear vessels is usually even stronger than that of adrenaline, and that this action is not antagonized by hexamethonium or tolazoline.

GADDUM and HAMEED (1954) demonstrated that the action of 5-HT on the ear preparation is greatly increased when ephedrine (10 μg/ml) or choline-*p*-tolyl ether bromide (1 μg/ml) is present in the perfusion liquid. This potentiation has been ascribed to inhibition of monoamine oxidase.

Pig ear preparation. On the isolated pig ear 5-HT produces intense vasoconstriction, which is suitable for recording at 5-HT doses of 0.01 to 0.1 μg. Complete suppression of vasoconstriction is obtained with dihydroergotamine (GRETTE 1957).

7. Vessels of the kidney

See pages 285—297.

8. Brain vessels

Results obtained by different investigators are partly divergent, probably owing to different 5-HT dosage and route of administration, different experimental methods and different animal species.

SCARINCI (1955) found that intravenous or intracarotid injection of 5-HT (50—1000 μg/kg) produced in the dog blanching of the exposed cortical area, and BARUCCI (1956) obtained the same result in the rabbit, following 1 mg/kg of intravenous 5-HT. Ischemia lasted 15 to 25 min and was sometimes followed by hyperemia. However, results obtained in the cat were at complete variance. In fact, MALCOLM (1957) observed that intracarotid injection of 200—300 μg 5-HT produced marked dilatation of the vessels of the exposed area of the cortex, which began within 20—30 seconds of the injection and lasted 10—15 min. The surface veins appeared to be filled with bright red arterial blood. Vasodilatation was accompanied by permeability changes of the vessels with oedema.

CASELLA, FUMAGALLI and NOLI (1957) have tried to follow more exactly the changes in cerebral blood flow by means of thermofluximetric elements applied to the cortex of the temporal lobe. 5-HT was given intravenously in doses of 0.2—4 mg/kg.

In the rabbit 5-HT caused a moderate drop in cerebral blood flow which lasted 5 to 6 minutes and closely followed the fall of the systemic blood pressure. In the cat a first phase of decreased blood flow was followed by an increase in flow, which was independent of any change in systemic blood pressure and was possibly due to regional vasodilatation.

Finally CLINI et al. (1960) found that 1—80 μg 5-HT injected into the ipsilateral external carotid artery of the cat, the controlateral being closed, hardly modified the carotid blood flow. In the spinal cat, on the contrary, 1—5 μg 5-HT always produced a decrease of blood flow. The slow intravenous infusion of adrenaline, which increased blood pressure up to the values of the pretrigeminal cat, abolished or even inverted the effects of 5-HT.

Although it is evident that further studies are needed to solve the important problem of whether 5-HT is capable, especially when given by intraarterial in-

jection, of provoking general or regional changes in the calibre and/or permeability of brain blood vessels, it seems that at present the conclusion by CLINI et al. that 5-HT plays little, if any part in the regulation of cerebral circulation is the most reasonable.

9. Vessels of the retina

Single intravenous injections of 4 mg/kg 5-HT produce a transient spasm of the retinal arteries in the rabbit; repeated doses also cause morphological changes consisting of a thickening of the muscular layer of the retinal vessels (MORLUNGHI and VOLPI 1959).

10. Vasa vasorum

5-HT causes a marked constriction of the vasa vasorum of both the swine carotid and coronary arteries (SMITH 1953).

11. Other vascular areas

Vessels of the rat mesoappendix. Intravenous injection of 0.1 mg of 5-HT or local application of 2—3 drops of a 0.1% solution at 37° provokes within a few seconds a constriction of the terminal arterioles and the arterial segment of the capillaries, accompanied by marked stasis in the remaining capillary bed (CORRELL et al. 1952).

It is well known that topically applied adrenaline constricts the arteriolar elements of the rat mesoappendix. Intravenous 5-HT tends to depress vascular reactivity to adrenaline in doses of 0.6 mg/kg, but renders the precapillaries hyperreactive to adrenaline in doses of 0.15—0.3 mg/kg (ZWEIFACH and METZ 1955).

Gastric vessels of the dog. Using the gated-sine electromagnetic flowmeter, gastric blood flow appears to be increased by administration of 5-HT (PETER et al. 1962).

Vessels of the hind leg of the frog and the toad. The outflow rate of the perfusion liquid from the frog hind leg shows rhythmical variations indicating an alternation of periods of vasoconstriction and periods of vasodilatation. This spontaneous rhythmical activity is stimulated, or evoked if lacking, by 5-HT at concentrations from 10^{-9} to 10^{-4}. Tryptamine is about 100 times less active than 5-HT (ZAMBONI and CARLEVARO 1954).

Apart from the above effect, 5-HT displays on the vessels of the hind leg of frogs and toads only a poor and variable constrictor action (ERSPAMER 1954, INOUE 1956). Bufotenine and gramine are even less active (HANDOVSKY 1920, POWELL and CHEN 1945).

12. Effect of local application of 5-HT

Mucous membranes. 5-HT applied topically onto the cheek pouch of the hamster produces intense vasoconstriction, the threshold concentration being 0.004—0.04 μg/ml. In half the experiments 5-HT is adrenaline-potentiating, in the other half it inhibits adrenaline (AKERS and ZWEIFACH 1955). However, a few drops of a 0.1% solution of 5-HT base cause hyperaemia of the conjunctiva, when introduced into the conjunctival sac of human subjects (CALÌ and LOMEO 1955).

Bleeding surfaces. 5-HT reduces haemorrhage of bleeding surfaces when put into direct contact with them in sufficient concentrations (0.02—0.1% solution). This has been demonstrated with musculo-cutaneous wounds in rats and guinea-pigs (FORNAROLI and KOLLER 1955, NIAUSSAT et al. 1958) and for wounds of

parenchymatous organs, such as guinea-pig liver (CONTI and RICOTTI 1955) and rabbit kidney (BAZAN 1956).

The above experimental results represent the basis of the recommended therapeutic use of 5-HT in the control of bleeding from small vessels during surgical operations on eyes (PALIAGA 1956), tonsils (DEL BO 1956) and teeth (TORRIELLI and MINOLA 1956, RYSKY 1957) as well as during plastic surgery (BERGONZELLI and FONTANA 1957, VISETTI 1958).

So far there is not sufficient evidence that 5-HT has any advantage over, or is even at parity with, the classical haemostatic drugs.

13. Action of 5-HT on isolated artery strips or rings

Isolated rings or spiral strips of ox, dog and especially sheep carotid were used for several decades in qualitative demonstration and in quantitative titration of the serum vasoconstrictor. The preparation has been re-evaluated by RAND and REID (1951, 1952), REID (1952b and SHAW and WOOLEY (1953, 1954) for the study of 5-HT and 5-HT antagonists.

The arterial strips respond to 5-HT with a contraction which is, within certain limits, satisfactorily dependent upon the amount of substance introduced into the bath. The threshold dose varies for 5-HT from about 0.005 to 0.01 μg/ml of nutrient liquid; that for tryptamine is 17 times greater.

VACEK (1960) found that the susceptibility to 5-HT of rabbit aorta strips is considerably below that normal in animals made hypertensive by DOCA and NaCl. The cause of the phenomenon is supposed to be found in secondary changes in the aorta wall. In this regard it should be remembered that according to MILLAHN (1961) 5-HT increases the elasticity coefficient of pig and calf aorta, thus reducing the extensibility of the vasal segment.

The contractile response to 5-HT of strips of sheep aorta is inhibited by yohimbine, ergotoxine and antimetabolites of the 5-aminoindole type (SHAW and WOOLEY 1953, 1954); the contraction of spirally cut sections of horse carotid artery elicited by 5-HT (0.04—3 μg/ml) is non-specifically antagonized by reserpine (1—25 μg/ml) and hydralazine (25—500 μg/ml) (KIRPEKAR and LEWIS 1958).

Finally, contractions of strips of rabbit aorta can be blocked by pretreating with dibenamine. There is no "cross-protection" against dibenamine blockade between 5-HT on the one hand an histamine, acetylcholine and catecholamines on the other. It is concluded by FURCHGOTT (1955) that the aortic smooth muscle has specific sets of contraction receptors for 5-HT.

Spiral strips, 2.5—4 cm long, cut from the left circumflex artery of the sheep heart are contracted by 5-HT in concentrations of 0.3—1 μg/ml (KOVALĆIK 1962).

The same concentrations of 5-HT are also active on coronary strips obtained from the pig heart. However, the response to 5-HT is less consistent than that to acetylcholine or to histamine (TAKENAKA 1959).

14. Conclusive remarks

Whereas at the beginning 5-HT was believed to be a pure, typical vasoconstrictor and hypertensive agent (hence the name "serotonin"), at present the decidedly dominant opinion is that the chief action of 5-HT on the vessels and, accordingly, one of the possible "physiological" functions of the circulating amine is to cause vasodilatation. The most authoritative sustainers of this theory are GORDON and co-workers (1958a, 1958b, 1959) and MCCUBBIN and co-workers (1962).

On the basis of synergistic and antagonistic actions manifested by 5-HT towards the adrenalines, GORDON et al. affirm that "a biological role of serotonin lies in its negative interaction with the adrenalines", and that 5-HT may decrease small vessel tone "through its capacity to antagonize the vasoconstrictor action of noradrenaline on small vessels". McCUBBIN et al., in their turn, suggest, as a working hypothesis, that the main action of 5-HT on the vascular smooth muscle is to affect the adrenergic vasodilator receptors in a manner that causes them to have a more prominent effect when stimulated, thus causing decrease in total vascular resistance. There would be no interference of the amine with sympathetic vasoconstrictor pathways.

It may be seen that the interpretation of the "vasodilator" action of 5-HT differs consistently from one group of research workers to the other. Moreover, results obtained in the musculo-cutaneous area under particular experimental conditions do not seem to be in accordance with other numerous results reported in detail in the preceding pages.

Actually, one cannot exclude the possibility that 5-HT may intervene, in particular vascular areas and in particular animal species, in the "physiological" regulation of tone and calibre of blood vessels, but this does not seem sufficient to allow us to draw conclusions of general value.

IV. Action on vascular permeability

ROWLEY and BENDITT (1956) first demonstrated that subcutaneous or intradermal injection of doses of 5-HT as small as 0.1—1 μg in 0.03—0.1 ml liquid produces oedema in rats, and that 10 times more tryptamine or 200 times more histamine is necessary to bring about oedema of equal severity.

These results were soon confirmed and extended by numerous research workers, especially using the Evans blue or Pontamine blue technique, and 5-HT oedema of the rat paw is now often employed in the study of 5-HT antagonists and in the evaluation of anti-inflammatory agents (GÖZSI and KÁTÓ 1957a, 1957b, SPARROW and WILHELM 1957, KELEMEN 1957, THEOBALD and DOMENJOZ 1958, PARRATT and WEST 1957b, 1958, DÖPFNER and CERLETTI 1958, CAUWENBERGE et al. 1959a, 1959b; MÖRSDORF and BODE 1959, STENGER 1959, GELFAND and WEST 1951, STONE et al. 1951, GIÃO and T. RICO 1962). Methods for a quantitation of 5-HT-induced oedema have been proposed by ECKHARDT et al. (1958), UNGAR et al. (1959), DOEPFNER and CERLETTI (1958), VOGIN and ROSSI (1963), and JAQUET (1963).

By far the most accurate study on the action of 5-HT on the permeability of rat vessels has been carried out, in the rat cremaster muscle, by MAJNO et al. (1961a, 1961b, 1961c).

0.3—2 μg 5-HT base or 18—180 μg histamine was injected subcutaneously into the scrotum, whence it spread into the underlying cremaster muscle. The cremaster vessels were "labelled" by intravenous injection of colloidal HgS or carbon. At electron microscopy examination numerous endotelial openings were present, in a diameter of 7 to 8 μ or more. These gaps were 0.1 to 0.8 μ in width. The underlying basement membrane was morphologically intact. The leaking vessels, as indicated by the HgS or carbon deposits, always belonged to the venous side of the circulation. The heaviest deposits were found in venules 20 to 30 μ in diameter. The deposits decreased towards larger venules up to a maximum diameter of 75 to 80 μ and towards the finer vessels until the calibre reached approximately 7 μ. Essentially spared by the deposits were the finest vessels, 4 to 7 μ in diameter. The changes induced by 5-HT and histamine were

indistinguishable, except that the former was roughly 100 times more potent than the latter. With regard to the pathogenesis of the endothelial lacks, which disappear within 3 hr, the electron microscopic findings suggest that the endothelial cells become partially disconnected along the intercellular junctions.

General acral swelling (paws and snout) is also observed in rats and hamsters following subcutaneous or intraperitoneal injections of 5-HT (ASBOE-HANSEN and WEGELIUS 1956, BOIS and SELYE 1956).

In sharp contrast to some rodents, 5-HT has only negligible potency, if any, as a permeability factor in the skin vessels of other species.

In guinea-pigs the response to local injection of 5-HT is 500 times less than that to histamine, and in rabbits 20,000 times less (SPARROW and WILHELM 1957). Furthermore, no raised permeability is apparent in the guinea-pig either in the fore-paw vessels or in the vessels of the brain stem following intravenous injection of 0.2—0.8 mg/kg 5-HT base (BERKINSHAW-SMITH et al. 1962).

In man, intradermal 5-HT is actually capable of producing capillary dilatation, as shown by erythema and flare, but does not cause any whealing (HERXHEIMER and SCHACHTER 1959, TROMPIZ 1961). In atopic skin there is either no reaction or a reaction greatly diminished in intensity and evanescent (CLENDENNING et al. 1959). Given by intravenous injection, 5-HT (0.1 mg/kg) seems to inhibit in man wheal production by histamine (CENCIOTTI 1957) and tuberculin (MONCALVO and GIORDANO 1958).

The above findings once again emphasize the danger of generalizing results after experimentation in only one or a few species.

V. Action on capillary resistance

It has been repeatedly claimed that 5-HT increases capillary resistance both in man and in experimental animals and, on the basis of this claim as well as of the circumstance that 5-HT is contained in large amounts in blood platelets, the drug has been considered to be one of the physiological factors involved in the maintenance of normal capillary resistance and has been recommended in the treatment of morbid syndromes characterized by abnormal capillary fragility.

Actually, experimental and clinical results obtained in this field are often contradictory, and the bulk of evidence is against the hypothesis of any relationship between 5-HT and capillary resistance.

a) Action of endogenous 5-HT on capillary resistance

Animals and human beings whose platelets have been nearly completely depleted of their 5-HT through acute or chronic administration of reserpine do not show any significant change in capillary resistance (HAVERBACK et al. 1957, ZAMBONI 1957). The same is true of rats in which biosynthesis and metabolism of 5-HT is halved by removal of the large intestine (ZAMBONI et al. 1959).

BLAIR et al. (1955) observed that following iontophoresis of a 1% solution of LSD into the skin of the anterior aspect of the arm, a larger number of petechiae was produced at a given site by a given fall in pressure than would otherwise have been expected. It seems difficult to conclude from this finding that the lowered "capillary resistance" is due to the anti-5-HT action of LSD and hence that endogenous 5-HT may be concerned in preserving the integrity of small vessels.

b) Action of exogenous 5-HT on capillary resistance

According to BRACCO et al. (1954), 5-HT given intravenously in doses of 1 mg/kg produces in guinea-pigs and rats a marked increase in capillary resistance.

The effect appears after 10 min and lasts for about 3 hr. With daily injections of 5-HT the capillary resistance remains high throughout the treatment period. The capillary crisis following surgical stress is similarly prevented or removed by intraperitoneal injections of 2.5 mg/kg 5-HT. Under daily administration of the same dose of 5-HT no fall of the capillary resistance is observed during treatment. From the results of their experiments BRACCO and his colleagues conclude that 5-HT possesses not only a local vasoconstrictor effect but also a protective action on capillaries.

No attention whatever has been paid by the above investigators to the behaviour of the systemic blood pressure. Yet it is well known that the large doses of 5-HT they used provoke in guinea-pigs and especially in rats a conspicuous and prolonged fall in blood pressure, accompanied by important changes in the calibre of the cutaneous vessels. The possibility that the observed increase in capillary resistance is, at least in part, a direct or indirect consequence of these systemic circulatory changes cannot be excluded.

More recently, BRACCO et al. (1958a, 1958b, 1958c) lay stress on the possibility that 5-HT is active on capillary resistance and permeability mainly after its transformation, by plasma enzymes, into oxidation derivatives. In fact, two of these derivatives have been found to possess a positive action on capillary resistance in guinea-pigs, both normal and with C-avitaminosis, as well as in adrenalectomized rats (active dose 50 μg/rat), to display an antidiffusory action in the albino rabbit (300 μg i.v.), to antagonize experimental inflammation provoked by croton oil or formalin, and finally to accelerate the transformation of fibrinogen into fibrin.

Concerning man, results are at complete variance, apparently depending upon the basic conditions of the capillaries.

In subjects with normal capillary resistance there is no change following single or repeated intravenous or intramuscular doses of 2—5 mg 5-HT (ANNONI et al. 1955a, CALÌ and LOMEO 1956, FUGA 1959). On the other hand, in subjects showing an abnormal capillary fragility, petechial count appears to be consistently reduced following repeated doses of 5-HT. This has been observed in elderly people (ABBATI et al. 1956, FUGA 1959, BASSANI and FANTINI 1956), in children (LANCIANO and RESTANTE 1956) and in tuberculous patients (ROSSINI et al. 1956). Increase of capillary resistance sometimes persists for days or weeks (BASSANI and FANTINI 1956, ROSSINI et al. 1956), and this frankly casts some doubt not only upon the interpretation but also upon the credibility of experimental results.

c) Therapeutical trial of 5-HT in haemorrhagic syndromes ascribed to increased capillary fragility

5-HT has been used, especially in Italy, in the treatment of WERLHOF'S disease and related haemorrhagic syndromes. The doses recommended were 2—4 mg 5-HT base, intravenously or intramuscularly, every 4—8 hours.

Unfortunately, the first enthusiastic reports (ALLEGRI and FERRARI 1954, BASERGA and BALLERINI 1955, BASERGA 1955, RAVETTA 1955, MARTINETTI and MARANGANI 1955, BARONI 1956) have not been confirmed by more accurate studies (MIESCHER 1955, SCHATZMANN 1955, SIEGENTHALER 1956, ZUCKER 1959, STEFANINI and MAGALINI 1956), and at the present time the use of 5-HT in the control of capillary fragility must be considered irrational.

Platelets and platelet derivatives have been used profitably in the management of thrombocytopoenic states. However, their beneficial effect is not due to their content of 5-HT (STEFANINI and KISTNER 1957).

VI. Participation in the mechanism of haemostasis

In vivo experiments. As early as 1912—1913 O'CONNOR and ZUCKER and STEWART advanced the hypothesis that the serum vasoconstrictor, released by the platelets at the moment of blood coagulation, might intervene in the process of haemostasis in consequence of its direct spasmogenic action on the vascular smooth muscle around the clot occluding the injured vessel. This hypothesis has been re-evaluated following the identification of the vasocontrictor with 5-HT and has been the object of extensive experimental work.

CORRELL et al. (1952) found that the injection of 0.01 to 1 mg 5-HT into the saphenous vein of the rat shortened significantly, though only transiently, the bleeding time following the severing of the tip of the tail. When applied topically, 5-HT had no effect. Similar haemostatic effects were observed in mice, guinea-pigs, hens and, to a lesser degree, in rabbits (0.25—1.5 mg/kg). The behaviour of the systemic blood pressure was not taken into consideration. CORRELL and co-workers conclude that the role of the substance in haemostasis is exclusively that of a humoral vasoconstrictor agent.

The above results have been generally confirmed in experimental animals. CORREALE (1954) stated that the haemostatic effect appearing in the rat after subcutaneous doses of 5-HT paralleled, in both intensity and duration, the hypotensive effect caused by the substance. There was no direct interdependence, however, between these two phenomena, as would be expected if the shortening of the bleeding time was caused by hypotension. LECOMTE et al. (1954) found that the action of 5-HT (10 μg/kg or more, i.v.) on the bleeding time in the rabbit was at least 10 times less intense than that possessed by adrenaline or adrenochrome, and more fleeting.

ESTÈVE and LAPORTE (1957) were unable to detect any reduction of the prolongation of bleeding time induced in rabbits by sodium salicylate, even following intramuscular doses of 5-HT base up to 6 mg/kg. Prolongation of bleeding time caused by isoniazid, on the contrary, was diminished by 0.25 mg/kg 5-HT. DJERASSI et al. (1958), in their turn, succeeded in increasing vascular resistance and shortening the duration of traumatic bleeding in irradiated thrombocytopoenic guinea-pigs and mice. The effect, however, was of short duration and was obtainable only with large doses of 5-HT (1.5 mg/kg, i.p., in guinea-pigs, and 12.5 mg/kg, i.p., in mice).

In five out of seven healthy persons, intravenous infusion of 0.2 mg/kg 5-HT base in 5% dextrose solution over a period of several hours caused significant reduction of bleeding time, from 4—6 min to 1—$2^1/_2$ min. The effect, however, was very fleeting and the bleeding time returned to pretreatment values within 15 min to 2 hr after suspension of the injection. These positive results of STEFANINI and MAGALINI (1956) were confirmed by BELLA and ROSSI (1957) (2 mg 5-HT base, i.m.), but not by SIEGENTHALER (1956) (4 mg 5-HT by slow i.v. injection, or 8 mg 5-HT/hour by i.v. infusion) nor by ANNONI et al. (1955) (2 mg 5-HT i.v. or i.m.).

In patients suffering from haemorrhagic disorders results were again at variance. A temporary reduction of bleeding time was observed by STEFANINI and MAGALINI (1956) in patients with vascular pseudohaemophilia, but not in patients with thrombocytopoenic purpura, either idiopatic or secondary. LEWIS (quoted by ZUCKER 1958) had short-lived positive results in thrombocytopoenic purpura. Finally, SIEGENTHALER (1956) obtained a reduction of the bleeding time only in the limited number of cases (5 out of 24) of essential or secondary thrombopoenia in which it was augmented.

The above data seem to be by themselves sufficient to prove the extremely erratic and inconstant character of the action of 5-HT on bleeding time, but the thesis that 5-HT in the platelets is important to the organism as a defence mechanism against bleeding has suffered the hardest and most definitive blow from experiments carried out in reserpinized human subjects and animals.

In fact, following nearly complete depletion of 5-HT provoked in animals and man by single or repeated doses of reserpine, no significant changes could be observed in constriction of cut vessels, as followed microscopically, in bleeding time, clotting time, prothrombin times, prothrombin consumption index, thromboplastin generation test with platelet dilutions, platelet adhesiveness or clot retraction (SHORE et al. 1956a, 1956b; WEINER and UDENFRIEND 1957, HUTCHISON et al. 1959, WITTE et al. 1961).

It is similarly highly improbable that death due to haemorrhage observed in rabbits subjected to a stress procedure plus reserpine administration is attributable, as suggested by JAQUES and FISHER (1960), to depletion of platelet 5-HT.

KWAAN et al. (1957) showed that intravenous or paravenous injection of 5-HT into human beings resulted in the development of fibrinolytic activity not only in the plasma of the blood within the vein but also within veins well removed proximally in the line of flow in the same arm and within veins of the opposite arm. Since this effect was abolished by atropine it was suggested that it was mediated through a cholinergic mechanism.

Similar results were obtained by the same research workers (KWAAN et al. 1958) in the marginal vein of the rabbit's ear in which experimental thrombi were produced by injection of 25 units thrombin in 0.05 cc ml liquid. Addition to the thrombin solution of 5-HT in amounts as low as 0.3—3 μg produced a significant acceleration of the lysis of the thrombi. Again a cholinergic mechanism was invoked, and it was suggested that 5-HT stimulated cholinergic effectors by producing constriction of the vasa vasorum and consequent ischaemia of the vein wall.

Unfortunately, these findings could not be duplicated by HOLEMANS and CHO (1962). In fact, no enhanced lysis of experimental thrombi in the marginal vein of the rabbit ear was observed by them following injection of 5-HT along the venous segment prior to, or after thrombus formation. Thus, the hypothesis of KWAAN et al. that a major function of the 5-HT liberated from disintegrating platelets *in vivo* is the stimulation of fibrinolytic activity must be accepted with much reservation.

In vitro experiments. According to FENICHEL and SEEGERS (1955) and to BALLERINI (1955), 5-HT enhances the retraction of bovine plasma clots in concentrations of 40 μg/ml and more, and must therefore be considered a clot retraction principle, possibly the only dialyzable one in platelets. On the other hand MAGALINI and STEFANINI (1955, 1956) failed to find any heightening by 5-HT of clot retraction or of prothrombin utilization during clotting of platelet-free human plasma.

The conversion of fibrinogen to fibrin in the presence of thrombin is accelerated by 5-HT (20—40 μg/ml of the base). However, in contrast to platelet factor 2, 5-HT inhibits the fibrinogen-fibrin reaction in a purified fibrinogen solution. It is postulated that 5-HT acts either through inhibition of an antithrombin which blocks the fibrinogen to fibrin reaction (MILNE and COHN 1957) or through a direct effect on fibrinogen (KÁTO and GÖZSY 1958).

In vitro 5-HT seems to inhibit fibrinolysis considerably. This was demonstrated by using two different procedures. In the first, solutions of a streptokinase activated human fibrinolysin in a PO_4-saline buffer were incubated with

or without 5-HT for 30 min at 37° and then placed on opposite sides of a fibrin plate; in the second, a fibrinolytic system consisting of bovine fibrinogen, human thrombin, imidazole-saline buffer, thrombolysin and test solution was used.

5-HT caused clear inhibition of fibrinolysis in concentrations as low as 2 μg/ml. 5-HTP was less effective (threshold 100 μg/ml), and tryptamine practically inactive. Heated or unheated fibrin plates showed equal inhibition of fibrinolysis by 5-HT. There was no inhibition of proteolysis of casein. It was not possible to determine whether 5-HT achieved its inhibition of fibrinolysis by modifying the fibrin substrate, inhibiting the fibrinolytic enzyme or both (TSITOURIS et al. 1961, 1962).

The inhibition of fibrinolysis by 5-HT was confirmed by CHRYSSANTHOU and ANTOPOL (1964).

Of limited interest, because the enormous doses required (1 mg of either 5-HT or tryptamine against 1 μg of heparin), is the observation that indolealkylamines are capable of reducing the antithrombin time prolonged by the action of heparin (KELLER 1958).

Addition of small amounts of 5-HT to whole blood alters the tendency of the platelets, leucocytes, and red blood cells of dogs, cats and rabbits to aggregate. The magnitude of this response is dose-dependent and biphasic. Very small doses (0.1—0.2 μg/ml) seem to decrease the aggregation tendency; larger amounts (5—10 μg/ml) greatly increase this tendency. The effect is abolished by very slight reductions of pH, by addition of KCN to blood and by removing adhesive platelets from the blood. 5-Methoxytryptamine has effects comparable to those of 5-HT; 2,3-dihydro-5-HT, tryptamine, melatonin and 5-HIAA have no effect at doses 10 times higher than 5-HT. SWANK et al. (1963) suggest that 5-HT may be a factor in reducing peripheral resistance to the flow of blood through the smaller blood vessels including capillaries.

5-HT (0.15 μg/ml) does not prevent platelet aggregation induced by thrombin or adenosine diphosphate (O'BRIEN 1962).

Despite the very poor experimental evidence supporting the view that 5-HT interferes in haemostasis, the drug has been tried clinically in the control of surgical bleeding (ANNONI et al. 1955a; ANTONA 1955, 1959; SANZIO GRECO 1957; BERGONZELLI and FONTANA 1957; PEREZ-BUFILL PICHOT 1957; SALA 1956), as well as in spontaneous haemorrhages from nearly all organs and of the most varied etiology: uterus and genital tract (BELLA and ROSSI 1957, EL TORAEI 1956, CATALDI 1956c, FAWZI 1956), kidney and urinary tract (EL TORAEI 1956), gastrointestinal tube (EL TORAEI 1956), lung (DI PASQUALE 1956), meninges (BALDUINI et al. 1955) etc.

The results reported have often been satisfactory, but the writer's impression is that not infrequently clinical experimentation has been carried out with insufficient accuracy and critical evaluation. Consequently it is highly questionable whether 5-HT may be considered a useful drug in the prevention or treatment of haemorrhage.

VII. Action on the heart

1. Heart in situ

Effects of 5-HT on the heart of intact animals are variable depending on animal species and on route and rapidity of 5-HT administration.

Man. In man both rapid intravenous injection (ANNONI et al. 1955, BALDRIGHI and FERRARI 1955, HOLLANDER and MICHELSON 1956), intravenous infusion (LEMESSURIER et al. 1959, BOJS 1961) and infusion into the pulmonary

artery (GROVER et al. 1958) generally produce an increase in heart rate (5 to 30 beats per minute) which precedes pressure changes by 10 to 20 seconds, suggesting a direct effect on the heart (LEMESSURIER et al. 1959). Although stroke volume is reduced (BALDRIGHI and FERRARI 1955), cardiac output rises (GROVER et al. 1958, BOJS 1961) or remains unchanged (HARRIS et al. 1960).

Dog. In the dog, rapid intravenous injection of 5-HT usually produces bradycardia (LOUBATIÈRES et al. 1955, JACOB and CUGURRA 1960) or initial bradycardia followed by marked tachycardia (BEN et al. 1962), or sinus tachycardia (MCCAWLEY et al. 1952). Acute vagotomy and carotid sinus denervation produce the disappearance of bradycardia (JACOB and CUGURRA 1960). Heart contractile force is increased, at least initially (LOUBATIÈRES et al. 1955, BEN et al. 1962). Stroke volume and minute volume behave differently, depending upon anaesthesia: they are increased in the unanaesthetized dog and in the dog anaesthetized with chloralose, decreased in animals anaesthetized with barbiturates (HOTOVY and ROESCH 1958).

The main ECG changes produced by intravenous injection of 200 μg/kg 5-HT consist of a marked negative T wave during the phase of increased blood pressure, with disappearance of this wave during the phase of hypotension (WALAWSKI 1959).

5-HT (0.35—0.8 mg/kg, i.v.) does not affect the auricular fibrillation established by vagal stimulation in the thyrotoxic dog, and fails to produce ventricular tachycardia in the dog under chloroform anaesthesia or ventricular fibrillation under cyclopropane anaesthesia. In doses of 2.2 mg/kg, 5-HT causes respiratory arrest in the anaesthetized dog. When the animal is protected by artificial respiration the cardiac effects of this lethal dose consist merely of transitory ventricular extrasystoles originating from abnormal foci (MCCAWLEY et al. 1952).

Working on a cord-transected dog, PAGE (1952) observed that after intravenous 5-HT stroke volume and minute output, measured from pressure-pulse tracing, are nearly doubled.

Upon rapid pulmonary arterial injection, 5-HT (200 μg of the base) causes bradycardia and electrocardiographic disturbances, quickly followed by a rise in cardiac output which helps to maintain the pressor response to 5-HT (MAC CANON and HORVATH 1954).

Given by infusion into the left or the right atrium of dogs anaesthetized with morphine and dial-urethane-nembutal, 5-HT (8 μg/kg/min) elicits a 21—61% increase in heart rate, an increase in right ventricular work and a 3% decrease in mechanical efficiency of the left ventricle. Cardiac output and stroke volume remain unchanged (MAXWELL et al. 1957, 1959; CRUMPTON et al. 1959) or show a significant increase (27.6%) (ROWE et al. 1963).

Finally, intravenously infused 5-HT gave completely different results at different dose levels and in the hands of different investigators. RUDOLPH and PAUL (1957) observed a 60% rise of cardiac output with an infusion rate of 60 μg/kg/min; MCGAFF and MILNER (1962) found no significant changes in cardiac output, in stroke volume or in left atrium mean pressure with 0.06—0.4 mg/kg/min 5-HT; and NOBLE and NANSON (1959) noted a reduction of cardiac output, despite pronounced tachycardia, at an infusion rate as low as 2.5 μg/kg/min.

Psilocybin given intravenously into dogs anaesthetized with morphine and a dial-urethane-nembutal mixture at a dose of 0.5 mg/kg, depresses cardiac output. Tachycardia is constant, and cardiac work well maintained (MAXWELL et al. 1962). 5-acetyltryptamine causes bradycardia with slight and transient alterations in heart contractile force (BEN et al. 1962).

Cat. Using the technique of isolated heart perfusion, both REID (1952) and SCHNEIDER and YONKMAN (1953, 1954) showed that 2—200 μg of 5-HT in the cat heart causes an increase in heart rate, an increase in coronary flow and an increase in contractile force, which, in sensitive hearts, occasionally results in persistent systolic contraction. These data suggest that bradycardia observed in the intact cat after intravenous or intracoronary injection of 5-HT is caused by vagal reflexes masking the direct stimulant action of the substance on the heart. The fact that bradycardia is reduced or disappears following vagotomy, cooling of the vagi or intravenous injection of local anaesthetics has been considered direct evidence of the influence of 5-HT on vagal afferent fibres (SCHNEIDER and YONKMAN 1953, 1954; KOTTEGODA and MOTT 1955; WEIDMANN and CERLETTI 1955).

Pressure rise elicited by psilocybin (50—100 μg/kg, i.v.) is similarly accompanied by relative bradycardia (CERLETTI 1959).

Rabbit. Hypotension produced by 5-HT is regularly accompanied by transient slowing of the heart rate, associated with cardiac irregularities (SCHNEIDER and YONKMAN 1954). Psilocybin (50—100 μg/kg, i.v.), on the contrary, causes marked increase in the heart rate (CERLETTI 1959).

Calf. Cardiac output, as measured by the dye dilution method, is not changed in response to a 3-minute infusion of 0.2 mg/kg/min 5-HT (KUIDA et al. 1961).

Chicken. Both 5-HT (20—50 μg/kg) and tryptamine (100—500 μg/kg) produce a marked diminution in the height of ventricular contraction. This is followed by a brief period of myocardial stimulation in 56% of the animals (BUÑAG and WALASZEK 1961).

Rat. Fifteen to thirty minutes after intraperitoneal injection of 4 mg/kg 5-HT base cardiac output is unchanged, whereas blood flow in the myocardium is increased. Conversely, intravenous infusion of 2.3 μg/kg/min 5-HT produces an increase of cardiac output (TAKÁCS and VAJDA 1963).

2. Heart-lung preparation

Dog. FREYBURGER et al. (1952) found that 5-HT introduced into the circuit of a heart-lung preparation not only lacked any stimulant action but produced a certain decompensation, as shown by the rise of pressure in the left auricle. MAGGI and NOLI (1958) failed to detect any sign of cardiac decompensation, even at mg doses of 5-HT. 150—500 μg displayed a positive inotropic effect preceded by short-lived inhibition; 1—20 μg was completely inactive. Finally, DUTEIL (1962) and DUTEIL and AVIADO (1962) observed that the injection of 5-HT into the right atrium of the dog heart-lung preparation caused a rise in mean pulmonary arterial pressure, a rise in right ventricular systolic pressure, no change in left atrial pressure and transient fall in cardiac output. The lack of increase in cardiac output which is seen in the dog prior to conversion to a heart-lung preparation is interpreted as being due to the loss of cardioaccelerator mechanisms, particularly the sympathetic reflex induced by a rise in right intraventricular pressure.

Rabbit. In the rabbit heart-lung preparation 25 μg 5-HT produces the following changes: 10—15% reduction of the heart rate, decrease of the stroke volume, 30—50% reduction of the left ventricular work, 25—60% decrease of the coronary flow with increase in the coronary resistances, and finally a 25—30% increase in the O_2 consumption.

The above phenomena last 3 min, and there is evident tachyphylaxis. Doses of 0.5—5 μg 5-HT are completely inactive (MAGGI and NOLI 1958, MAGGI 1960).

Rat. On the heart-lung preparation of rats, 5-HT does not produce any change in heart rate or cardiac output in doses up to 40 μg/ml. Large doses cause the appearance of extrasystoles (MINELLI 1961).

3. Isolated heart

Rabbit. The effects of 5-HT on the isolated perfused rabbit heart have been thoroughly studied by JACOB and POITE-BEVIERRE (1960) over a wide dose range of 5-HT (2 μg to 5 mg of the base). In general three successive phases are observed:

a) irregular negative inotropic and chronotropic effect, antagonized by atropine:

b) positive inotropic and chronotropic effect, which disappears after pretreatment with reserpine and is considered to be mediated by catecholamines;

c) negative inotropic effect, resistant to atropine and often accompanied by a tonus increase. This effect is the predominant one for doses of 0.5 mg and more.

With 4 mg and more, atropine-resistant arrhythmias develop, consisting of cardiac arrest, atrioventricular block, flutter and fibrillation. BAS in this preparation appears to be an ambiguous 5-HT antagonist, sometimes mimicking rather than counteracting the 5-HT effects.

The positive inotropic and chronotropic effect of the medium doses of 5-HT (20—50 μg) has already been described by FREYBURGER et al. (1952) and by LOUBATIÈRES et al. (1955).

Bufotenidine is 50 times more potent than 5-HT. At 1—2 μg doses it causes an increase in amplitude of cardiac movements; at 5—10 μg doses the inotropic effect is accompanied by a positive chronotropic effect (UEDA et al. 1957).

Dog. 30—300 μg of 5-HT injected into the perfusion fluid of an isolated heart produce a marked increase in the heart rate and a clear increase in coronary flow, whereas the increase in amplitude of contractions is small (SCHNEIDER and YONKMAN 1954).

Cat. As already stated, both REID (1952) and SCHNEIDER and YONKMAN (1954) showed that 2—200 μg 5-HT infused into the isolated cat heart caused an increase in heart rate, an increase in coronary flow and an increase in contractile force which, in sensitive hearts, occasionally resulted in persistent systolic contraction.

Frog. On the frog heart 5-HT and tryptamine display a very moderate inotropic effect. This is potentiated by iproniazid and isoniazid, probably as a consequence not of MAO inhibition but of decreased penetration of the amines into the muscle cells (BURFORD et al. 1960). 56 μg of bufotenine has no effect on the preparation; 230 μg causes, after a latency period, a decrease in heart rate and a subsequent arrest of the organ (HANDOVSKY 1920). Gramine (500 μg) shows a similar negative inotropic and chronotropic action (POWELL and CHEN 1945).

4. Isolated atrium

Rabbit. Effects observed on the isolated rabbit atria are at variance. Whereas LOUBATIÈRES et al. (1955) could not see any influence of 5-HT (0.05—1 μg/ml) on the frequency and contractile strength of this preparation, others (MCCAWLEY et al. 1952; SINHA and WEST 1953; LÉVY and MICHEL-BER 1956a, 1956b; TRENDELENBURG 1960) found that the amine (0.1—10 μg/ml) produced a pure stimulant effect (increase in amplitude of contraction and in rate of beat), or a stimulant effect which was preceded by short-lived inhibition and eventually followed by a more marked depression. Atropine (10^{-7}) and hexamethonium (10^{-5}) abo-

lished the initial inhibiting effect, but not the subsequent one; procaine (0.5 γ/ml) caused a 50% reduction in 5-HT stimulation (SINHA and WEST 1953). It has been suggested that the initial inhibition is cholinergic in nature and that the predominant stimulant action of 5-HT is the result of the liberation of noradrenaline. In fact, atria of rabbits pretreated with reserpine show very little or no response to 5-HT (TRENDELENBURG 1960).

Guinea-pig. Guinea-pig atria respond to 5-HT (1—10 μg/ml) with a pronounced and regular increase in amplitude of contractions and in rate of beat. The effect of the amine is mainly direct (LSD-sensitive), but also indirect, morphine- and cocaine-sensitive effects may contribute to the stimulant response to 5-HT. The response of atria of animals pretreated with reserpine is not significantly different from the response of atria isolated from untreated animals (TRENDELENBURG 1960).

Cat. The response of cat atria to 5-HT (1 μg/ml) consists chiefly of an increase of rate. Changes in amplitude of contractions are seen, but are small and variable. The effect of 5-HT is blocked by LSD, but is not affected by pretreatment with reserpine (TRENDELENBURG 1960).

5. Papillary muscle

On papillary muscle preparations of cats, dogs and rabbits, LOUBATIÈRES et al. (1955) could not see any increase of the contractile strength at final concentrations of 5-HT ranging from 0.05 to 100 μg/ml. LEUSEN and LACROIX (1959), on the other hand, observed a positive inotropic effect on the cat papillary muscle at final concentrations of 1—100 μg/ml. This, however, was sometimes rather short-lived and was often preceded by a short depressive phase.

6. Strips of turtle and frog ventricle

Ventricular strips from turtle *(Pseudonymus elegans)* and frog *(Rana pipiens)* were isolated, suspended in air, superfused with buffered Ringer solution and driven at a constant frequency.

The force of mechanical contraction of turtle ventricular strips was not altered by 5-HT in concentrations from 0.1 to 100 μg/ml; at concentrations of 1000 μg/ml it was depressed. Moreover, no significant changes in refractory period, conduction time or stimulus threshold were seen.

Concerning the frog, concentrations of 5-HT from 1 to 10 μg/ml did not change the force of contraction of ventricular strips but, occasionally, periods of premature systoles and periods of autorhythmicity were seen.

5-HT did not alter the toxic effects of ouabain or procainamide (HANSON and MAGILL 1961, 1962).

7. Heart of molluscs

The stimulant action of 5-HT on the molluscan heart was first described by ERSPAMER and GHIRETTI (1951) who found that 5-HT provokes a marked increase in the amplitude and frequency of systolic contractions of *Octopus* and *Helix* hearts, whether isolated or *in situ.* The tonus, too, rises conspicuously, and with larger doses of the substance a persistent systolic arrest can be seen. The stimulant action extends over the pulsatile arteries, e.g. those of the kidney and gills, with reinforcement of their contractions or with renewal of their rhythmic activity if this has disappeared. The hearts of *Murex trunculus, Murex brandaris, Dolium galea* and *Aplysia limacina* are less sensitive than *Helix* or *Octopus* hearts. Tryptamine shows a similar action, which is, however, less prompt and 20 to 25 times less intense.

The above results were confirmed by all subsequent research workers and from extensive investigations it clearly appears that the sensitivity of the heart and regularity of its response varies a great deal in different molluscan species (BACQ et al. 1952, ZETLER and SCHLOSSER 1954, WELSH 1954, GADDUM and PAASONEN 1955, JAEGER 1962).

Since the studies of WELSH (1953, 1954, 1957) the heart of *Venus mercenaria* is considered one of the most suitable preparations and is largely used in the bioassay of 5-HT. The response of this heart to 5-HT shows, like that of the *Helix* and *Octopus* hearts, three components: an increase in amplitude, an increase in frequency and an increase in the resting tone of the muscle. The relative importance of these components varies with the concentration of 5-HT. At low to moderate concentrations (10^{-9} to 10^{-6} M) a positive inotropic effect is dominant; at high concentrations (10^{-5} M and more) a large increase in muscle tone.

Hearts exposed to high concentrations of 5-HT or other tryptamine analogues for long periods become tachyphylactic to low doses of these substances. However. large doses of 5-HT (about 2×10^{-5} M) still excite the tachyphylactic heart, but the response is then different (decrease in amplitude of beat) and like the response to catecholamines. When high bath temperatures render the heart insensitive to 5-HT, high concentrations of this compound again have the catecholamine effect (GREENBERG 1960a).

GREENBERG (1960b) and BERTACCINI and ZAMBONI (1961) have tested a number of tryptamine analogues on the isolated hearts of *Venus mercenaria* and *Helix luconum*, respectively. Results of these studies are in part summarized in Table 4 of chapter 3.

From the more numerous data obtained on the *Helix* heart, some prudent conclusions may be drawn concerning structure-activity relationship:

a) Shifting of the phenolic —OH group from position 5 to other positions regularly produces a decrease of biological activity, which is moderate when the transposition is to position 4, greater when it is to position 6, and tremendous when the transposition is to position 7.

b) Substitution on the indole nucleus of groups other than —OH groups does not always reduce biological activity. In fact 5-methoxytryptamine is more potent than 5-HT, 5-methoxy-α-methyltryptamine more potent than 5-hydroxy-α-methyltryptamine, and 5-aminotryptamine as potent as 5-HT.

c) The effect of alkyl substitution on the amino nitrogen is variable. In the case of 5-HT, substitution of two methyl groups (bufotenine) produces a 3-fold increase of activity, in the case of tryptamine a 5-fold decrease.

d) Substitution of an —OH group on the β-carbon of the side chain of bufotenine causes the disappearance of any activity.

e) Indazolealkylamines show a remarkable 5-HT-like activity, which is particularly evident for the first member of the series, more strictly related to 5-HT from a chemical point of view.

Table 4 further shows that results obtained with *Helix* heart are sometimes considerably different from those obtained with the *Venus* heart.

It should be added that, according to GREENBERG (1960b) congeners without a 5-hydroxy group and with methyl substitution tend to act not only less strongly than 5-HT, but also more slowly and irreversibly.

The effect of 5-HT is regularly antagonized by BOL, whereas LSD behaves in a strikingly different way: on the *Cyprina* and *Buccinum* hearts LSD acts as a good 5-HT antagonist, but on the *Venus* heart the drug displays a powerful irreversible 5-HT-like action (WELSH 1957, WELSH and MCCOY 1957, SHAW and WOOLEY 1956).

8. Heart of crustaceans

The response of the crustacean heart to 5-HT is strikingly different from one crustacean species to another not only from a quantitative but also from a qualitative point of view. In fact, whereas the heart of some crustacean species is potently stimulated by 5-HT, that of other species is potently inhibited.

Among the hearts which give a positive response to 5-HT the most sensitive are those of *Carcinus moenas* (threshold for 5-HT, 0.001 μg/ml; threshold for adrenaline, 0.1 μg/ml) and of *Cancer borealis* (threshold for 5-HT, 0.1 to 1 μg/ml) (FLOREY and FLOREY 1953, WELSH 1957).

Also in isolated lobster (*Homarus americanus*) hearts 5-HT causes an increase in rate and amplitude of beat. Experiments on isolated cardiac ganglia and on preparations in which simultaneous recordings of the heart beat and electrical activity of the ganglion are made show that all the effects of 5-HT can be explained as a primary action on the cardiac ganglion (COOKE 1962).

In evident contrast to the above findings, SANBORN and PAX (1962) observed that when the 8th and 9th pairs of nerves from the *Limulus* suboesophageal ganglion, which contain the inhibitory fibres to the heart, were stimulated with square-waves for 0.2 m sec duration, the action potentials in the cardiac ganglion decreased to less than half the frequency before stimulation and then gradually returned to their normal rate over a period of approximately 1 minute. Because this time course indicated chemical mediation a variety of compounds was tested. It was found that 5-HT produced the same cardiac effects as did nerve stimulation, the effective doses of 5-HT being 4 μg/kg when the drug was injected distant from the heart and 2 μg/kg when it was injected directly into the heart. SANBORN and PAX suggest that the rate of heart-beat of *Limulus* is controlled by neural secretion of indoleamine-like compounds.

These results confirm the previous ones of BURGEN and KUFFLER (1957) who noted that the rhythmic electrical bursts of activity of the isolated cardiac ganglion of *Limulus* were slowed or abolished by 5-HT, an effect which was blocked by BOL.

Recent reports have called attention to two other indolealkylamines occurring in the crustacean organism which are highly active on the crustacean heart.

On the one hand KERKUT and PRICE (1964) found that 6-HT, which seems to be a normal constituent of the *Carcinus* heart, is 10 times as active as 5-HT in exciting this heart, on the other hand CARLISLE (1964) observed that 5,6-dihydroxytryptamine, which appears to be a normal constituent of the pericardial organ of *Cancer pagurus* and *Maia squinato*, is 100 times more active than 5-HT on the prawn (*Leander serratus*) heart.

Results described in this chapter do not support the eventual hypothesis that 5-HT plays a role in controlling normal cardiac activity in vertebrates. Hence, all the actions of 5-HT on the *in situ* and on the isolated vertebrate heart must be considered pharmacological actions.

Things are different in molluscan and crustacean hearts. The hearts of molluscs, at least those of some molluscs, contain detectable amounts of 5-HT and respond to the amine at extremely low, physiological dose levels with no sign of tachyphylaxis and with changes in their activity similar to those produced in the mammalian heart by catecholamines. Moreover, 5-HT is present, in considerable amounts, in the ganglia and nerves of molluscs.

All these findings support the view, originally advanced by WELSH (1954a, 1954b, 1956, 1957), and now shared by others (MENG 1958, 1960; LOVELAND 1963) that 5-HT in molluscs may be a humoral excitory agent released by cardioregulator nerves.

However, there are some other observations which are difficult to reconcile with the hypothesis that 5-HT is a cardiac neurohumor or a cardiovascular hormone in all molluscs (ERSPAMER and GHIRETTI 1951, BACQ et al. 1952). The most important of them is that the hearts of different species present conspicuous differences in their sensitivity to 5-HT. Whereas the hearts of *Venus mercenaria*, *Cyprina islandica*, *Octopus vulgaris*, *Helix pomatia* and *Spisula solida* are excited by concentrations of 5-HT as low as 0.1—1 ng/ml, those of numerous other molluscs show a considerably lower sensitivity and present irregular responses to the amine (ERSPAMER and GHIRETTI 1951, WELSH 1954, GADDUM and PAASONEN 1955).

As for the crustacean heart, the directionally opposite effects of 5-HT in different species, joined to the different sensitivity to the amine, represent serious obstacles against considering 5-HT a neurohumor or a transmitter substance of general significance. It is premature to say whether 6-HT or 5,6-dihydroxytryptamine is the sought-for neurohumor.

VIII. Action on the circulation and function of the kidney

Rat. The most extensive researches on the action of 5-HT on the function of the rat kidney have been carried out by the writer and his co-workers (ERSPAMER 1952a, 1954b, 1954c; ERSPAMER and OTTOLENGHI 1950, 1953; ERSPAMER and SALA 1954; ERSPAMER and CORREALE 1955; ERSPAMER et al. 1956).

Experiments performed on about 3500 groups of 4 rats each have made it possible to gather a number of data and to reach some definite conclusions.

5-HT displays in the rat a powerful antidiuretic action. This appears under most varied conditions of hydration, but is especially evident after a single oral dose of 5 ml tap water per 100 g of body weight (Fig. 6) (ERSPAMER 1952, ERSPAMER and OTTOLENGHI 1953). The substance inhibits not only water diuresis but diuresis produced by osmotic diuretics and xanthine derivatives. When 5-HT and posterior pituitary extracts are administered simultaneously the antidiuretic effect of the two hormones is simply additive (ERSPAMER 1953d).

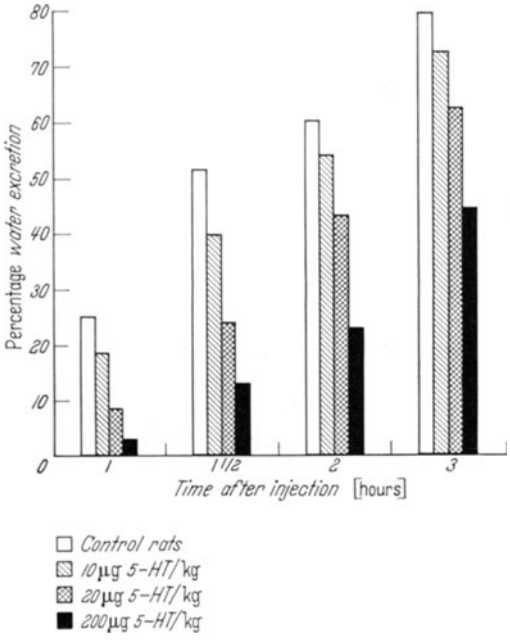


Fig. 6. Antidiuretic effect of subcutaneous 5-HT in hydrated rats. Each column represents the mean of results from 24—48 groups of 4 animals each. [From Fig. 8, ERSPAMER, V., Triangle (Basel) 2, 135 (1956).]

Among the species studied the rat is the most sensitive to 5-HT. It is sufficient to inject subcutaneously as little as 4 μg/kg 5-HT base to produce a significant reduction in the volume of urine during the first 60 min period following the water load. This dose is at least 50—100 times less than the minimum required to lower the systemic blood pressure (ERSPAMER 1952, CORREALE 1954) and at least 20,000 times less than the LD 50 by the subcutaneous route (FREYBURGER

et al. 1952, ERSPAMER 1952). It corresponds to about 1/70 of the 5-HT content of the rat organism, per kg of body weight, and is certainly less than the quantity of endogenous 5-HT which is destroyed by amine oxidase every hour, as estimated by the urinary output of 5-HIAA (4—8 μg/kg/hr).

Higher doses cause a very conspicuous reduction in diuresis or even a virtual suppression of urine flow for several hours. The final result is that even 7 to 9 hr after the water load the animals treated with 5-HT excrete 10 to 20% less water than the control animals. The reduction in urine volume is accompanied by a simultaneous reduction in chloride excretion (ERSPAMER and CORREALE 1955).

The most appropriate and effective way of administering 5-HT is subcutaneously, as shown by the intensity, and still more by the duration of the antidiuretic effect. After intraperitoneal or intravenous injection the substance is several times less active; when given by mouth it is practivally inactive (ERSPAMER and OTTOLENGHI 1953, ERSPAMER and SALA 1954). These results explain why AMES and VAN DYKE (1952) did not succeed in producing antidiuresis by intravenous administration of 2—3 μg 5-HT base/rat.

Through the simultaneous evaluation of urine flow and renal excretion of test substances (thiosulphate, creatinine, PAH) in large groups of animals, it can be demonstrated that 5-HT antidiuresis in the rat is due primarily and essentially to a reduction in the glomerular filtration rate. This reduction, which is accompanied by a simultaneous reduction of the blood flow through the peritubular capillary network, must be ascribed, at least to a great extent, to a constriction of the afferent glomerular vessels, leading to a fall in intraglomerular hydrostatic pressure. The point of attack of 5-HT in the rat kidney is therefore the smooth muscle, or analogous contractile structures of the afferent glomerular system. Systemic hypotension and increase in the endocapsular pressure should really be listed among the factors causing a reduction in the filtration pressure, but neither of them can interfere when the dose of 5-HT is less than 0.4 mg/kg.

After 5-HT the percentage reduction in the urine volume is greater than that in the glomerular filtration rate and still more than that in the renal plasma flow, as measured by the PAH excretion. A higher percentage of the glomerular filtrate has therefore been reabsorbed by the tubules of the treated animals than by those of the controls. Even without excluding other possibilities, such as that of some direct or indirect stimulant effect of 5-HT on the tubular epithelium, a satisfactory explanation of the phenomenon may be based on the theory that, when the glomerular filtration rate is decreased, the reduced glomerular load is more completely reabsorbed during the slower passage down the nephron and less is excreted (SELKURT et al. 1952).

Other pieces of direct and indirect evidence in favour of a prevailingly vascular point of attack of 5-HT in the rat kidney, and hence of the possibility of a temporary, partial exclusion of the organ from the general circulation are as follows:

a) after the administration of high, unphysiological doses of 5-HT (2—10 mg/kg) the afferent vasoconstriction induced by the substance becomes visible even macroscopically through the mottled aspect of the kidney surface, due to the presence of ischemic cortical areas interposed between areas with an apparent normal blood supply. If the injury is particularly intense or repeated, ischemia results in degeneration and necrosis (ERSPAMER 1952, 1954d).

b) recovery in urine of subcutaneously injected thiosulphate is considerably higher (32.5%) in control rats than in rats given large doses of 5-HT (down to 9.3%). This means that the substance, owing to the more prolonged stay in the organism caused by renal ischemia, has been metabolized to a larger extent (ERSPAMER and OTTOLENGHI 1953).

c) sublimate intoxication is less severe in rats given repeated high doses of 5-HT than in control rats. This is so in spite of the nephrotoxicity of the high doses of 5-HT, on their own. The protection may be interpreted as being due to reduced flow of blood, and hence of the poison, through the kidney (ERSPAMER 1953b).

5-HT antidiuresis (0.1—0.5 mg/kg, s.c.) can be prevented but not suppressed once it has begun, by dibenamine, by the natural or hydrogenated ergot alkaloids of the ergotamine and ergotoxine groups, and by LSD (ERSPAMER 1953c, 1954b) and other lysergic acid derivatives. In the experiments of DE CARO (1963), confirmed by CHODERA (1963), none of the five investigated lysergic acid derivatives (100 μg/kg) were capable of completely blocking the antidiuretic action of 2 mg/kg 5-HT injected subcutaneously 30 min later. The relative potency of the compounds ranged in this order: MOB (1-methyl-BOL) = MLD (1-methyl-LSD) > UML (1-methyl-D-lysergic acid butanolamide) > BOL = LSD. Gramine and gramine derivatives (ERSPAMER, 1953c, 1955b), the N-methyltryptamines, the aminoindoles of WOOLEY and SHAW, including "medmain" and "1-methyl-medmain" (ERSPAMER, 1953c, 1954b), as well as some antihistaminic agents had a less consistent action (ERSPAMER, 1952c). The antidiuretic effect of 5-HT does not appear to be significantly affected by ganglion-blocking drugs, atropine, papaverine, nitrites, ethyl alcohol, 1-hydrazinophthalazine, histamine, adenosine or theophylline (ERSPAMER 1953d).

The fact that 5-HT is much more active when injected subcutaneously than when given intraperitoneally or intravenously and the fact that the majority of the drugs antagonistic to 5-HT are capable of preventing 5-HT antidiuresis but not of interrupting it is explained, without excluding alternative interpretations, by assuming that 5-HT occupies its receptors within the walls of the afferent renal vessels slowly and gradually, but very tenaciously. The gradual occupation would account for the necessity of a prolonged supply of small quantities of substance, as experimentally ensured by subcutaneous injection; the tenacity of occupation explains satisfactorily on the one hand the conspicuous duration of the antidiuretic effect and on the other the inability of some of the most powerful antagonists to remove 5-HT from its renal receptors (ERSPAMER 1954b, 1954c).

The writer's data on the powerful antidiuretic effect of 5-HT in the rat have been fully confirmed and the suggestion that this effect is mainly due to afferent glomerular vasoconstriction has been generally accepted (DEL GRECO and CORCORAN 1956, DEL GRECO et al. 1956).

VAN ARMAN and JENKINS (1956), for example, found that 5-HT had a highly significant ($P > 0.01$) antidiuretic effect in well-hydrated rats in subcutaneous doses as low as 10 μg/kg and that this effect could not be ascribed either to lowering of blood pressure or to painful sensations produced by the injection. Without excluding the possibility that 5-HT directly stimulated the kidney tubule to cause increased water reabsorption, the main cause of reduced diuresis was considered to be diminished glomerular filtration produced by changed blood flow. The frequently observed dissociation between diuresis and creatinine excretion, the latter being less reduced than the former, has been better explained by the assumption that a very slight drop in filtration can cause a large drop in water output (WHITE 1951). VAN ARMAN and JENKINS have criticized the conclusion of ERSPAMER (1954b) that dibenamine is incapable of removing 5-HT from its renal receptors once it has occupied them. Having found that dibenamine on it own has effects on the kidney which superficially resemble those of 5-HT, VAN ARMAN and JENKINS affirm that it would be difficult to say whether dibenamine can displace 5-HT from the renal receptors. We think that the most

pertinent answer to the above criticism is the finding that lysergic acid derivatives also (LSD, BOL) given at dose levels which on their own completely lack any antidiuretic effect (e.g. 10 μg/kg, i.p.) consistently reduce 5-HT antidiuresis when administered prior to 5-HT injection, but have no effect at all when given after 5-HT (ERSPAMER 1954b, DEL GRECO and CORCORAN 1956, DEL GRECO et al. 1956).

Although subcutaneous administration of 5-HT is far more efficacious in producing antidiuresis than intraperitoneal or intravenous administration (AIRAKSINEN et al. 1960, ERSPAMER 1954b), a transient sharp drop in the rate of urine flow may be obtained in alcohol-anaesthetized hyperhydrated rats even by injection into the femoral vein of doses of 5-HT as low as 0.5 μg/100 g (SINCLAIR 1957), and in anaesthetized rats brought into osmotic diuresis with mannitol by intravenous infusion of 3—5 μg/kg/min 5-HT base. At this infusion rate a depression of glomerular filtration rate is observed, together with persistent decreases in urine volume, urinary osmolarity and urinary chlorides. Larger doses of 5-HT (6—8 μg/kg/min) cause severe and persistent depression of renal function, sometimes associated with macroscopic renal infarcts. These effects are largely independent of the changes in blood pressure (DEL GRECO and CORCORAN 1956, DEL GRECO et al. 1956).

Besides being decreased by sympatholytic drugs and lysergic acid derivatives, the antidiuretic effect of 5-HT (160 μg/kg, s.c.) is also significantly reduced by chlorpromazine (5—50 mg/kg) given 30 min before hydration. Antidiuresis produced by posterior pituitary extract (0.06 *u.*/kg) is not however counteracted by chlorpromazine (DASGUPTA 1957).

According to FRENKL et al. (1964) the antidiuretic effect of 5-HT is strongly reduced in rats trained for six weeks by forced swimming.

Isolated rat kidneys perfused with isotonic dextran solutions respond to 5-HT added to the perfusion liquid with reversible vasoconstriction, and within a certain range the degree of vasoconstriction depends on the concentration of 5-HT. For example, 0.034, 0.125 and 1 μg/ml 5-HT reduce the perfusion rate by 25—30, 60 and 70—75%, respectively. After a short initial period during which the vascular resistance rises, a constant vascular tone is reached and maintained for a long time. There is no significant tachyphylaxis up to 2 μg/ml 5-HT concentrations, but at a concentration of 10 μg/ml a slight effect of desensitization is noted. Even maximal effects of 5-HT can be fully reversed or suppressed with suitable doses of LSD (0.2 μg/ml) (PASSOW et al. 1960). The 5-HT constriction of the rat renal vessels is 5—10 times less than that produced by adrenaline (CERLETTI et al. 1955).

The opinion of BENDITT (1957) that trapping of fluid peripherally seems to offer an adequate explanation of the antidiuretic effect of 5-HT administered by the subcutaneous route cannot be seriously taken into consideration. Similarly, all the available experimental evidence is against the participation of post-pituitary ADH in the production of antidiuresis caused in rats and mice by single low doses of 5-HT (ERSPAMER and CORREALE 1955, DASGUPTA 1957, VAN ARMAN and JENKINS 1956). This statement is not in contrast with the histochemical findings of KIVALO et al. (1957, 1958b, 1959) that repeated subcutaneous doses of 5-HT (0.2 mg/kg of the base, daily for 7 days) cause depletion of the neurosecretory substance in the hypothalamus and in the posterior lobe of the hypophysis.

As already stated, the preliminary observations by ERSPAMER (1952a) on the nephrotoxic action of large doses of 5-HT have been fully confirmed by numerous other investigators (see p. 739) and this represents additional strong evidence

supporting the view that the site of action of 5-HT in the rat kidney is mainly vascular.

Morphological studies on the effects of 5-HT upon the intrarenal circulation were carried out in the rat by DOLCINI et al. (1960) using a modified benzidine staining technique and intravascular injections of India ink. A marked vasodilatation with increased filling of glomeruli and peritubular capillaries was noted 15 min after the injection of 4 mg/kg 5-HT base, reaching a maximum at 30 min. At 90 and 180 min there was a striking change in the cortical zone, where the glomeruli appeared bloodless, while the circulation in the juxtamedullary area remained unaltered. According to DOLCINI and co-workers the glomerular filling effect is more likely to be on the basis of active vasodilatation rather than of stasis secondary to constriction and maintenance of juxtamedullary circulation throughout the experiment is due to a shunting of blood away from the cortex at the juxtamedullary area.

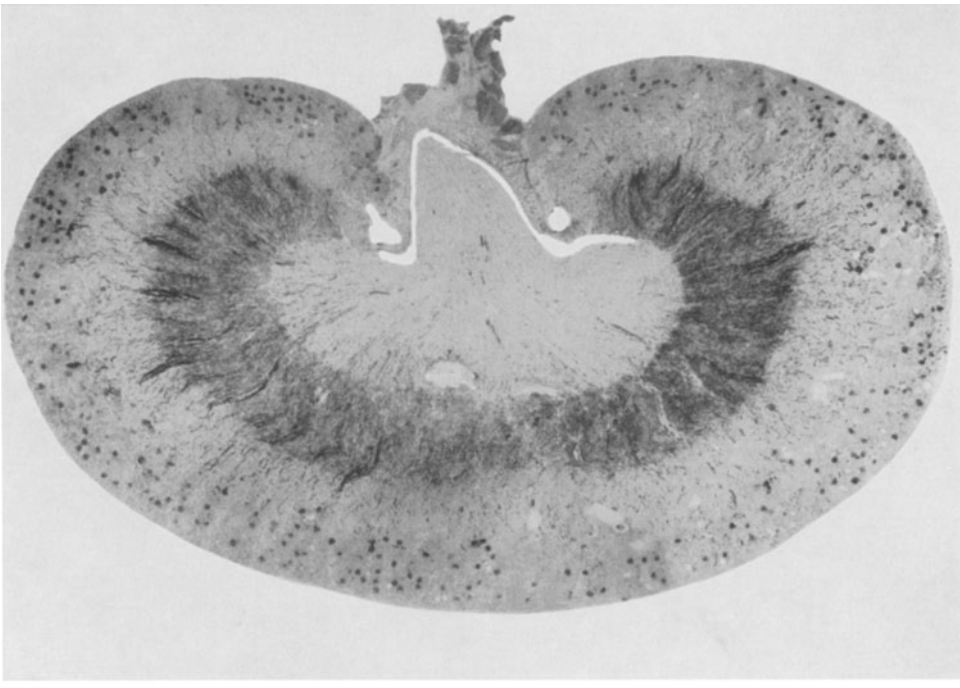
The above observations are, on the whole, in accordance with previous similar observations of FIORE-DONATI and ERSPAMER (1957) (Fig. 7). However, initial cortical blood filling is interpreted by these research workers as a frankly passive phenomenon, due to stasis secondary to afferent vasoconstriction. This is mainly based on the demonstration that at the time of maximal filling of the glomeruli there is complete block of glomerular filtration and diuresis, an event which evidently is incompatible with active vasodilatation.

It has been observed that several 5-HT antagonists (9-(N-methyl-piperidyliden-4')thioxanthene, methysergide, cyproheptadine, imipramine) produce a more or less pronounced diuretic effect in non-hydrated and in hydrated rats. The question whether this diuresis could be related to a 5-HT mechanism was answered negatively, owing to lack of correlation between anti-5-HT and diuretic activity of these compounds (TRAPOLD and BRINER 1962).

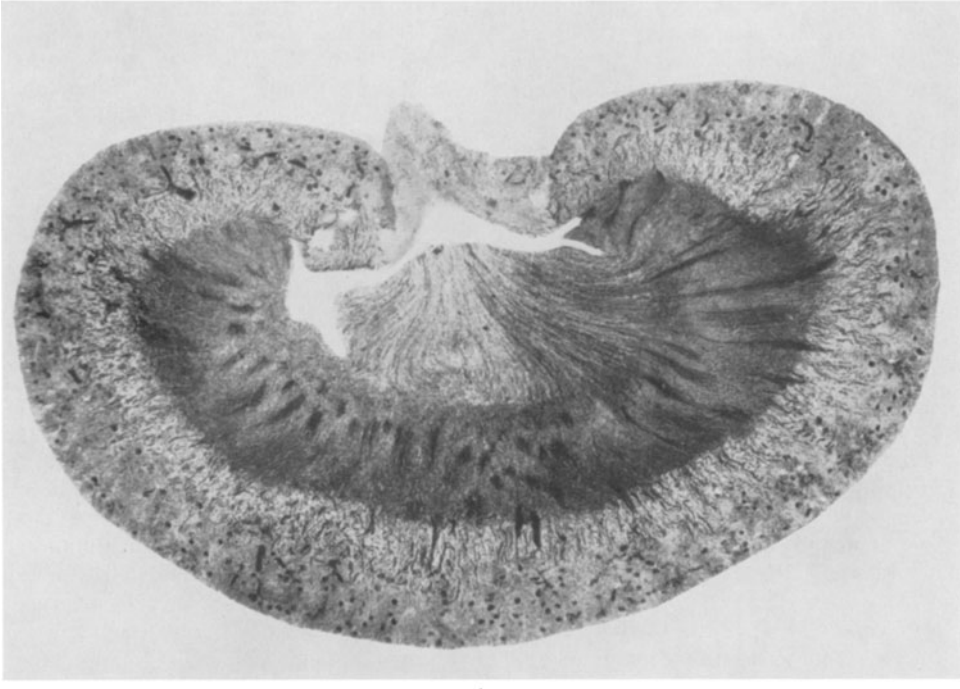
Among the indolealkylamines, 5-HT is by far the most active on diuresis. The isomers of 5-HT are devoid, or nearly so, of any antidiuretic activity. In fact, 7-HT and 6-HT are ineffective in subcutaneous doses up to 20—40 mg/kg, and even 4-HT is more than 100 times less active than 5-HT (ERSPAMER and NOBILI 1962a, ERSPAMER unpublished observations).

The percentage activity of other indolealkylamines is a follows: N-methyl-5-HT 30–40, bufotenine 6–7, bufotenidine 0.3, 5-methoxytryptamine 25–40, tryptamine 0.3–0.5, 1-methyltryptamine 0.1–0.3, N-methyltryptamine and N,N-dimethyltryptamine 0.3.

No antidiuretic activity is shown by bufothionine, dehydrobufotenine, 6-methoxytryptamine, gramine, 2-methylgramine, 2-methyl-5-aminogramine, 2-methyl-5-nitrogramine, 2-methyl-5-chlorogramine, nor by indole derivatives lacking the amino group in the lateral chain (ERSPAMER 1952b, 1954b, and unpublished observations). Besides indolealkylamines some indolealkylaminoacids also produce antidiuretic effects, provided that they are transformed in the organism into active amines. So far, the aminoacids which have been found to comply with this condition are 5-HTP, 4-HTP (decarboxylation to 5-HT and 4-HT, respectively), 5-hydroxy-N-acetyltryptophan and 5-acetoxy-N-acetyltryptophan (hydrolysis to 5-HTP followed by decarboxylation), and tryptophan (direct decarboxylation to tryptamine or 5-hydroxylation to 5-HTP followed by decarboxylation to 5-HT) (ERSPAMER and BERTACCINI 1962, ERSPAMER and NOBILI 1962a, 1962b). None of the numerous other tryptophans investigated are decarboxylated in the organism to active amines (except, possibly, in traces) and hence, as expected, they are all completely inactive on diuresis (ERSPAMER et al. 1961, ERSPAMER unpublished observations).



a



b

Fig. 7 a and b.. a Normal rat kidney stained with benzidine. The glomeruli are well filled with blood, whereas the filling of the inner band of the outer medullary zone is only a moderate one. b Kidney of a rat killed 60 min after a subcutaneous injection of 20 mg/kg 5-HT. Benzidine staining. Conspicuous congestion of the whole renal parenchyma: the peritubular capillary network, the outer and the inner bands of the outer medullary zone and the inner medullary zone are well filled with blood. ×6.5. [From Fig. 7, ERSPAMER, V., Triangle (Basel) **3**, 134 (1956).]

The minimum dose of DL-5-HTP and DL-4-HTP active on diuresis is approximately 10—20 mg/kg, by intraperitoneal or subcutaneous route. Oral aminoacids are at least 10 times less effective. Large doses of both 5-HTP and 4-HTP produce signs of cortical necrosis in a certain number of animals. The puzzling fact that exogenous 4-HT has, in sharp contrast to the 4-HT originating in the organism from 4-HTP, a very limited effect on diuresis, can be explained assuming that exogenous 4-HT, owing to its rapid inactivation, is not available for the renal receptors in sufficiently large amounts or, more probably, for a sufficiently long time to produce afferent vasoconstriction. The 4-HT originating from 4-HTP, on the other hand, may continue to circulate for long enough to allow firm occupation of the renal receptors (ERSPAMER et al. 1960, ERSPAMER and NOBILI 1962a).

5-Hydroxy-N-acetyltryptophan and 5-acetoxy-N-acetyltryptophan are considerably less effective than 5-HTP, even though they cause the appearance in the urine of large amounts of 5-HT (up to 50 μg/ml). This demonstrates that only 5-HT reaching the kidney via the blood is capable of reducing urine flow, whereas the amine generated within the kidney by decarboxylation of 5-HTP is inactive (ERSPAMER and NOBILI 1952b).

Although not directly pertinent to the topic dealt with in this chapter, some other experimental data are worth remembering. BERTACCINI and ERSPAMER (1962) have shown that single or repeated administration of tap water or of physiological NaCl solution produces in rats a conspicuous increase in urinary excretion of 5-HIAA which generally but not necessarily coincides with diuresis. One of the possible explanations of the phenomenon is that hydraemia and/or expansion of blood volume influence in some way renal excretion or reabsorption of 5-HIAA.

Mouse. Mice behave like rats in regard to the action of 5-HT on the kidney. The amount of urine collected in groups of mice after two hours, expressed as per cent of the water given, is 61% for the controls, but only 34% for the animals injected with 0.2 mg/kg 5-HT base. 2 mg/kg 5-HT has a more marked effect. Similar results are obtained with 0.5 μ/kg of posterior pituitary antidiuretic hormone, but whereas the chloride concentration in the urine of mice treated with 5-HT is significantly lower than that for the controls, the opposite may be seen for mice treated with antidiuretic hormone. It is suggested that the antidiuretic effect of 5-HT is the result of diminished blood flow through the kidney (WAAL and VEALE 1956).

Dog. The antidiuretic effect of 5-HT in the dog as well as in all other animal species examined is considerably less intense and constant than that observed in rats and mice. If we add that practically every research worker has used, in investigating the effect of 5-HT on the dog kidney, different doses of 5-HT, different routes of administration and different methods, it is small wonder that results have often been at apparent variance and that the mechanism of action of the drug in the dog kidney is controversial and largely obscure.

The minimum antidiuretic dose of 5-HT by single intravenous injection varies from 10 to 20 μg/kg (ABRAHAMS and PICKFORD 1956a) and by intravenous infusion from 3 to 10 μg/kg/min (SPINAZZOLA and SHERROD 1955, 1957, BLACKMORE 1958, LITTLE et al. 1961). The subcutaneous or intramuscular doses required to produce antidiuresis are considerably higher. SALA and CASTEGNARO (1953) obtained positive results with subcutaneous doses varying from 40 to 800 μg/kg; ABRAHAMS and PICKFORD (1956a) failed to produce antidiuresis with subcutaneous doses of 22—74 μg/kg and intramuscular doses of 14—36 μg/kg 5-HT.

5-HT is most effectively antidiuretic when injected into the cubital vein, less so when injected into the malleolar vein or carotid artery, and still less so when given into the aorta at a point above the origin of both renal arteries (ABRAHAMS and PICKFORD 1956a).

SALA and CASTEGNARO (1953) first injected 5-HT by subcutaneous route (0.04—0.8 mg/kg 5-HT base) into a series of 30 trained colpotomized bitches. They found that the amine constantly produced a more or less conspicuous reduction in urine volume, whereas the glomerular filtration rate remained unaltered for lower doses of 5-HT, while frequently showing a slight reduction for higher doses. The behaviour of the renal plasma flow was rather surprising: it remained unchanged or slightly diminished at first and increased, in the majority of cases, 20 to 30 minutes after the injection of the drug. These observations were largely confirmed by other research workers who gave 5-HT by single intravenous injections to anaesthetized dogs.

BARAC (1953a, 1955) noted that intravenous injections of 0.5—1 mg/kg 5-HT base elicited in dogs intravenously infused with saline a conspicuous reduction in the urine volume (80—100%), which was unaccompanied by any increase in chloride excretion and was largely independent of fluctuations of blood pressure. Antidiuresis was also evoked after adrenalectomy, after hypophysectomy as well as after section of the renal nerves. Ascorbic acid suppressed the antidiuretic effect of 5-HT (BARAC 1953b).

ABRAHAMS and PICKFORD (1956a) obtained similar results with lower doses of 5-HT (20—30 μg/kg). The amine not only reduced urine flow in both innervated and denervated kidneys, but also reduced the renal clearance of diodone and creatinine. One or both values, however, might increase towards and above preinjection level before urine flow recovered. The kidney surface became pale for several minutes, and injected bromophenol was found abundantly in the medullary zone, but only in a few radial streaks in the cortex. Juxtamedullary glomeruli were devoid of dye. 5-HT antidiuresis was always accompanied by obvious respiratory changes, by increase of systemic blood pressure and by changes in the colour of vaginal mucous membrane.

In a dog suffering from diabetes insipidus (daily elimination of 5—6 litres of urine), urine flow was reduced by 30 to 40% with 15 μg/kg 5-HT, and by 40—70% with 30 μg/kg 5-HT, given intravenously.

ABRAHAMS and PICKFORD (1956a) and PICKFORD (1957) repeatedly insist on the fact that the antidiuretic effect of 5-HT varies greatly from one animal to another and in the same animal from one observation period to another.

KHAZAN et al. (1962) injected 0.8 mg/kg 5-HT base into the veins of anaesthetized hydrated dogs (10 ml/kg water by stomach tube) and measured the volume of urine excreted through the ureters. A long-lasting, 30—40% reduction of urine volume was accompanied by a more conspicuous reduction in Na^+ and Cl^- excretion (from 80 ± 2.9 and 63 ± 2.4 to 38 ± 2.7 and 25 ± 0.26 meq/l, respectively) and by a consistent increase in K^+ excretion (from 223 ± 5.5 to 335 ± 3.4 meq/l). This pattern was the opposite of that caused by pitressin (2 u./kg) administration.

The renal venous pressure showed, after intravenous injection of 0.1 mg 5-HT base only a small transient reduction; then it increased at the same time with systemic pressure (MAZZELLA and MAQUIEIRA 1957).

Results obtained following intravenous infusion of 5-HT into unanaesthetized dogs were, on the whole, in good accordance.

SPINAZZOLA and SHERROD (1955, 1957) administered 5-HT to hydrated, trained female dogs in the postabsorptive state. A definite antidiuretic effect

occurred at a threshold dose of 10 μg/kg/min 5-HT and became more pronounced until a dose of 20 μg/kg/min was administered. Increasing the dose to 25 μg/kg/min caused little or no further significant reduction in the rate of urine formation. Antidiuresis began within 15 min following start of the drug infusion, and lasted approximately 15 min following cessation of infusion. This was followed by a diuresis lasting 30 to 45 min. A reduction in GFR occurred beginning at a dose level of 15 μg/kg/min and it became more pronounced at the 20 μg/kg/min dose (maximum decrease = 30%). Increasing the dose up to 25 μg/kg/min resulted in little or no further decrease in GFR. An elevation of the effective renal plasma flow was noted beginning with the 10 μg/kg/min dose, which became quite significant (20—30%) and reached a plateau at about the 20—25 μg/kg/min dose. There was no important change in the mean arterial blood pressure at any of the above dose levels.

Working under similar experimental conditions, BLACKMORE (1957, 1958) found that 5 μg/kg/min 5-HT base produced as small but significant decrease in GFR, associated with increased RPF, and that 10 μg/kg/min caused the same changes plus a marked antidiuretic effect (from 3.5 to 0.6—0.9 ml urine/min). In all experiments there was a marked decrease in sodium excretion during 5-HT infusion, which returned to control values or above after cessation of the infusion. There were no changes in mean arterial blood pressure.

LITTLE and co-workers (1960, 1961) infused 5-HT into dogs infused with 0.9% NaCl solution at a rate of 0.5 ml/kg/min. At an infusion rate of 1.5 μg/kg/min 5-HT base only sodium ion excretion was significantly decreased; at a rate of 3 μg/kg/min there was a significant decrease in the renal excretion of sodium, chloride and potassium ions and a significant increase in sodium ion reabsorption. Rate of urine flow, GF and RPF were not changed during the infusion of 5-HT, but decreased significantly during the postinfusional period.

Finally, VILLAMIL et al. (1962) infused 5-HT creatinine sulphate at a rate of 30 to 60 μg/kg/min into dogs subjected to osmotic diuresis with 5% mannitol. Urine was collected from the bladder and blood samples were drawn from the femoral artery and the renal vein. 5-HT elicited a fall in the renal clearances and extractions of both creatinine and paraaminohippurate, as well as in total RPF and in the filtration fraction. Blood pressure fell slightly and renal resistance tended to increase.

A last set of experiments is concerned with the effects of 5-HT introduced directly into the artery of the *in situ* or the perfused kidney.

5-HT infused directly into the renal artery of laparotomized, anaesthetized dogs at a rate of 4—40 μg/min produced regularly an increase of the geometric component of renal vascular resistance through some mechanism unrelated to extrinsic nerves or to endogenous catecholamines. Dynamic changes in blood viscosity or interstitial pressure elevation were highly unlikely. The constriction of the renal vascular bed produced by 4 μg/min appeared to be nearly maximal. Urine flow rate did not appreciably change (EMANUEL et al. 1958, 1959).

Whereas single injections of 5-HT were found by PAGE (1957) to produce a strong and sustained constriction in perfused dog's renal vessels, the same injections (20 μg 5-HT base) appeared to possess, in the experiments of CERLETTI et al. (1955) only a slight and fleeting constrictor effect, which was less intense than that provoked by a 100 times smaller dose of adrenaline.

During stimulation of the peripheral end of a cut renal nerve, injection of 5-HT (0.3—7 μg) into the renal artery caused an initial rise of perfusion pressure approximately equal to that before stimulation, but this was followed by a

sustained vasodilatation not present in the absence of stimulation (McCubbin et al. 1962).

5-HT perfused through a kidney transplanted to the neck in concentrations up to 7 μg/ml caused no significant change in the blood flow through the organ. This happened in sharp contrast to adrenaline which potently constricted renal vessels in concentrations as small as 0.02 μg/ml (Cuypers et al. 1957).

It is rather difficult to draw from the preceding data any definite conclusion about the mechanism of action of 5-HT on the dog kidney.

The only certain thing is that the renal effects of 5-HT are independent of the extrinsic innervation of the kidney and of the integrity of the posterior pituitary lobe (Barac 1955, Abrahams and Pickford 1956a, Blackmore 1958, Khazan et al. 1962), and that these effects, and hence the mechanism of action of 5-HT, may vary according to the dose and the way of administration of the drug. Whereas Abrahams and Pickford (1956a) and Pickford (1957) believe that it is necessary to look beyond the kidney for the effect of 5-HT on urine flow, suggesting that this is dependent on changes in the systemic blood pressure brought about by reflexes set up from the thorax, the great majority of investigators point to a direct action of 5-HT on the tubules and/or the intrarenal vascular bed. Concerning the possible vascular action of 5-HT, it should be stressed that a fall in intraglomerular pressure and, as a consequence, in GFR may be produced a) by an increase in renal vascular resistance due to constriction of afferent arterioles, b) by decrease in this resistance due to dilatation of both afferent and efferent arterioles, and finally c) by an intrarenal diversion of blood from the cortex towards the juxtamedullary zones and/or opening of vascular shunts simultaneously skipping glomeruli and proximal tubules. The last possibility has been proposed by Villamil et al. (1962).

It has been suggested that changes in renal haemodynamics and even moderate renal lesions found in dogs and rabbits subjected to extracorporeal circulation may be ascribed to 5-HT and ATP release following corpuscular blood thrauma (Frick 1960, Sarajas and Saure 1960). The amine, on the contrary, does not seem to play any role in the oliguria seen in dogs after burns (Renson et al. 1959).

Psilocybin provokes in the dog an active reduction of the kidney volume, when given intravenously in doses of 50—100 μg/kg (Weidmann et al. 1958).

Cat. In cats slightly anaesthetized with chloralose small intravenous doses of 5-HT (threshold 3 μg/kg) reduce the flow of urine into the bladder for $^1/_2$ to 2 minutes. Paling of the kidney and obvious spasms of the ureter are never observed. Antidiuresis is followed by a secondary diuresis.

The mechanism of this fleeting antidiuretic action is obscure. Reflex fall of blood pressure seems to play little part, and Fastier and Waal (1957) similarly hesitate to attribute the antidiuretic effect of 5-HT in the cat to either ureteral spasm or to constriction of renal blood vessels. In fact, if it is true that a moderate reduction of the blood flow through the kidney was observed by Cerletti et al. (1955) in direct perfusion experiments, it should be noted that the required dose of 5-HT was rather high (10—20 μg) and that adrenaline appeared, in this preparation too, to be 15—20 times as active as 5-HT.

Psilocybin produces, in doses of 50—100 μg/kg, an active increase in kidney volume, indicating vasodilatation (Weidmann et al. 1958, Cerletti 1959).

Rabbit. Intravenous doses of 5-HT of the order of 20—200 μg/kg constantly produce striking and persistent paling of the kidney. Ischemia is particularly evident in the cortex. Concomitantly there is a transient drop in the flow of urine from the ureters (Fastier and Waal 1957, Rovati et al. 1956).

In rabbits receiving chronic 5-HT treatment (3—5 mg/kg. over 13 to 23 days) a spotty ischemia of the renal cortex develops with both tubular and glomerular changes. Tubules present signs of hyaline degeneration; protein appears in the capsule of Bowmann and the basement membrane of the glomerular loops increases in thickness (ROVATI et al. 1956, BEREGI et al. 1962).

In contrast to the above results, VIRTAMA and JÄNKÄLÄ (1961) failed to demonstrate either in the rabbit or in the guinea-pig signs of constriction of the intrarenal arteries following injection of 5-HT (0.2—5 mg/kg) through a polyethylene catheter into the aorta just above the origin of the renal arteries. A radiographic contrast mass was injected immediately after or simultaneously with 5-HT.

In the writer's opinion these results only show that rapid intraaortic injection of 5-HT does not produce an immediate intrarenal vasoconstriction, as is necessary for arteriographic visualization.

Chicken. 60—80 μg 5-HT base injected into the leg vein of a chicken together with phenol red does not apparently affect the blood flow of the kidney, as shown by the normal phenol red excretion (SANNER 1963).

Man. Normal subjects. As in the case of the dog, the effect of 5-HT on diuresis and renal circulation varies conspicuously not only with the dose and the manner of administration of the drug, but also with the methods used in evaluating the effects of 5-HT on the kidney. Moreover, under exactly the same experimental conditions, striking differences in the reaction to 5-HT can be observed in different individuals.

HOLLANDER and MICHELSON (1956, 1957) found that following the intravenous injection of 0.5 mg 5-HT base (approximately 10 μg/kg) urine flow was reduced moderately but significantly for about 45 minutes. Concomitantly there was a slight but significant (30%) decrease in RPF often, but not necessarily, accompanied by a reduction in GFR and excretion of sodium and potassium. These changes were inconsistently related to changes in blood pressure. There is little possibility that reductions in renal functions might not have been due to actual reductions in renal haemodynamic function or electrolyte excretion but to inadequate washout of "dead space" consequent to the reduction in urine flow, because in some instances they occurred without any reduction of diuresis. HOLLANDER and MICHELSON conclude that 5-HT acts in man as a moderate antidiuretic but a weak renal vasoconstrictor agent.

DEL GRECO et al. (1956) and SCHNECKLOTH et al. (1957) observed that during osmotic diuresis 5-HT was marginally effective even when infused at a rate of 2 μg/kg/min and that doses of 4—9 μg/kg/min reduced not only urine flow, but also RPF and Na output. Maximum rate of water absorption was unchanged and K output increased.

SINCLAIR (1957) and AMBANELLI and SALVI (1960) showed that when doses of 4—8 mg 5-HT base were given by slow intravenous injection simultaneously with a rapid intravenous infusion of 850 ml of isotonic dextrose, the intensity of the diuretic response tended to be reduced, and the duration to be shortened. In two of the experiments of SINCLAIR reduction of urine volume after 90 min was from 1050 to 630 ml, and from 750 to 490 ml. In the experiments of AMBANELLI and SALVI on 18 normal subjects, average reduction in urine flow was 50, 30 and 20% after 30, 60 and 90 minutes, respectively.

ANNONI and LUCCHELLI (1955, 1957) observed that even intramuscular 5-HT (4 mg of the base) produced in 60% of hydrated subjects a significant reduction in urine volume, together with irregular changes in RPF and GFR. In some cases there was a conspicuous delay in the appearance in urine of injected phenol-

sulfonphthaleine. The effect of 5-HT was clearly appreciable also on diuresis produced by mercurial diuretics, while barely visible or lacking under conditions of normal hydration.

BOJS (1951), who has certainly carried out the most complete investigation on the action of 5-HT on the renal function in man, found that decreased renal sodium excretion was the most prominent finding during intravenous infusion of 5-HT (4.3—8.7 μg/kg/min). This effect was statistically highly significant ($P < 0.001$) even at the smallest 5-HT dose and often showed a close dose/response relationship. The average decrease at the largest 5-HT dose was 63%. The effect was rapid in onset (within 10 min) and reversal (within 20 min). Renal potassium excretion was not influenced by 5-HT. The fall in chloride excretion and osmolar clearance during 5-HT infusion was similar to the sodium decrease. The influence of 5-HT on water excretion was variable but antidiuresis was often observed when the initial urine flow was high. Parallel and small decreases in GFR and RPF were found during 5-HT infusion. However, these responses showed adaptation and were not statistically significant. BOJS suggests that augmented tubular sodium reabsorption is the main mechanism of 5-HT action, although decreased tubular sodium load may sometimes be a contributing factor.

To the above positive results, those of other investigators should be added, confirming that antidiuresis produced by 2—4 mg 5-HT given by the intravenous or intramuscular route is particularly evident after a water load (CORREALE 1957), and showing that GFR varies rather slightly, in general in the direction of a diminution (CENACCHI and CARIANI 1958, CENACCHI et al. 1959), that RPF changes insignificantly in some cases, but presents a clear decrease in others (CENACCHI et al. 1959), and finally that there is generally a reduction in NaCl excretion (HULET and PERERA 1956, CORREALE 1957).

At complete variance with the preceding data are those of other investigators who found that 5-HT does not produce any change in the renal function or circulation of normal subjects (CURTI and FORNAROLI 1955, CARRETTI and RONCHETTI 1955, CALÌ et al. 1956, NOTTER 1956, CORÀ et al. 1957, VERCILLO and MAZZETTI 1957). However, in this regard it immediately must be stressed that some of the negative results cannot be taken into consideration because of unsuitable experimental procedure, e.g. determination of urine volume and composition only at the end of a 24 hr observation period (CARRETTI and RONCHETTI 1955, VERCILLO and MAZZETTI 1957), and that in other cases negative conclusions are not in accordance with partly positive experimental results. CALÌ, LOMEO and BOMPIANI (1956), for example, while affirming that 5-HT does not display any effect on the kidney function of normal subjects, present a table showing that 90 min after the administration of 6 mg 5-HT base, 6 subjects out of 10 showed a reduction in urine volume, 2 no change, and 2 an increase in urine volume.

FRICK et al. (1961) suggest that the 5-HT released into plasma after major operations may participate in postoperative antidiuresis.

Diabetes insipidus. SERRAVALLI (1955) and CURTI and FORNAROLI (1955) could not demonstrate any appreciable action of 5-HT on the diuresis. ERSPAMER (unpublished observation) and ANNONI and LUCCHELLI (1955, 1957), on the contrary, found a consistent reduction of polyuria and polydipsia following single or repeated intramuscular injections of 2—5 mg 5-HT. In a case of juvenile diabetes mellitus with polyuria, 5-HT (2 mg every 8 hours) reduced not only diuresis (from 5—6 to 1.5—2 litres *pro die*), but also glycosuria (from 60—80 to 15—30 g) and albuminuria, with unchanged glycaemia.

Carcinoidosis. In some cases of carcinoidosis occasional periodic oliguria was observed clinically, often preceding flushing attacks (SINGLAIR 1957). During

study of kidney function, severe renal vasoconstriction has been found in some instances unassociated either with hypertension or with abnormalities of renal function (DEL GRECO et al. 1956. SCHNECKLOTH et al. 1957).

It is difficult from the above data to draw definite conclusions on the site and mechanism of action of 5-HT in the human kidney. Evidence in favour of a direct vascular action of the amine is balanced by evidence in favour of a direct action on the tubules.

5-HT has been considered for some years by the writer (ERSPAMER 1954b, 1954c) to be a hormonal substance participating in the regulation of the intrarenal circulation and the function of the kidney. In spite of the fact that the existence of an antidiuretic effect of 5-HT has been generally confirmed in all the mammals studied, it must be admitted that so far only for rats do the renal actions of 5-HT fulfil the main conditions necessary for them to be considered "physiological". For all the other mammalian species, the renal effects, besides being more irregular, short-lasting and inconstant, are obtained with high, unphysiological doses of 5-HT.

Thus the theory of a specific renal effect of 5-HT should be dropped or drastically limited as lacking sufficient experimental evidence.

IX. Action on cellular permeability

This has been investigated in several representative cell models.

1. Slices of red beetroot. 5-HT, indoleacetic acid and, to a lesser degree, tryptamine (1—100 μg/ml) increase the effusion of pigment from beetroot slices, and strongly inhibit sodium uptake by this material, although they display little effect on the potassium efflux. These effects are not necessarily associated with any appreciable change in the rate of oxygen consumption by the tissue. They are generally irreversible in experiments lasting only a few hours, but may be completely reversible over long periods of time (PICKLES 1955, PICKLES and SUTKLIFF 1955).

2. Erythrocytes. Pretreating human erythrocytes with 5-HT (0.1—1 mM) accelerates their subsequent hypotonic haemolysis as shown by the haemoglobin release, but diminishes the amount of potassium lost in proportion to haemoglobin. Similarly, 5-HT pretreated erythrocytes lose potassium more slowly in cold-storage than controls do. Tryptamine in similar concentrations does not have either of these effects. LSD (0.1—1 mM) inhibits the effects of 5-HT (PICKLES 1955, 1956).

Addition of 0.4—20 μg 5-HT to 100 ml normal human blood causes increase of serum bilirubin, as a consequence of increased escape of the pigment from the red blood cells (NILSSON et al. 1960).

3. Blood platelets. The movement of potassium (^{42}K) from plasma into blood platelets is increased when 5-HT is added to the plasma at a concentration of 1 to 10 μg/ml. 5-HT which is bound to the platelets does not display this effect (BORN 1958).

4. Amphibian skin. Addition of 5-HT (15—400 μg/ml of the base) to distilled water used to bathe the outer surface of isolated abdominal frog or toad skin produces no significant effect on the net water flux from the outer surface inward, while increasing the net fluxes of sodium and potassium from the inner surface bathed in RINGER'S solution outward. In skin showing very high initial Na and K fluxes, the addition of 5-HT decreases rather than increases the net movements. Addition of 5-HT does not alter the short-circuit current but does decrease

the skin electrical potential difference, confirming that the increase in net Na efflux results from increased passive efflux and not from decreased active influx. Tryptamine has effects similar to those of 5-HT, whereas bufotenine is practically inactive (PICKLES 1957a, 1957b).

It has been suggested by PICKLES (1956) that the above effects may be explained by a selective alteration in cell-membrane permeability and that this may be relevant to the problem of the physiological function of 5-HT.

In the intact frog even large doses of 5-HT (0.1—8 mg/kg, into the dorsal lymphatic sac) fail to affect significantly the passage of water through the skin. It is, therefore, doubtful whether the substance plays any part in the cutaneous regulation of water metabolism (ERSPAMER 1954a). This conclusion is of interest because only in amphibians among the vertebrates does the skin play a highly important role in regulating water metabolism, and only in amphibians does the skin contain 5-HT or related indolealkylamines, which are often present in enormous amounts.

5. Amphibian urinary bladder. Concentrations of 5-HT up to 0.2 g/ml do not affect the permeability of the isolated frog urinary bladder (RASMUSSEN et al. 1963).

X. Action on extravascular smooth muscles

1. Gastro-intestinal tract

Man. Single intravenous injections of 5-HT produce in normal volunteers, studied by the balloon-kymographic method, a sharp rise in intestinal tone and the disappearance of mixing waves. In 25% of the subjects doses as low as 0.4 mg 5-HT base have a pronounced effect: however in another 15% doses up to 1.5 mg are ineffective and in yet another 10—15% 5-HT produces a decrease in tone. The stimulant effect appears 30 sec after the injection and disappears within 3—4 min, followed by a period of hypomotility and refractoriness to 5-HT. The increase in tone is accentuated by prior administration of monoamine oxidase inhibitors, inhibited by anticholinergic drugs and BAS (benzyl analogue of serotonin) and left unchanged by hexamethonium. 5-HT in doses up to 13 mg of the base fails to elicit any intestinal response when given intrajejunally to normal volunteers. However, 12 cirrhotic patients and two patients with non-tropical sprue showed a typical response when 5-HT was instilled into the jejunum (CLIFTON et al. 1956, HENDRIX et al. 1957).

It has been suggested that 5-HT stimulates intestinal motor activity through cholinergic nerves at a site distal to the ganglionic synapse (HENDRIX et al. 1957), and that hypersensitivity to oral 5-HT seen in certain pathological conditions may be due to a deficit in monoamine oxidase (CLIFTON et al. 1956).

In patients with ileostomies the intravenous injection of 1 mg 5-HT base produces an initial spasm of the intestine, followed by rhythmic contractions which last several minutes and then by a period of mechanical inactivity. The electrical activity of the ileal bud just distal to the intestinal segment containing the balloon is characterized by an initial continuous burst of action potentials followed by inhibition of electrical activity and then by intermittent bursts of action potentials. The effect of 5-HT is not inhibited by atropine, morphine or promethazine, but is blocked by large doses of LSD (3 mg, i.v.) (DANIEL et al. 1960).

The above observations have been substantially confirmed by experiments in which 5-HT was given by intravenous infusion, at rates of 2—10 μg/kg/min for 7—18 min. It was seen, however, that 5-HT, while stimulating the muscula-

ture of the jejunum and the ileum (in half of the cases the amine elicited contraction waves lasting 2—3 min, in the other half spasms), frequently reduced

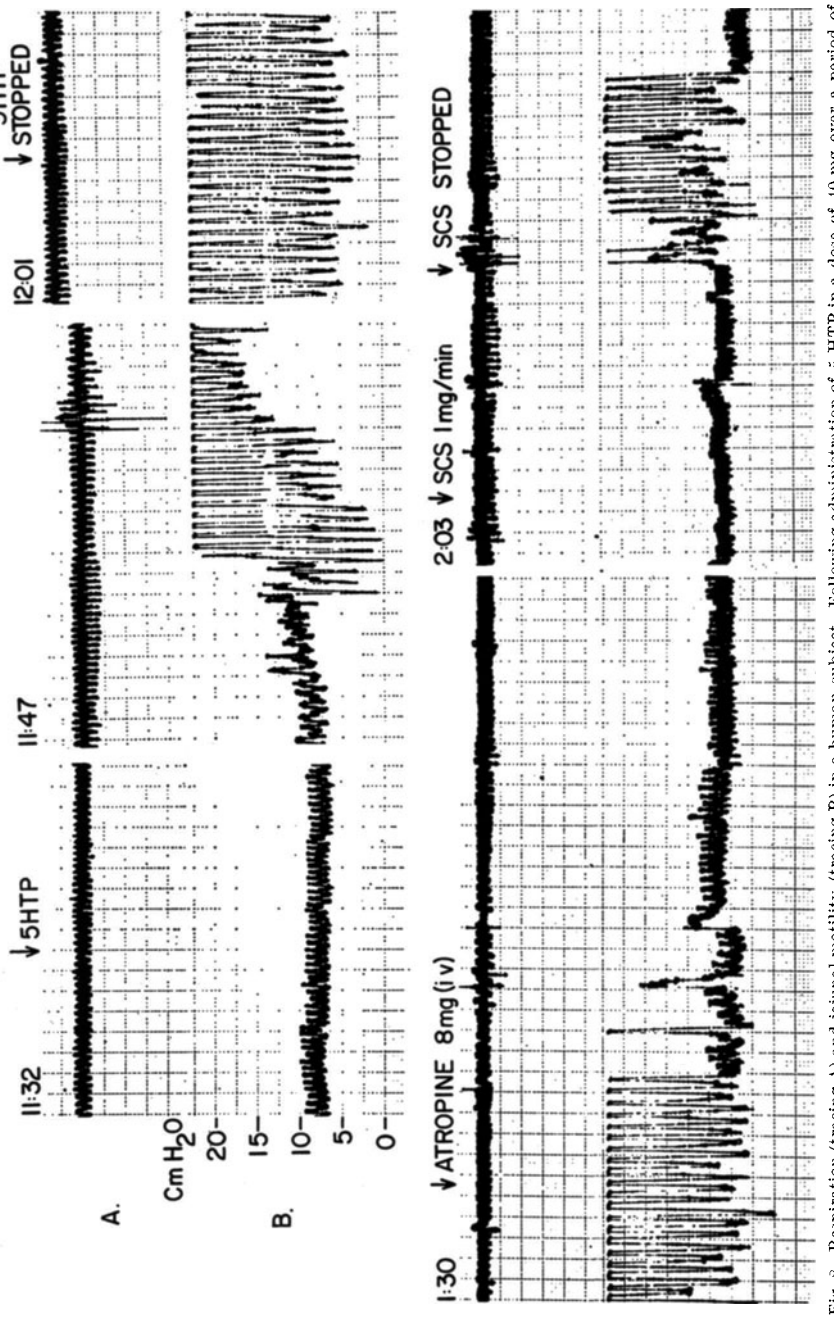


Fig. 8. Respiration (tracing A) and jejunal motility (tracing B) in a human subject. Following administration of 5-HTP in a dose of 40 mg over a period of 30 min (1.33 mg/min) a marked and sustained stimulus to motility occurred. Atropine sulphate inhibited motility stimulated by 5-HTP but not that stimulated by 5-HT creatinine sulphate (SCS: 1 mg/min for 2 min). A large division represents 10 seconds. [From Fig. 4, Haverback, B. J., and S. K. Wertschaftler Advanc. Pharmacol. **1**, 318 (1962).]

tonus and spontaneous movements of the stomach, and constantly inhibited the movements of the large intestine. Inhibition lasted 10—20 min. BOL (2 mg

orally) effectively counteracted the effects of 5-HT; atropine (1 mg, i.v.), reserpine, chlorpromazine, diphenhydramine and tripelennamine were inactive. Tachyphylaxis developed during the continuous intravenous infusion of 5-HT irrespective of dose, but within 10 min after cessation of the infusion the bowel regained its former sensitivity (HAVERBACK and DAVIDSON 1958, HAVERBACK and WIRTSCHAFTLER 1962, SCHMID and KINZLMEIER 1959).

Inhibition of movements of the large intestine and the appearance of tachyphylaxis could explain the failure by O'HARA and COLE (1959) to observe any change in intestinal transit time following infusion of 5-HT into human subjects at a rate of 15 to 260 μg/min for 1 hr.

The effects of intravenous infusion of 5-HTP differ from those of 5-HT in that the aminoacid provides a more sustained stimulation of the small intestine with no tachyphylaxis. Within 6 to 40 min after the start of the 5-HTP infusion (25—50 mg over a 30 min period) a marked increase in intestinal motility is observed in normal subjects (Fig. 8). Usually there is no marked increase in the intraluminal pressure, but in a few instances a pressure rise of up to 15 cm of water is noted and abdominal cramping is experienced. The pressure of the motility waves increases up to approximately 25—30 cm of H_2O. The increased motility persists for at least 90 min following the start of the 5-HTP infusion. At the employed 5-HTP dose no effect on pulse, blood pressure, respiration or mental status is noted. The stimulant action of 5-HTP is partially inhibited by BOL in an oral dose of 2—6 mg, and almost completely blocked by 1 mg of atropine sulphate, given subcutaneously. In one patient with non-tropical sprue, the response of the intestine to 5-HT and 5-HTP was identical with that in the normal subject. However, in another patient the intestinal response to 5-HTP was markedly diminished (HAVERBACK and DAVIDSON 1958, HAVERBACK and WIRTSCHAFTLER 1962).

In contrast to the small intestine, stomach and colon are again inhibited by the drug (SCHMID et al. 1960).

HAVERBACK and WIRTSCHAFTLER (1962) tend to explain the differences noted between 5-HT and 5-HTP in their effects on intestinal motility (unlike that of the latter, the action of the former shows tachyphylaxis and is resistant to atropine) by possible differences in dosage and in the site of action, intracellular or extracellular, of the two compounds.

In accordance with the results of CLIFTON et al. (1956), HAVERBACK and WIRTSCHAFTLER (1962) failed to elicit any intestinal stimulation following intraluminal introduction of 10 mg 5-HT or 30 mg 5-HTP. Similarly, the writer could not see any obvious effect on gastro-intestinal motility following oral introduction of 200—1000 mg of DL-4-HTP (ERSPAMER and NOBILI 1961).

The incapacity of 5-HT to stimulate all segments of the alimentary canal was confirmed by several other research workers both *in vivo* and *in vitro*.

FINK and FRIEDMAN (1960) made simultaneous intraluminal pressure measurements, in 16 human subjects, in two colonic segments 40 cm apart, using a perforated polyvinyl tube connected to an external electrical transducer system. They found that intravenous injection of 1.5 mg 5-HT increased the phasic activity of the proximal colon and depressed, for 4—6 min, that of the distal colon. 5-HT stopped not only spontaneous distal colon motility but also motility induced by prior administration of neostigmine.

SHEPHERD (1963) observed that 5 μg 5-HT either injected, during laparatomy, into an artery adjacent to the colon or applied directly to the surface failed to elicit any local increase of activity, whereas the same procedure applied to an ileal loop in another patient produced profound and prolonged contractions.

Finally, BESANÇON (1961) and DEBRAY and BESANÇON (1961) found that in intubated patients, whose intestinal motility was recorded by an electromanometric method, rapid intravenous injection of 0.2—0.45 mg 5-HT base was followed by an evident stimulation of the motility of the duodenum, the jejunum and the middle small intestine in 83, 63 and 47% of the experiments, respectively. The effect lasted 3 to 6 min. The ileum responded only in 15% of the experiments, and the large intestine never. There were striking differences from one patient to another even in the response of the more sensitive intestinal loops. A second injection of 5-HT administered 1 to 5 min after the disappearance of the response to a first injection was nearly always ineffective.

In spite of the above rather ambiguous results, DEBRAY and BESANÇON suggest that 5-HT may play a physiological role in controlling the motility of the duodenum and the jejunum, more precisely in provoking movements which cause an evacuation of these segments. This is based on the analogy existing on the one hand between motor responses to 5-HT and certain prolonged sequences of spontaneous waves, and on the other hand between the physiological refractory state seen after spontaneous contractions and the tachyphylaxis seen after 5-HT injections.

ADAMS (1960) found that in subjects given either 0.2 mg carbachol subcutaneously or 30 g magnesium sulphate orally serum 5-HT increased from 0.14 to 0.18 μg/ml, and from 0.184 to 0.2 μg/ml, respectively. He concludes that during increased small bowel activity a larger quantity of 5-HT is released into the circulation. Similar results were reported by BOJS (1961).

However, neither PAASONEN et al. (1960) nor BOJS could observe any increase in the urinary excretion of 5-HIAA after administration of cholinergic drugs or cathartics.

Concerning experiments *in vitro* it was found that the circular muscle of human ileum contracted in the presence of 5-HT in concentrations of 5 ng/ml upward, whereas the circular muscle of all regions of the colon relaxed in the presence of 5-HT (100 ng/ml upwards). The ascending colon appeared to be the least sensitive, and the change in response occurred sharply in the ileocaecal region (FISHLOCK and PARKS 1963, FISHLOCK 1964).

Dog. 5-HT, in intravenous doses as low as 4 μg/kg/min of the base, is a potent stimulus to jejunal motility in dogs in which an open end tube has been passed through a gastrostomy into the upper jejunum. The response is not modified by bilateral vagotomy. In all instances, increasing doses of 5-HT (4—32 μg/kg/min) evoke increasingly greater responses in jejunal motility. Tachyphylaxis develops during the continuous infusion of 5-HT irrespective of dose, and the increased motility elicited by a given dose usually ceases within 5 min. Within 10 min after cessation of the infusion, the bowel regains its former sensitivity. The action of 5-HT is not blocked by atropine (0.75 mg/kg, i.v.), hexamethonium (4 mg/kg, i.v.), mepyramine (5 mg/kg, i.v.) or reserpine (0.5 mg/kg). Compound 48/80 (0.5 mg/kg, i.v.) produces an inconstant inhibition of the 5-HT response; LSD (50 μg/kg, i.v.) potentiates it markedly and hinders the appearance of tachyphylaxis (HAVERBACK et al. 1957, HAVERBACK and WIRTSCHAFTLER 1962).

Given by injection into a terminal artery of the colon, 5-HT is as potent as acetylcholine in its contractile effect upon the intestinal musculature, the threshold dose varying from 0.001 to 1 μg. However, even with 1—10 μg doses the effect is short-lasting, not exceeding 30—90 sec. Atropine is 100 times more active towards acetylcholine than against 5-HT. The spasmogenic effect of 5-HT is enhanced by monoamine oxidase inhibitors and blocked by BAS and prochlorperazine. Hexamethonium is ineffective. SLEISENGER et al. (1958, 1959)

suggest that 5-HT, although not directly acting via a cholinergic pathway, may be a modulator of the cholinergic system.

When 5-HT is applied (filter paper soaked with 0.1% solution of the amine) to the mucosal or serosal surface of a denervated dog's jejunal loop the intestinal motility is stimulated above and inhibited below the stimulated spot. This response is left unchanged by removal of the villi, but is abolished by cauterization of the basal part of the mucosa surrounding the crypts as well as by application of ganglion blocking agents. Evident tachyphylaxis occurs after repeated application of 5-HT. HUKUHARA et al. (1960) suggest, on the basis of the above results, that 5-HT acts upon the peripheral nerve endings distributed in the tunica propria surrounding the crypts.

The intestinal villi are stimulated in their rhythmic automatic activity both by intraarterial and intravenous injections of 5-HT (4—40 μg base), as well as by direct application of the drug to the exposed mucosa (4 μg/ml). Simultaneously there is an enhancement of the peristalsis of the intestinal muscle layer and a constriction of the capillaries. The effect lasts for about 10 min and is reversible. It is blocked by LSD (10 μg/kg, i.v.) and chlorpromazine (5 mg/kg, i.v.), but not by atropine. Tryptamine is 100 times less active (LUDÁNY et al. 1959).

Hypermotility of the intestinal tract occurring in dogs above an intestinal obstruction, and present also after hepatectomy or Eck fistula, was found by TYCE et al. (1961, 1964) to be accompanied by a marked increase (up to 500%!) of the 5-HT content in the pyloric mucosa, and by a slight increase in the duodenal mucosa. No changes were appreciable in the 5-HT content of jejunal or ileal mucosas, nor in the blood or brain 5-HT levels. Similarly, the urinary excretion of 5-HIAA was normal.

SIGEL et al. (1960) noted that urinary excretion of 5-HIAA in large dogs did not change in the first 4 hours after severe bowel ischemia, as produced by ligation of the arterial supply to the mesenteric small bowel followed by strangulation of the mid two feet of small intestine by a cord. However, analytical data are not in full accordance with the above statement.

Cat. The isolated small intestine responds to 5-HT with a prompt but transient tonus increase, the threshold dose being 10 μg/ml (ERSPAMER 1952a). Tryptamine and gramine, too, increase the tonus of this preparation (CHEN and CHEN 1933, SUPNIEWSKI and SERAFINOWNA 1938).

The cat bowel *in situ* seems to be more sensitive to 5-HT. In fact, an increase in intestinal motility may be produced by intraarterial administration of amounts of 5-HT as low as 1—2 μg/kg. The onset of the action begins 2—3 min after the injection and lasts 2—4 min (LEMBECK 1957).

Sheep. 5-HT stimulates in concentrations of 0.2—2 μg/ml isolated strips of sheep reticulum, abomasum and rumen, but is ineffective on omasum (SANFORD 1958).

Rabbit. The small intestine reacts to 5-HT (threshold concentration 0.01 to 0.1 μg/ml), as well as to bufotenine (0.01—0.1 μg/ml), bufotenidine (0.01 μg/ml) and tryptamine (2—10 μg/ml) with a short-lived tonus increase and with an increase in the amplitude of the pendulum movements. The reproducibility of the response is, however, unsatisfactory and so the preparation may be used only as a subsidiary test-object in the quantitative titration of the 5-hydroxyindolealkylamines (ERSPAMER 1946a, 1952a; SINHA and WEST 1953; POWELL 1955; UEDA et al. 1957).

The 5-HT stimulation of the rabbit intestine is not inhibited by sympatholytic drugs, nor by hexamethonium 10^{-4} or atropine 10^{-6}; higher concentrations

of this alkaloid may, however, exert a partial antagonism (FINGL and GADDUM 1953, ROBERTSON 1953).

In contrast to the above indolealkylamines, gramine may produce moderate depressive effects (POWELL and CHEN 1945, POWELL 1955).

The rabbit rectum is less sensitive than the small intestine (ERSPAMER 1952a).

The rabbit intestine *in situ* shows a poor sensitivity to 5-HT. In fact, to obtain a clear stimulant action on the intestinal tone, intravenous doses as high as 0.2 mg/kg 5-HT base are required, the threshold dose being 10 μg/kg. Even at enormous dose levels (5 mg/kg, i.v.) tonus increase lasts less than one minute and tachyphylaxis appears with subsequent doses. The spasmogenic activity of 5-HT is abolished by banthine (5 mg/kg) and atropine (0.12 mg), but not by LSD (100 μg). GEORGES and HEROLD (1957, 1958) suggest that 5-HT acts on the rabbit intestinal smooth muscle both directly and indirectly, through central tvagal stimulation.

As in guinea-pigs, 5-HT in rabbits is also released from the intestinal wall into the lumen during peristalsis. However, the amount released by the caudal portion of the distal colon is barely 10% of that released by the small intestine (9.1 ng/min).

At partial variance with the guinea-pig, in the rabbit 5-HT, applied either outside or inside the intestine (1—10 μg/ml), stimulates propulsive activity after an initial contraction, although the stimulant effect is less rapidly obtainable if 5-HT is applied inside. Serosal application of 5-HT also facilitates the response to pelvic nerve stimulation (LEE 1960).

According to KÄRKI et al. (1960), when the intraluminal pressure and/or motility in a section of the ileum of anaesthetized splenectomized rabbits is elevated by intravenous injection of neostigmine or by direct introduction of air or paraffin into the intestinal lumen, the plasma 5-HT level of venous blood coming from this section shows a 2- to 4-fold increase for 10 min or longer. The interest of these results is obvious, but it seems that they should be accepted with caution, owing to the ambiguous significance of small changes in plasma 5-HT levels.

Guinea-pig. Very important work has been devoted to the study of the influence of 5-HT on intestinal motility in this species and results obtained in the guinea-pig constitute the basis for the theory which considers 5-HT to be a hormone participating in the physiological regulation of peristalsis.

The isolated small intestine of the guinea-pig responds to 5-HT, in dilutions down to 1 in 10^8—10^9, with a contraction resembling that produced by histamine. Even the most intense spasmogenic effects, however, e.g. those provoked by 2—4 μg/ml of 5-HT, are transitory and the smooth muscle becomes refractory to further doses of the substance (FREYBURGER et al. 1952, GADDUM 1953, GADDUM and PICARELLI 1957, GADDUM and HAMEED 1954). Guinea-pig ileum exposed to large doses of 5-HT not only becomes desensitized to subsequent doses of 5-HT, but its response to histamine, nicotine and to a lesser extent to acetylcholine is depressed (SZERB 1958). Gradual cooling of the bath temperature from 35° to 20—17° first abolishes the emptying phase of the peristaltic reflex, then progressively inhibits the longitudinal contraction due to intestinal distension and also the action of 5-HT (0.025—0.1 μg/ml) (INNES et al. 1957). While it is generally accepted that the spasmogenic action of 5-HT is diminished by atropine (0.01 to 1 μg/ml), there is no agreement about the degree of the antagonism (GADDUM 1953, RAPPORT and KOELLE 1953, ROCHA E SILVA et al. 1953). A partial explanation of the discrepancies existing in the literature is suggested by ROBERTSON (1953), who found that 0.01—0.1 μg/ml of atropine blocked the action of 2 ng of 5-HT, but not that of 20 ng of 5-HT.

HARRY (1963) has recently described a preparation of circular muscle from the guinea-pig isolated ileum which differs from the longitudinal muscle in that it is insensitive to drugs which act on autonomic effector tissues but, after inhibition of cholinesterase, it responds readily to choline esters, 5-HT, histamine and nicotine.

Before application of N,N-diisopropylphosphodiamidic fluoride (100 μg/ml) the strip does not respond even to 100 μg/ml 5-HT, but after 90 min exposure to the anticholinesterase drug it reacts readily to 0.5—4 μg/ml 5-HT.

The contraction of the strip is depressed, although less readily than the contraction by histamine or nicotine, by procaine, botulinum toxin, morphine and hemicholinium, as well as by atropine and hyoscine.

The point of attack of 5-HT in the guinea-pig ileum is controversial in spite of accurate studies on the interference, in 5-HT action, of procaine, cocaine, β-tubocurarine, hexamethonium, atropine, morphine, LSD, dibenzyline and other compounds as well. According to ROCHA E SILVA et al. (1953), 5-HT acts upon the post-ganglionic cholinergic fibres of the intramural nervous system; according to LÉVY and MICHEL-BER (1956), 5-HT stimulates both post-ganglionic cholinergic and post-ganglionic adrenergic fibres, without excluding the existence of particular receptors in the intramural ganglia; finally, according to GADDUM and HAMEED (1954) and GADDUM and PICARELLI (1957), there are two kinds of tryptamine receptors in the guinea-pig ileum, namely the M receptors which can be blocked with morphine and the D receptors which can be blocked with dibenzyline. Atropine, cocaine and methadone inhibit effects due to the M receptors even after dibenzyline, but have no additional effects after morphine; LSD, dihydroergotamine and 5-benzyloxygramine inhibit effects due to the D receptors, even after morphine, but have no additional effect after dibenzyline. The M receptors are probably in the nervous tissue and the D receptors are probably in the muscle.

In the case of the longitudinal muscle of the ileum, stimulation of receptors in nervous tissue, more precisely of specific receptors sited at the intramural parasympathetic ganglion cell, seems to be decidedly predominant (DAY and VANE 1963, BROWNLEE and JOHNSON 1963). Smooth muscle receptors are considered to be of negligible importance unless the neuronal mechanisms have been inactivated.

For the relative potency of other indolealkylamines on the isolated guinea-pig ileum see Table 4 of chapter 3.

In recent years the action of exogenous 5-HT and 5-HTP on intestinal motility has been thoroughly reinvestigated using accurate methods for recording the different phases of the peristaltic activity. Moreover, particular attention has also been paid to the influence of peristalsis on liberation of endogenous intestinal 5-HT.

The main results obtained by BÜLBRING and co-workers, LEMBECK, GINZEL and other research workers are as follows:

a) 5-HT (0.5—10 μg/ml) introduced into the bath in which an intestinal loop is suspended causes a transient muscle contraction followed by abolition of the peristaltic reflex (KOSTERLITZ and ROBINSON 1957, BÜLBRING and CREMA 1958, BÜLBRING and LIN 1958, LEMBECK 1958, GINZEL 1957a, 1957b). This predominant inhibitory effect is constant for the small intestine, whereas as a rule the colon ascendens shows increased propulsive work (LEMBECK 1958). Initial stimulation of peristalsis is rapid in onset but of shorter duration than that caused by mucosal application of 5-HT.

When the peristaltic reflex is blocked by introducing procaine into the lumen or by serosal application of 5-HT, morphine, dibenzyline or dihydroergotamine, serosal application of 5-HT has no effect; when the reflex is blocked by the presence in the bath of atropine or hexamethonium, serosal application of 5-HT restores peristalsis more effectively than mucosal application (BÜLBRING and CREMA 1958).

5-HT added in low concentration (0.005—0.02 μg/ml) to the fluid outside the intestine restores slight peristaltic activity after this activity has been abolished by cooling. If the peristalsis has been depressed but not abolished by cooling, 5-HT in the bath sometimes abolishes it (BELESLIN and VARAGIĆ 1958).

The transient or persistent facilitation of peristalsis produced by 5-HT applied to the serosal surface has been interpreted as being due to sensitization of the muscle to the transmitter substance acetylcholine (BÜLBRING and CREMA 1958) or to facilitation of transmission at synapses involved in the peristaltic reflex arc (BELESLIN and VARAGIĆ 1958); the inhibition of peristaltic reflex has been attributed to ganglionic block (BÜLBRING and CREMA 1958, LEMBECK 1958).

b) Introduction of 5-HT into the lumen of the isolated guinea-pig intestine stimulates peristalsis in concentrations from 10^{-9} to 10^{-5}. The threshold of the intraluminal pressure required to elicit peristaltic waves is lowered, the contractions are more frequent, and a larger volume of fluid is propelled (BÜLBRING and LIN 1957, 1958). LEMBECK (1958), for example, found that the frequency of peristaltic waves is increased by 90 and 200% after intraluminal infusion of 5-HT at a rate of 1.7 and 4.8 μg/min, respectively.

Stimulation of peristalsis can be observed in isolated strips of both ileum and colon. During irregular muscular activity of this last intestinal section, 5-HT applied intraluminally abolishes non-propulsive contractions and produces coordinate waves; however, higher concentrations of 5-HT cause an initial contraction and stimulation of peristalsis which is followed by depression (LEE 1960).

Mucosal application of 5-HT is highly effective in restoring the block of the peristaltic reflex produced by morphine, dibenzyline, procaine and 5-HT applied to the serosa, less effective in removing the block produced by atropine and hexamethonium and completely ineffective towards that caused by BOL and LSD (BÜLBRING and CREMA 1958).

c) When peristalsis is recorded from loops of *in situ* intestines with their normal blood supply, it can be seen that in the absence of spontaneous activity at low intraluminal pressure, intraarterial (0.1—0.2 μg), intravenous (4—10 μg) and intraluminal (100—200 μg) injections of 5-HT cause the appearance of short bursts of peristalsis (Fig. 9). Similarly, slow intraarterial infusion of 5-HT (0.2 to 1 μg/min) and 5-HTP (0.1 to 2.4 μg/min) causes vigorous peristalsis at pressure 10 mm below the normal threshold. However, tachyphylaxis occurs readily with all three routes of administration and large doses of 5-HTP always cause a diminution of fluid transport. Desensitization is more evident *in vivo* than *in vitro* (BÜLBRING and CREMA 1958b).

d) Small amounts of 5-HT (0.1—0.2 μg in 30 min) were found to be released into the fluid flowing through the lumen of an isolated or *in situ* loop of small intestine at an intraluminal pressure subthreshold for the initiation of peristaltic waves. When the intraluminal pressure is raised and the fluid is actively pushed out by peristalsis, the amount of 5-HT increases 2—8 times (BÜLBRING and LIN 1957, 1958). A further increase occurs in the presence of iproniazid, but the most striking increase (up to 2000 times the normal) is observed following intraluminal or intraarterial administration of 5-HTP. It should be emphasized that 5-HTP

produces only a small increase in the mucosal 5-HT content (BÜLBRING and CREMA 1958b).

At a constant filling pressure the 5-HT release is very much greater during bursts of peristaltic activity than during the intervening periods of rest. When the augmentation of intraluminal pressure caused by muscle contraction is excluded by blocking the reflex with hexamethonium or by inverting the intestine, a residual 3-fold increase of 5-HT release is observed when the pressure is raised (BÜLBRING and CREMA 1958a). However, if the peristaltic contractions are abolished either by adrenaline or by asphyxiation of the muscular layer no 5-HT release occurs (LEE 1960).

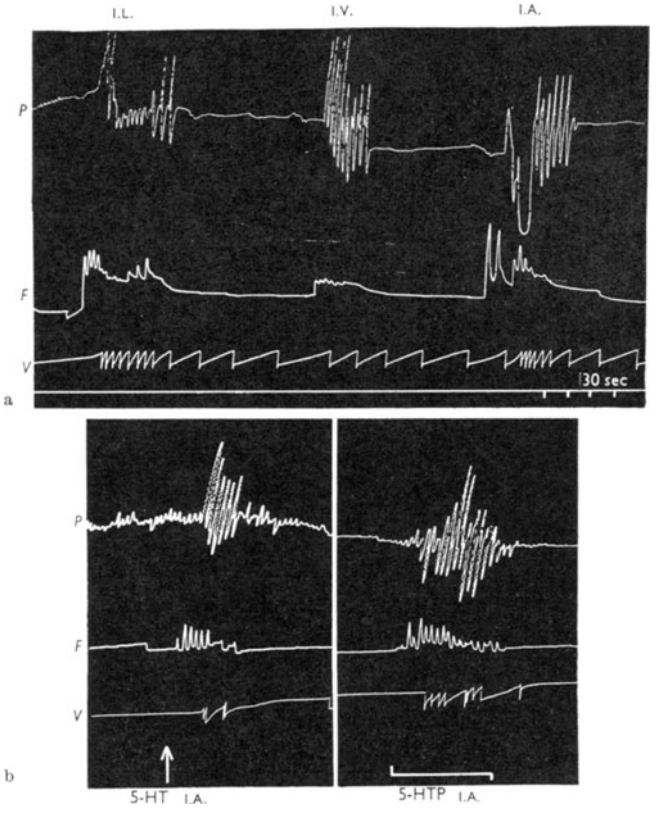


Fig. 9a and b. Guinea-pig, chloralose-urethane. Record of peristalsis of a piece of ileum in response to injections of 5-HT. (a) Comparison of the effects produced by injecting 5-HT: 100 μg into lumen (I.L.); 2 μg intravenously (I.V.), 0.1 μg intra-arterially (I.A.); (b) from another experiment: 0.2 μg 5-HT and 50 μg 5-HTP intra-arterially (I.A.). P = intraluminal pressure; F = fluid propulsion: V = volume transported (each vertical line = 1 ml). It may be seen that intra-arterial 5-HT is nearly 1000 times more effective than intraluminal 5-HT, and that 5-HTP is at least 100 times less effective than 5-HT. [From Fig. 2, BÜLBRING, E., and A. CREMA, J. Physiol. (Lond.) **146**, 33 (1959).]

The amount of 5-HT released into the lumen during peristalsis of the oral portion of the guinea-pig distal colon (6.3 ng/min) is of the same order of magnitude as in the small intestine (5.7 - 9.6 ng/min), whereas the amount released from the caudal portion is considerably smaller (1.6 ng/min). Sympathetic nerve stimulation reduces the amount of 5-HT on the average by only 30% whereas pelvic nerve stimulation causes no significant change (LEE 1960).

e) Peristalsis is abnormally active in reserpine-treated animals and occurs at low threshold. It declines gradually but does not stop in spite of extremely low mucosal 5-HT content (1 to 10% of the normal) and very small amounts of 5-HT being released. Peristalsis does not stop even when in these animals BOL is introduced into the lumen (BÜLBRING and CREMA 1959b).

According to BÜLBRING and LIN (1957, 1958) and to LEMBECK (1958), 5-HT stimulates intestinal motility mainly by sensitizing the sensory receptors in intestinal mucosa which are sensitive to pressure and trigger the peristaltic reflex. In addition, 5-HT might also stimulate chemoreceptors whose fibres converge on the same motor ganglion cells on which the fibres from pressure receptors impinge. The stimulation of both types of receptors would be additive and the reflex would thus be triggered off more readily.

However, on the basis of results listed under e), BÜLBRING and CREMA (1958b) themselves have recently advanced the opinion that 5-HT might not be of primary importance in initiating and maintaining peristalsis.

At this point it seems pertinent to recall that DOUGLAS and RITCHIE (1957) found that intravenous injection of 10—100 μg 5-HT causes in the cat firing of non-medullated afferent fibres in the cervical vagus which come from the gastro-intestinal tract. The effect is exerted at the endings of the fibres but it is not possible to establish whether these endings are excited directly by 5-HT, or indirectly as a consequence of some change in the gastrointestinal tract, such as muscular contraction.

Careful experiments have been carried out by BÜLBRING and BURNSTOCK (1960) on the membrane potential changes associated with tachyphylaxis produced in smooth muscle by application of 5-HT and other stimulant drugs for short periods in rapid succession. In the ganglion-free intestinal smooth muscle taken from the taenia coli of the guinea-pig, 5-HT (2×10^{-9}—1×10^{-6}), like acetylcholine and histamine, causes depolarization and, after removal of the drug, hyperpolarization, which is followed by a sequence of damped oscillation of the membrane potential. The average rate of depolarization is slowest with 5-HT and fastest with acetylcholine; the readiness with which tachyphylaxis occurs is, on the contrary, maximal with 5-HT. Increasing concentrations of 5-HT cause a progressively slower rate of depolarization and it is possible that 5-HT produces some more permanent alteration of the membrane properties than acetylcholine or histamine.

The taenia coli preparation is capable of taking up radioactive 5-HT from the bathing solution for about 120 min at both 0^0 and 37^0. But whereas the radioactivity is not concentrated at 0^0, at 37^0 its concentration is up to 5 times higher in the taenia than in the bathing fluid. Radioactivity taken up by the taenia is lost from it into the bathing fluid at two successive exponential rates, the half time of the first rate being ca. 4 min (5-HT in the extracellular space), and that of the second rate about 32 min (5-HT diffused into the smooth-muscle cell). According to BORN (1962), who made these observations, tachyphylaxis to 5-HT may be explained by the assumption that the continued presence of the amine in the tissue, on or near the receptors, brings about a reduction in its responsiveness.

Rat. The rat duodenum is a very sensitive test-object for 5-HT (0.001—0.01 μg/ml), bufotenine and bufotenidine, to which it responds, even when atropine is present, with a short-lived increase of tonus frequently accompanied by a reinforcement of spontaneous movements (ERSPAMER 1940b, 1946a, 1952a). The duodenal smooth muscle, however, seldom shows that reproducibility of response which is indispensable for an acceptable quantitative titration. Tachyphylaxis is particularly evident with bufotenine and bufotenidine (ERSPAMER 1946a). The stimulant action of 5-HT is strongly and irreversibly reduced by dibenamine. A clear inhibition is also produced by bufotenine (ERSPAMER 1946a, 1953a).

The rat colon has been used successfully by FELDBERG and TOH (1953) not only in the qualitative demonstration but also in the quantitative estimation of 5-HT in crude tissue extracts. Though the sensitivity of the preparation is somewhat variable, good responses are usually to be obtained with 0.01—0.02 μg of the substance per ml of nutrient liquid, and sometimes with considerably smaller doses, too. On the isolated rat ileum the *O*-sulphate of 5-HT is 100 times less active than 5-HT (YOSHIKO 1961).

Both 5-HT (10 mg/kg, s.c.) and 5-HTP (100 mg/kg, s.c.) first increase (by 15—20 times during the first 30 min) and then reduce the number and weight

of faeces produced. 1 mg 5-HT or 10 mg/kg 5-HTP is just effective and 0.1 mg or 1 mg/kg is ineffective (ERSPAMER 1946a, BRITTAIN and COLLIER 1958).

Concerning gastrointestinal propulsion, as followed by the distribution of a dye or of charcoal given by mouth, results are at partial variance.

BRITTAIN and COLLIER observed that whereas 5-HTP failed, in subcutaneous doses up to 100 mg/kg, to influence significantly the distance travelled by a 5% suspension of charcoal in 10% gum acacia, 10 mg/kg 5-HT reduced this distance by 30—50%. This retardation probably occurred at the pyloric sphincter, since the effect disappeared if charcoal was allowed to enter the duodenum before 5-HT was given.

LISH et al. (1959) noted that both 5-HT (threshold subcutaneous dose 0.1 mg/kg; threshold oral dose 10 mg/kg) and 5-HTP (threshold subcutaneous dose 0.4 mg/kg) produced a definite inhibition of intestinal transit. Stomach emptying, however, was stimulated by 5-HT and inhibited by 5-HTP.

Like 5-HT, 5-methoxytryptamine produces defaecation in rats. Subcutaneous doses of 10 mg/kg are highly effective, doses of 1 mg/kg are ineffective (ERSPAMER 1946a).

Mouse. The mouse jejunum is stimulated by 5-HT in dilutions down to 10^{-8} (ERSPAMER 1946a).

As in rats, 5-HTP produces in mice a conspicuous increase in the number and weight of faeces (WOOLEY 1959). The ED 50 by the intraperitoneal route is 25 μg/mouse, the ED 100 300 μg/mouse. 4-HTP gives very inconstant and variable effects, the ED 50 being not less than 400 μg/mouse (ERSPAMER et al. 1960).

Chicken. The 5-HT content of the small intestine was estimated comparatively in conventional, contaminated and in germ-free white Leghorn chicks at four weeks of age. It was found that germ-free animals showing poor tonus of the intestinal tract and distension of the caeca had a higher 5-HT content in their gut, especially in the ileum (11 μg as compared to 6.1 μg/g), than conventional animals possessing elevated tonus of the intestinal musculature (PHILLIPS et al. 1961).

Many preparations of fowl rectal caecum are rather insensitive to 5-HT, but a concentration in the bath of 0.1 to 2 μg/ml often produces a biphasic contraction. A concentration of 5 μg/ml tryptamine causes a prolonged contraction with little or no tachyphylaxis (CLEUGH et al. 1961).

Tortoise. The isolated small intestine of the land tortoise *(Cyclemis amboinensis)* does not contract to 0.01—0.1 μg/ml of 5-HT, but is slightly stimulated by 1 μg/ml. The same concentrations of 5-HT inhibit the contractions of the intestine to acetylcholine. Atropinization abolishes the stimulant effect of 5-HT (TOH and MOHIUDDIN 1958).

Frog. The frog rectum *(Rana esculenta)* has been extensively used by VOGT (1954) in his researches on "Substanz DS", a principle which has been identified as 5-HT. The preparation seems to be highly sensitive to 5-HT (threshold concentration 0.01 μg/ml), to which it responds with the appearance of rhythmic movements and increase in tone. Atropine (1 μg/ml) and dibenamine do not influence the spasmogenic effect of 5-HT; dihydroergotamine 5×10^{-6} produces a reversible blockade.

Of the same sensitivity is the intestine of *Rana pipiens* (FÄNGE 1962).

The stomach of *Rana esculenta* is insensitive to bufotenine and bufotenidine in concentrations up to 10 μg/ml (ERSPAMER 1946a).

Fish. Fish afford another very impressive example of species difference in the sensitivity of the gut to 5-HT. In fact, whereas concentrations of 5-HT as low as

0.001—0.005 μg/ml are sufficient to stimulate the isolated intestine of *Pleuronectes platessa*, *Labrus bergylta* and *Salmo trutta*, concentrations 100—200 times higher are barely effective on the intestine of *Squalus acanthias*, *Raja batis*, *Myxine glutinosa* and *Tinca vulgaris* (EULER and ÖSTLUND 1957, BURNSTOCK 1958, VALETTE and AUGEREAU 1958).

Cyclostomata. The rectal part of the intestine of *Lampetra fluviatilis* shows strong rhythmic contractions in response to 100 μg/ml of 5-HT (JOHNELS and ÖSTLUND 1958).

Invertebrates. Peristalsis of the foregut of larvae of *Galleria melonella* is stimulated both by 5-HT and adrenaline (BEARD 1960).

The isolated stomach of *Helix pomatia* is potently contracted by 5-HT at exceptionally low concentrations (threshold 5×10^{-8} to 1×10^{-7} μg/ml). The response is not affected by atropine. LSD imitates the action of 5-HT (GRYGLEWSKI and SUPNIEWSKI 1963a). The *Helix* oesophagus is 10^5 times less sensitive than the stomach and the ileum 10^7 less sensitive (GRYGLEWSKI and SUPNIEWSKI 1963b).

The rectum of *Mercenaria mercenaria* is similarly stimulated by 5-HT, threshold being about 0.05 μg/ml. Small doses, usually below 1—2 μg/ml, often induce rhythmical activity; higher concentrations inhibit the beat while greatly increasing the tone. Tachyphylaxis occurs readily at high doses. Tryptamine is 10 to 100 times less effective than 5-HT. 5-HT appears to stimulate cholinergic nerves as well as directly exciting the rectal musculature. Its effects are mimicked by LSD and antagonized by UML (GREENBERG and JEGLA 1963).

The role of 5-HT in the physiological control of intestinal peristalsis. Since the main site of production and storage of 5-HT in the mammalian organism is the enterochromaffin cell of the gastrointestinal mucosa, and since 5-HT in several species has a powerful stimulating action on intestinal motility, it has been suggested that the chief physiological function of 5-HT, or at least one of its functions, is to control the motor activity of the gut. SMITH et al. (1957) and LEMBECK (1958) go even further, since they believe that the effects of 5-HT outside the gastrointestinal tract are always unphysiological, because they become apparent only after administration of exogenous 5-HT or following hyperproduction of 5-HT by malignant argentaffinomas.

The hypothesis of a local function of 5-HT within the gastrointestinal mucosa soon after its release from the enterochromaffin cells is at first sight very attractive, and it has been substantiated recently by the important results reported in detail in the preceding pages. On the basis of these results, BÜLBRING and LIN (1958), LEMBECK (1958) and HAVERBACK and WIRTSCHAFTLER (1962) maintain that the formation of 5-HT by the enterochromaffin cells could be part of the physiological mechanism required for peristalsis; more precisely, that 5-HT has a physiological modulating function in peristalsis.

The results and conclusions of BÜLBRING and co-workers are undoubtedly of great importance. However, once again extreme caution seems to be necessary in generalizing results obtained in one or two animal species or in transferring experimental data obtained on isolated intestines, or even on intestinal loops *in situ*, to the gastrointestinal tract of the intact animal. In fact, if we assume that the 5-HT which enhances the peristaltic reflex has a local origin, then it is rather difficult to give an acceptable explanation of the conspicuous differences in the distribution of the enterochromaffin cell system and of 5-HT along and outside the gastrointestinal tract of the various vertebrate species. What is the meaning of the enormous accumulation of enterochromaffin cells and 5-HT in

the intramural portion of the pancreatic duct of the rabbit? What is the reason for the predominant accumulation of 5-HT in the stomachs of mice, hedgehogs and dogs, in the small intestines of guinea-pigs and chickens, and in the large intestines of rats, horses and cows? What, finally, is the significance of the enterochromaffin cells in the pancreatic islets of some mammals, and in the thymus of some birds? Moreover, if the 5-HT introduced into the lumen of an isolated guinea-pig intestine produces a stimulation of peristalsis in very low concentrations, the same 5-HT requires a decidedly larger dosage to produce short bursts of peristalsis when introduced into a loop of the guinea-pig intestine *in situ*, and requires a dosage far beyond any physiological limit to influence the motility of the intestine in the intact animal. In fact, the threshold oral dose capable of accelerating intestinal transit in rats is 4 mg/kg of the base, and doses of 5-HT or 5-HTP up to 10—15 mg given intrajejunally to normal volunteers fail to elicit any intestinal or systemic response.

Similarly, the stomach of the guinea-pig is, in sharp contrast to the ileum, very insensitive to 5-HT, as shown by the observation that 5-HT applied to the mucosal side of the stomach produces no effects with concentrations up to 100 μg/ml, and applied to the serosal side only sometimes does a concentration of 10 μg/ml elicit a slight contraction followed by a slight relaxation (PATON and VANE 1963).

This is not all. In fact, in man only the upper part of the small intestine seems to be stimulated by 5-HT, whereas stomach, ileum and large intestine are not affected by the amine, or are even inhibited. Yet all the sections of the gastrointestinal tract contain enterochromaffin cells and 5-HT and it is difficult to imagine how the same substance could carry out different functions in the different segments of a single apparatus.

Finally, nobody has so far brought any decisive evidence to demonstrate that distension or hypermotility of the intestines, kept within physiological limits, actually produces in the intact animal a local discharge of 5-HT from the enterochromaffin cells into the interstitial liquid of the mucosa, which evidently represents an essential condition for the stimulation of neuronal elements.

PATON and VANE (1963) did not succeed in controlling the factors governing the output of histamine and 5-HT in the stomach. They suggest that any procedure which changes the tone of the stomach, whether this is produced by transmural or vagal stimulation, by drugs or by mechanical distension may affect the amine output, possibly through the simple mechanical action of the smooth muscle in the stomach wall on the histamine- and 5-HT-containing cells in it.

It is evident that the above findings and considerations are not in favour of the hypothesis that 5-HT has a *general* significance as a *local* hormone modulating peristalsis.

Of course, 5-HT could also act on the gastrointestinal tract via the blood. But, frankly, it would be rather surprising if the 5-HT released from the intestines had to return to the same intestines, after having been exposed to severe enzymatic attacks and to large losses, to carry out there its main physiological action.

At any rate, if there are experimental results which demonstrate that stimulation of intestinal motility may be produced in some mammalian species by physiological amounts of 5-HT injected intravenously or intraarterially, there are other results which show that in other species parenteral 5-HT acts on peristalsis only at very high dosage levels, considerably exceeding those required to produce other biological effects, e.g. antidiuresis in rats.

Furthermore, there is as yet no proof that diurnal variations in the urinary excretion of 5-HIAA, indicative of variations in 5-HT release, may be correlated

with gastrointestinal secretory or motor activity, nor that mechanical distension of the intestines or hyperperistalsis produced by drugs or toxic agents produces a discharge of 5-HT into the blood.

Whereas PELTOLA and LEPPÄNEN (1960) and BETTENDORF et al. (1962) concordantly observed that as much as 50% of the daily amount of 5-HIAA is excreted during the night between 10 p.m. and 7 a.m., there are striking discrepancies concerning the period of maximum excretion of 5-HIAA during the day. The peak occurs in the 3-hour period on either side of noon according to JOHNSEN et al. (1958), between 1 and 4 p.m. according to BETTENDORF et al. (1962), and finally between 5 and 9 p.m. according to PELTOLA and LEPPÄNEN (1960).

BERTACCINI and ERSPAMER (1962) were unable to detect any increase in urinary 5-HIAA excretion in rats given by mouth 4 ml/100 g of paraffin oil, in spite of evident distension and hyperperistalsis of the intestine; PAASONEN et al. (1960) found that cholinergic drugs and cathartics did not increase the urinary excretion of 5-HIAA in man; finally, several research workers (HAVERBACK 1961, KOWLESSAR et al. 1958, SCHMID et al. 1961) concordantly demonstrated that by chronic diarrhoea and cholitis ulcerosa urinary 5-HIAA was within normal limits.

The obvious conclusion is that before the hypothesis of a *general* significance of 5-HT in controlling intestinal motility can be accepted, additional positive experimental evidence is required, obtained, if possible, in representatives of all vertebrate classes, because all vertebrates contain enterochromaffin cells and 5-HT in their gastrointestinal mucosa.

2. Extrahepatic biliary tract

5-HT does not display, in concentrations up to 1 mg/ml, any effect on the isolated guinea-pig biliary bladder nor, *in vivo*, on the human biliary tract, as explored radiographically (2 mg 5-HT base, i.v.). The volume of the rabbit gall-bladder, on the contrary, is reduced by the i.v. administration of 0.4 mg/kg 5-HT base (GIRO et al. 1960).

Given intravenously, in doses of 20—40 μg/kg, 5-HT causes a short-lasting but complete interruption of the flow through the cat sphincter of Oddi perfused from the choledocus, leaving unaffected the gall bladder (GRANSER et al. 1956).

On the calf isolated ODDI'S sphincter 5-HT displays a strong contractile action in doses as low as 0.01—1 μg/ml. There is an increased tone of the longitudinal fibres and a block of the flow through the sphincter (CREMA et al. 1962).

3. Bronchial smooth muscle

Guinea-pig. To HERXHEIMER (1953a, 1953b, 1955, 1957) belongs the credit for having carried out the first and most complete study on the bronchial actions of 5-HT administered by inhalation in guinea-pigs.

Guinea-pigs exposed to a 1% aerosol of 5-HT develop severe dispnoea, followed by convulsions. The shock syndrome resembles that produced by histamine, acetylcholine and anaphylaxis, but the animal does not usually die. If the guinea-pigs are exposed to 5-HT at intervals ranging from several hours to two days, they become tolerant to it after three to four exposures.

When guinea-pigs actively sensitized to egg albumin are desensitized by repeated exposure to the antigen, their tolerance to 5-HT increases. When they are resensitized, their tolerance to 5-HT falls to the previous value. Conversely, if guinea-pigs are made tolerant to 5-HT, they become less sensitive to egg albumin. When they lose their tolerance to 5-HT, their previous sensitivity to egg albumin returns.

Nicotine sulphate aerosol elicits a shock syndrome similar to that caused by 5-HT. Again, tolerance develops after repeated exposure and, at the same time, desensitization to anaphylaxis develops, as with 5-HT. Conversely, desensitization to anaphylaxis also causes tolerance to nicotine.

The mechanism responsible for the development of mutual tolerance must therefore be regarded as non-specific and it may be concluded that if there exists some relationship between the mechanism of 5-HT shock and anaphylactic shock, the same relationship exists between nicotine shock and anaphylactic shock.

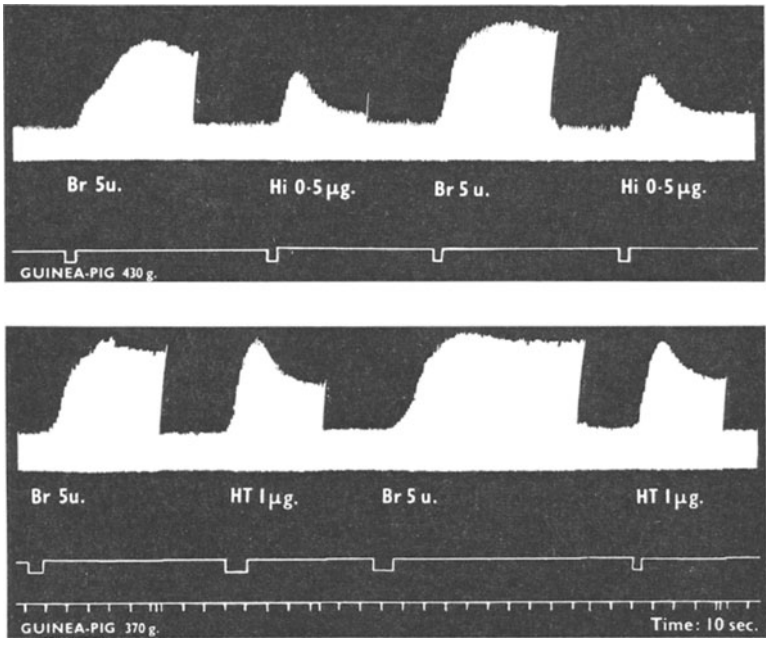


Fig. 10. Resistance to inflation of guinea-pig lungs *in vivo*. Increased resistance caused by bradykinin (Br), histamine (Hi), and 5-hydroxytryptamine (HT). Doses were administered intravenously at 10 min intervals. It may be noted that 5-HT is approximately as active as histamine, and that the response to bradykinin is more sustained than that to either 5-HT or histamine. [From Fig. 1, COLLIER, H. O. J. et al., Brit. J. Pharmacol. **15**, 291 (1960).]

0.16 mg/kg atropine or 5 µg/kg LSD affords weak and inconstant protection against 5-HT; 0.65—1.3 mg atropine and 50—200 µg LSD a 60—75% protection; 400 µg LSD complete or nearly complete protection. Mepyramine, 1 mg/kg, has no effect.

The above results were generally confirmed. FRAHM (1957) found that with aerosols containing 0.5—0.7% 5-HT initial hyperpnoea turned into definite asthmatic attacks only in 30—40% of the animals and that, despite continuous administration of the aerosol, these attacks resolved spontaneously. Atropine (300 µg/kg) and isopropylnoradrenaline (0.2—1% aerosol) displayed a more or less intense protective effect against 5-HT attacks, nembutal and local anaesthetics (pantocaine aerosol) aggravated them.

Tuberculous guinea-pigs tolerate 5-HT inhalations better than healthy animals and bronchial spasm is delayed from 2 to 15 min and more (FÖLDES et al. 1959). Similarly, the average preconvulsion time is prolonged from 1 to 3 min in splenectomized animals (SANYAL and WEST 1959).

It is of interest that parenterally administered 5-HT is capable of affording complete protection against 5-HT bronchospasm, but not against

bronchospasm produced by histamine or acetylcholine. This paradoxical auto-antagonistic action seems to be unique (COURVOISIER and LEAU 1959).

Bronchoconstriction can easily be elicited also upon intravenous injection of 5-HT (KONZETT 1956, MEIER et al. 1956, BALZER et al. 1956, JÄNKÄLÄ and VIRTAMA 1961).

In producing resistance to inflation of guinea-pig lungs *in vivo*, 5-HT is as potent as histamine. The response to bradykinin differs slightly in its slower onset and longer persistence at or near peak level (COLLIER et al. 1960) (Fig. 10).

Reduction of spontaneous respiration, increase of endotracheal pressure and decrease of tidal air are produced by doses of 5-HT as low as 2—10 μg/kg 5-HT base. Bronchial spasm is inhibited by lysergic acid derivatives (LSD, BOL, 1-acetyl-LSD) adrenaline, regitine and dihydroergotamine, whereas section of the vagi, atropine and antihistaminic drugs yield inconstant or no effect (BALZER et al. 1956, KONZETT 1956).

A moderate protective action is also shown by heparin and related anti-coagulant drugs administered by 5% aerosols (SCHMID et al. 1959).

The isolated guinea-pig lung behaves like the *in situ* lung. Here again the bronchoconstrictor action of 5-HT (10—40 μg) is strongly antagonized by UML, LSD (0.25—4 μg), adrenaline and isopropylnoradrenaline (5 μg) and moderately so by dihydroergotamine (25 μg), dibenamine and regitine. Atropine, even at 0.5 mg doses, BAB and BAS are feeble antagonists and antihistamines show no action whatsoever (BHATTACHARYA 1955, SICUTERI et al. 1960, STORMORKEN 1959). Chlorpromazine is effective when given prior to the administration of 5-HT, but only weakly active in reversing 5-HT bronchoconstriction (KING 1957).

When perfused through a cannula in the pulmonary artery, the broncho-constrictor action of 5-HT (0.2—0.4 μg) is 2 times as intense as that of histamine (GREEFF and MOGG 1964).

Whereas the isolated intact trachea of the guinea-pig gives a contractile response to very low concentrations of 5-HT, the threshold being 0.05 μg/ml (JAMIESON 1962), the isolated tracheal chain is contracted only by large doses of the amine (SINHA and WEST 1953, BALZER et al. 1956). Surprisingly enough, the medium-sized bronchioles respond to the amine (threshold 0.4 μg/ml) with relaxation (BROCKLEHURST 1957).

Man. In normal human subjects inhalation of a 0.7% aerosol of 5-HT does not modify the vital capacity of the lung nor the respiratory rate. However, in asthmatic patients the same inhalation produces a prompt fall in vital capacity and decrease in respiratory flow rate sometimes resulting in a severe attack of bronchospasm, which regresses spontaneously or is abolished by isopropyl-noradrenaline (HERXHEIMER 1953b, MICHELSON et al. 1958).

Other mammalian species. REID and RAND (1952b) and COMROE et al. (1953) showed that intravenous 5-HT provokes a moderate bronchoconstrictor action in the cat. This has been confirmed by KONZETT (1956) in intact and spinal cats. In intact anaesthetized cats the reduction of tidal air due to 5-HT (threshold dose 3—35 μg/kg, i.v.) is usually identical before and after vagotomy, as well as before and after section of the spinal cord at C_1, suggesting mainly a direct action on the bronchi, and not a reflex effect. LSD, BOL and acetyl-LSD specifically antagonize the effect of 5-HT on tidal air; atropine and anti-histamines are incomplete and non-specific antagonists.

The spasmogenic action of 5-HT on the bronchial musculature of the dog has not been studied in detail, but it does not seem to be conspicuous (BALZER et al. 1956, NOBLE and NANSON 1959).

In the isolated rat lung perfused through the pulmonary artery 5-HT displays a very moderate bronchoconstrictor effect. In fact, with 100 μg 5-HT respiratory amplitude is reduced only by 23% (GREEFF and MOOG 1964).

As in the guinea-pig, so in all other examined species, 5-HT causes a relaxation of the medium-sized bronchioles. The most sensitive bronchioles are those of rats and cats (0.01 μg/ml), followed by those of dogs (0.05 μg/ml). The bronchioles of rabbits, monkeys and man are practically insensitive (5—20 μg/ml) (BROCKLEHURST 1957).

In sharp contrast to the above relaxing effect, 5-HT appears to be a potent contractile agent on the isolated intact trachea of the rat. The amine is almost as active as acetylcholine and some 100,000 times more potent than histamine (JAMIESON 1962).

Frog. 5-HT was found to cause a relaxation of the smooth muscle of the frog lung at extremely low concentrations (10^{-5} μg/ml), and within the region of low concentrations the amplitude of relaxation was nearly proportional to the logarithm of the concentration. Catecholamines were approximately 1000 times less potent. Atropine, morphine, cocaine, LSD, dibenzyline and iproniazid did not show any anti-5-HT action and the only certain antagonist of 5-HT appeared to be acetylcholine which caused contraction of the lung smooth muscle. BRECHT and JESCHKE (1960, 1962) suggest that 5-HT may display on the frog lung the function of "adjusting substance" or inhibitory neurohormone.

4. Uterus

Rat. The isolated diestrous uterus is barely sensitive to 5-HT and related indolealkylamines and shows marked tachyphylaxis. The estrous uterus and, less regularly, the uterus removed in advanced pregnancy or immediately after delivery is, on the contrary, highly sensitive. The introduction into the bath of as little as 2 to 10 ng of 5-HT per ml of nutrient liquid is enough to produce a noticeable response, i.e. appearance or reinforcement of movements. Higher doses not only cause increased motility, but also provoke a tonus increase, which is, within ample limits, proportional to the dose (Figs. 11, and 1 of chapter 1). On washing out with fresh nutrient solution, relaxation is immediate and the original reactivity of the preparation is promptly restored (ERSPAMER 1940b, 1940c, 1954c, 1956; GADDUM and HAMEED 1954).

Table 3 of chapter 1 shows the activity of a number of indolealkylamines, as compared to that of 5-HT. It is interesting to note that even 5-HTP possesses a very small stimulant action on the uterus, which, however, is at least 10,000 times smaller than that displayed by 5-HT. Since incubation of the isolated uterus with α-methyldopa (a potent dopadecarboxylase inhibitor) completely inhibits the oxytocic action of 5-HTP, this activity must be ascribed to the minute amounts of 5-HT formed by decarboxylation in uterine tissue (LOVAŠEN et al. 1961).

Owing to its high sensitivity to 5-HT, the conspicuous specificity of its response to the substance, and the easy reproducibility of this response, the estrous uterus of the rat has become one of the most often used preparations in the quantitative and qualitative assay of 5-HT, and in the study of substances antagonistic to 5-HT. For further details turn to pages 115—117.

When non-pregnant rats, either normal or pretreated with estrogens, gonadotropic hormones or estrogens + progesterone, are given intramuscularly 6—9 mg/kg of 5-HT base, no gross morphological alterations are visible in the uteri (CATALDI 1956b).

1.6 to 6.4 mg/kg 5-HT injected i.m., in 4 divided doses at 2-hr intervals, in pregnant rats at various stages of pregnancy fail to interrupt pregnancy and do

not produce appreciable alterations of the uterus or the placenta. Interruption of pregnancy, on the other hand, is observed following larger doses of the amine (14—17 mg/kg given i.m. in divided doses over a period of 2 hours, or 3—5 mg/kg given by single intravenous injection). Generally foetal death, which is caused by vasoconstriction and severe placental haemorrhage, is not followed by premature delivery (CORRELL et al. 1952, CATALDI 1956a, MAROIS 1960, CRAIG 1962).

Subcutaneous administration of 1.2—4 mg/kg 5-HT base daily for 4 days to 25-day-old rats, together with 0.1 μg estradiol in 0.1 ml of sesame oil enhances the effect of estradiol, as demonstrated by increase in uterine wet weight and percent uterine water (ZILBERSTEIN 1962).

0.1—0.25 mg 5-HT given to rats by intrauterine administration produces acute vasodilatation, hyperaemia and increase in capillary permeability, with consequent rise of uterine water concentration from 78.6 to 83—84%. In producing

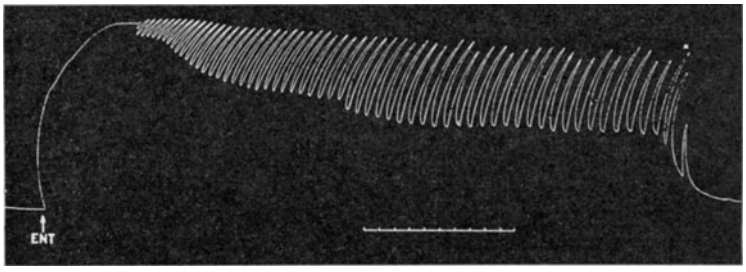


Fig. 11. Isolated oestrus-uterus of a rat, suspended in a 10 ml bath of Tyrode solution at 30°. Time in min. 40 μg of 5-HT base produced a tremendous tonus increase accompanied, after a few minutes, by lively rhythmic movements. The sustained response was immediately interrupted by washing with fresh nutrient liquid (x). [From Fig. 19, ERSPAMER, V., R. C. sci. Farmitalia **1**, 65 (1954).]

the above effects 5-HT is approximately 17 times as effective as histamine. However, 5-HT has less intense an influence on epithelial mitoses. According to SZEGO and SLOAN (1961) it is possible that 5-HT acts through histamine release, thus augmenting the action of estrogen.

Mouse. The isolated mouse uterus behaves in a manner exactly similar to that of the rat (ERSPAMER 1952a).

When administered subcutaneously at high dose levels (1 mg/mouse/day divided into two injections) 5-HT interrupts pregnancy both in its early and its later stages. Only a limited number of mice become pregnant (prevention of implantation?), and pregnancy is discontinued in all mice given 5-HT during the 11th to 16th day of pregnancy. At this time a single subcutaneous dose of 1 mg 5-HT is sufficient to produce death of the foetuses within half an hour. At autopsy death of foetuses is found to be caused by contraction of the blood vessels supplying the placenta with ensuing haemorrhage and disorganization of the placenta (POULSON et al. 1960a, 1960b; ROBSON and SULLIVAN 1963).

The effect of 5-HT in early pregnancy can be antagonized by progesterone and prolactin, as can the toxic effects of the drug on experimental decidual reaction. In late pregnancy progesterone produces little, and prolactin no reversal of the toxic action of 5-HT. It is suggested that in early pregnancy 5-HT interferes with the hormonal mechanisms responsible for the maintenance of gestation, while later on its main toxic action is exerted directly onto the uterine contents (LINDSAY et al. 1963).

Pretreatment (30 min) of the females with D-lysergic acid derivatives preserves the life of the young, the ED 50 for LSD being of 30 μg/kg and that for UML of only 3.7 μg/kg (FLÜCKIGER and SALZMANN 1961, POULSON and ROBSON 1963).

Smaller doses of 5-HT (0.05—0.25 mg/mouse, s.c. or i.v.) have no effect whatever on pregnancy (SAVI 1956, POULSON et al. 1960b).

Rabbit and guinea-pig. The non-pregnant isolated uteri of these animals respond only to large doses of 5-HT, with contractions which are irregular both in appearance and amplitude. On washing out, relaxation is slow (FREYBURGER et al. 1952, REID and RAND 1952). The stimulant action possessed by bufotenine, bufotenidine, tryptamine and gramine is still weaker. Threshold concentrations on the rabbit uterus are 2×10^{-5} to 5×10^{-6} for 5-HT, 1×10^{-5} to 2×10^{-6} for bufotenine, 1×10^{-5} for bufotenidine, and 1×10^{-4} to 1×10^{-5} for tryptamine and gramine (POWELL and CHEN 1945, ERSPAMER 1946, POWELL 1955); on the guinea-pig uterus 1×10^{-6} for 5-HT, 1×10^{-5} to 3×10^{-6} for bufotenine, 1×10^{-5} to 1×10^{-7} for bufotenidine, and 5×10^{-5} to 1×10^{-5} for gramine and tryptamine (POWELL and CHEN 1945, ERSPAMER 1946, POWELL 1955, UEDA et al. 1957).

Tryptamine shows on the rabbit uterus preparation a specific adrenolytic effect which is some 50 times weaker than that possessed by ergotamine. 5-HT and N,N-diethyltryptamine are even more potent, but their adrenolytic action does not seem to be specific (GLAZ et al. 1956).

A daily subcutaneous dose of 2—2.5 mg/kg 5-HT causes foetal death in rabbits, as in mice and rats, when given in late pregnancy (25th to 30th day), but has no effect on implantation and early foetal development. In late pregnancy, foetal death also occurs when 5-HT is administered by intravenous infusion (10 mg over 45 min), and large haemorrhagic areas become visible in the placenta (POULSON et al. 1960a).

It seems probable that the interruption of pregnancy seen in rats, mice and rabbits following large doses of 5-HT is due to a direct action of the amine on the placental vessels which are known to be particularly sensitive to the drug.

Cat. According to REID and RAND (1952) the *in situ* uterus of the non-gravid, adrenalectomized cat relaxes on intravenous injection of 24 μg of 5-HT or on the introduction of 9 μg of the substance into the low thoracic aorta. Tryptamine, too, relaxes the cat uterus *in situ* (LAIDLAW 1912).

The isolated cat uterus is contracted by 5-HT, tryptamine and gramine, but relaxed by bufotenine (POWELL 1955).

Dog. The *in situ* uterus of both conscious animals and of animals anaesthetized with chloralose responds to an intravenous injection of as little as 1 μg/kg 5-HT with a contraction, followed by a period of inhibition lasting up to 7 min. The action appears to be wholly peripheral (ABRAHAMS and PICKFORD 1956c).

Hamster. The isolated uterus is stimulated by large doses of gramine (POWELL and CHEN 1945).

Man. 5-HT seems to be poorly active both on the isolated and the *in situ* human uterus. Concentrations of 10 μg/ml 5-HT cause an increase in amplitude with a reduction in frequency of contractions; 100 μg/ml produces a frank stimulation of excised human myometrium.

By intravenous infusion 5-HT has no definite effect on uterine activity in pregnancy or labour when given at a rate of 100—300 μg/min for 1 to 14 min, but often produces transitory stimulation when infused at higher dose levels.

It is concluded that 5-HT holds little place in the physiology of human myometrial contraction (GARRETT 1958) and that the use of the substance as an oxytocic agent is highly questionable (VALSECCHI 1959).

Dogfish. Isolated uterine horns of the spiny dogfish which do not show spontaneous contractions respond upon addition of 0.2—1.6 μg/ml 5-HT base with powerful contractions often followed by smaller periodically occurring movements. A similar response is elicited by the clasper-siphon secretion of the

fish, which is an extremely rich source of 5-HT. It is suggested that by eliciting uterine contractions, the clasper-siphon secretion may well play a physiological role during copulation, perhaps by facilitating sperm ascent to the site of fertilization (MANN and PROSSER 1963).

5. Urinary bladder

Dog. The isolated dog urinary bladder responds to 5-HT and related indolealkylamines with a tonus increase which is roughly proportional to the dose. At the beginning the sensitivity is 1 to 3 in 10^5, then it declines (ERSPAMER 1952a) (Fig. 1).

The *in situ* bladder of the anaesthetized dog reacts to intravenous 5-HT with an increase of tonus and with the appearance or reinforcement of rhythmic motility. The minimum active dose of 5-HT is 1 to 4 μg/kg. The stimulant action of 4-HT is approximately half as intense as that of 5-HT, but is more sustained. The percentage activity of other indolealkylamines, in comparison with 5-HT, is as follows: 5-methoxytryptamine 30—35; bufotenine 5—10; tryptamine 1.5; 1-methyltryptamine 1—1.5; N-methyltryptamine and N,N-dimethyltryptamine <0.5. Bufothionine, dehydrobufotenine and, possibly, bufotenidine are inactive (ERSPAMER 1952a, 1952d; ERSPAMER et al. 1960). Another indolealkylamine mimicking 5-HT already at low microgram levels is 5-acetyltryptamine (OSBORNE et al. 1962). Even 5-HTP and 4-HTP produce a remarkable contraction of the bladder, which is evidently caused by the amines originating from the decarboxylation of the precursor aminoacids. The contraction produced by 2—4 mg/kg of intravenous 4-HTP is 3 to 4 times more intense and considerably more sustained than that caused by the same dose of 5-HTP (ERSPAMER et al. 1960).

When 5-HT is injected into the abdominal aorta it produces a biphasic response: at first a transient, twitch-like reaction, then a second contraction of longer duration. Moreover, it enhances the action of various stimuli, such as pelvic nerve stimulation, methacoline, acetylcholine and KCl. 5-HT is 20 times more potent than acetylcholine, but 5 times less potent than muscarine.

The bladder contraction caused by 5-HT is highly resistant to atropine and hexamethonium, but is more or less completely blocked by dibenamine, 2-methyl-5-chlorogramine, chlorpromazine, BOL, LSD, imipramine and papaverine (ERSPAMER 1952a, 1952e, 1953a, 1954; GYERMEK 1962a, 1962b).

GYERMEK (1962b) suggests, on the basis of the above findings, that normal, physiological fluctuations of the 5-HT level in the organism may markedly influence the sensitivity of the bladder.

It does not seem conceivable that released 5-HT plays an important role in the urinary bladder tension produced by the intravenous injection of 0.5—1 mg/kg of reserpine (MAXWELL et al. 1956).

Given by subcutaneous route to the anaesthetized dog, 5-HT is practically devoid of any stimulant action, up to doses of 1 mg/kg. Intravenous doses of 5-HT greater than 50 μg/kg and subcutaneous doses greater than 200—400 μg/kg regularly provoke micturition and resistance to vesical catheterization in the intact conscious dog (ERSPAMER 1952a, 1954c).

Other animals. The rat urinary bladder and, still more, that of the guinea-pig are insensitive to 5-HT (ERSPAMER 1952a). The same may be said of the rabbit urinary bladder, in contact with bufotenine or bufotenidine (ERSPAMER 1946a). The cat bladder is weakly stimulated by tryptamine (LAIDLAW 1912).

6. Ureter

The perfused *in situ* dog ureter, with blood supply intact, responds to intravenous 5-HT (threshold dose 3—4 μg/kg) with a contraction which completely prevents the passage of fluid through its lumen for 1 to 2 min and slows the flow for a further period of 1 to 2 min (ABRAHAMS and PICKFORD 1956b).

The isolated dog ureter, on the other hand, does not react to 5-HT, even at concentrations up to 4—30 μg/ml (BORGSTEDT 1959, SPIRITO and TEODORO 1959).

7. Seminal vesicles

When added to the nutritive bath, 5-HT contracts the seminal vesicles of castrated rats but is practically inactive on the same organs excised from normal animals. However, 5-HT (1—10 μg/ml) added to the nutrient bath 30—60 seconds prior to adrenaline or noradrenaline (0.05—4 μg/ml) increases by 2—2.5 times the stimulant action of the catecholamines even on the seminal vesicles taken from normal rats. Synergism is not due to antioxidant action of 5-HT nor to inhibition of monoamineoxidase. It is possible that it depends on inhibition of catechol-O-methyl transferase. Low concentrations of tryptamine (20 μg/ml) do not affect the response to adrenaline, higher concentrations (200 μg/ml) diminish it (PICARELLI et al. 1962).

8. Spleen

5-HT (100 μg/ml) produces a contraction of isolated strips of cat spleen. Since the sensitivity to 5-HT of spleen strips from cats treated 24 hr earlier with reserpine is only one-fiftieth of that of normal strips, and the effects of tyramine on spleen strips almost exactly parallel the effects of 5-HT, it is suggested by INNES (1962b) that 5-HT has a dual action, viz. a major action due to release of stored noradrenaline and a minor direct action on adrenaline receptors.

9. Nictitating membrane

5-HT and related indolealkylamines contract both the *in situ* and the isolated nictitating membrane of the cat. This was first observed by REID and RAND (1952) and by ERSPAMER (1952a).

The retraction produced by 5-HT is 3 to 25 times smaller but more prolonged than that caused by adrenaline or noradrenaline (ERSPAMER 1954, LECOMTE 1955, TRENDELENBURG 1956, SCHAEPPI 1962, 1963). The denervated membrane is more sensitive than the innervated membrane (REID and RAND 1952). According to COSTA and ZETLER (1958, 1959) the threshold intravenous doses causing the normal and denervated membrane to contract are 14.4 and 1.69 μg/kg for 5-HT, and 30.8 and 4.27 μg/kg for bufotenine. However, large amounts of 5-HT (100 to 300 μg) cause a greater contraction of the normal membrane. This does not apply to the perfused cat head preparation, in which 5-HT in all doses causes a larger response on the denervated than on the normal side (TRENDELENBURG 1956). The chronically denervated membrane is 50 times more sensitive to 5-HT than the acutely denervated membrane (SCHAEPPI 1962, 1963).

Cocaine and other local anaesthetics moderately enhance the response to 5-HT, but, in every instance, less than that to catecholamines (ERSPAMER 1954, GYERMEK and POSSEMATO 1961); imipramine, on the contrary, potentiates the effect of 5-HT more markedly than that of catecholamines. Following administration of 0.15—2.4 mg/kg imipramine the membrane becomes 3 to 7 times more sensitive than before (SOFFER and GYERMEK 1961, GYERMEK and POSSEMATO 1961, SIGG et al. 1963).

Previous administration of 5-HT or bufotenine potentiates the retraction produced by subsequent injection of adrenaline and noradrenaline (LECOMTE 1953, 1955). The minimum intravenous dose potentiating the response of normal nictitating membrane to intravenous adrenaline is 88 μg/kg for 5-HT and 4.8 μg for bufotenine. For the denervated membrane the values are 23.9 and 6.6 μg/kg, respectively (COSTA and ZETLER 1958, 1959). The effect is generally ascribed to an inhibition of the enzymic inactivation of catecholamines. However, small doses of 5-HT (10—25 μg/kg) are found to decrease rather than to potentiate the action of catecholamines (SCHMITT and SCHMITT 1959). Besides that of adrenaline, intravenous 5-HT (10—200 μg/kg) increases the effect on the nictitating membrane of pre- or postganglionic stimulation of adrenergic nerves (BACQ and RENSON 1961).

On the innervated membrane 5-HT is consistently more potent than N-methyltryptamine or N,N-dimethyltryptamine, some 5 times more potent than tryptamine, and 2—5 times more potent than 4-HT. Bufotenidine, on the contrary, is more active than 5-HT (RAND and REID 1952, REID and RAND 1952, ERSPAMER 1954c, LECOMTE 1955, ERSPAMER et al. 1960, SCHAEPPI 1963). The tryptamine contraction is potentiated by cocaine and diphenhydramine, but depressed by yohimbine (REID and RAND 1952). Small doses of tryptamine (10—30 μg) appear to be slightly more effective on the chronically than on the acutely denervated membrane, whereas large doses (100—300 μg) retract both membranes equally (SCHAEPPI 1962). Single intravenous doses of 2—5 mg/kg 5-HTP do not contract the membrane; the same doses of 4-HTP produce a contraction lasting 30 to 50 min (ERSPAMER et al. 1960).

The isolated membrane brought into contraction by 5-HT (threshold dose (0.05—0.1 μg/ml) relaxes only slowly after washing out the drug and tachyphylaxis appears following successive administration of the same amount of 5-HT. It is not possible to obtain maximum contraction of the muscle even with large doses of 5-HT. Contractions are potentiated by cocaine and antagonized by atropine, dibenamine, dibenzyline, hyoscine, dihydroergotamine and LSD (THOMPSON 1958).

10. Iris smooth muscle

Isolated iris. D'ERMO and BONOMI (1961) first demonstrated that the isolated constrictor pupillae of the horse eye possessed very high sensitivity to 5-HT, the threshold concentration varying between 0.001 and 0.1 μg/ml. The response, which showed a good relationship with the dose, was not affected by atropine or mepyramine, up to 10^{-4}, but was partially inhibited by promethazine.

These results have been confirmed and extended by KOELLA and SCHAEPPI (1962) who thoroughly investigated the reaction to 5-HT of the isolated cat iris. The reaction of the pupillary opening on the intact iris was recorded by means of a photoelectric technique. The reaction of the isolated muscles was measured by means of isometric mechanoelectric transducers. 5-HT acted on the isolated iris as a powerful constrictor. The threshold dose appeared to be 0.15 μg 5-HT base. Doses as small as 2.5 and 5 μg often induced complete or almost complete closure of the pupil. Two-peaked pattern occurred often with larger doses. The pupillary constriction and ensuing dilation lasted up to 15 or more min. 5-HT treatment desensitized the preparation to later injections of 5-HT.

The isolated constrictor pupillae reacted to 5-HT with contraction. Threshold was less than 1 ng/ml, and maximal degree of contraction was obtained with 0.03—0.5 μg/ml. Repeated application of the same dose did not reveal desensitization. The isolated dilator pupillae reacted to 5-HT usually with dilatation

(threshold 0.3 ng/ml), followed with larger doses by a prolonged slight contraction. It is suggested, from the above data, that pupillary constriction in response to 5-HT is the result of a dual mechanism, namely contraction of the constrictor muscle and relaxation of the radial dilator muscle, and that the basis for the constrictive effects of 5-HT is a direct action of the drug on the smooth muscle.

In contrast to the isolated cat iris, where 5-HT imitates the action of acetylcholine, the isolated pig iris responds to 5-HT doses as small as 0.025 μg with a decrease of the tone and a reduction of the amplitude of contractions produced by electrical stimulation (SCHAEPPI 1963).

In situ iris. Intravenous (100—500 μg/kg) or intracarotid (0.5—5 μg/kg) injection of 5-HT provokes in the anaesthetized cat a conspicuous constriction of the pupil, sometimes preceded by a transient dilatation. The action appears also in the decerebrated animal with sectioned oculomotor nerves and cervical sympathetic fibres (RAND and REID 1952, REID and RAND 1952a, REID 1952). Intracarotid administration of 5-HT to a waking cat induces a slight dilatation of the pupil immediately followed by a marked myosis (PAGE 1952). This effect is restricted to the eye ipsilateral to the site of injection. The contralateral iris usually reacts with a slight dilatation. Furthermore, constriction is obtained only if fairly large doses of 5-HT are used, whereas with smaller doses bilateral dilatation ensues in the waking animal. According to KOELLA and SCHAEPPI (1962) this rather complex pattern defies a simple explanation on the basis of one locus of action of the drug. The pupillary response could be interpreted as a resultant of at least two competing influences: a direct constrictive effect of 5-HT upon the iris restricted to the side of injection and a shift towards sympathetic preponderance and thus bilateral pupilla-dilating outflows paralleling a generalized central arousal, this latter effect being the result of drug action in the carotid sinus area as well as at intracranial sites. Furthermore it is possible that 5-HT acts upon the ciliary and the superior cervical ganglion and thus, by alteration of synaptic transmission, introduces two complicating factors.

20 μg 5-HT injected into the anterior chamber of the rabbit eye does not affect the musculature of the iris (SCHUMACHER and CLASSEN 1962a).

In the anaesthetized cat tryptamine has essentially the same effect as 5-HT, but in 10 times larger doses (LAIDLAW 1912, REID 1952). Gramine causes a transient pupillary constriction only at very high dose levels (v. EULER et al. 1936).

Bufotenine (up to 20 mg, i.v.) produces mydriasis in man (TURNER and MERLIS 1959) and the same effect is observed, both in man and in the waking experimental animal, following administration of psilocybin. Doses were 5—30 mg in man, by mouth or by parenteral route (DELAY et al. 1959), at least 10 mg/kg in mice, subcutaneously, and at least 20 μg/kg in rabbits, intravenously (CERLETTI 1959).

Large doses of 5-HTP (30—100 mg/kg), given intravenously or intraperitoneally, generally produce mydriasis in dogs, cats and rabbits (BOGDANSKI et al. 1958). However, in the rabbit also a slowly-appearing but long-lasting myosis has been described (SCHUMACHER and CLASSEN 1962a). In man the intravenous injection of 10—120 mg 5-HTP has no effect on pupillary size, evidently owing to insufficient dosage (DAVIDSON et al. 1957a, 1957b). Administered by intracarotid injection, 5-HTP (10—100 mg) elicits mydriasis in man, but striking myosis in the cat. The effect is ipsilateral to the site of injection (MANTEGAZZINI, personal communication).

11. Chick amnion

Preparations of the amnion of the developing chick are of interest because it is devoid of nervous elements of any description. Generally 5-HT increases motility in a rhythmic preparation already at concentrations as low as 0.01 μg/ml; quiescent strips require higher concentrations. Low or moderate doses of 5-HT cause responses which are reproducible without any sign of tachyphylaxis, at high doses the responses are variable and difficult to evaluate. However, at no concentration does the drug depress activity. Atropine decreases the responsiveness of the preparation; hexamethonium shows no effect (EVANS and SCHILD 1953. FERGUSON 1957).

12. Molluscan smooth muscle

Mytilus edulis. 5-HT concentrations as low as 0.01 μg/ml display a powerful relaxing action on the anterior bissus retractor muscle of *Mytilus edulis* when

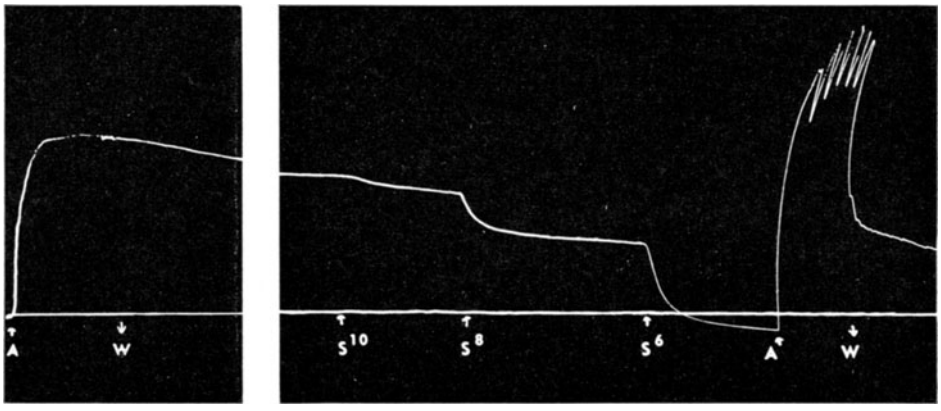


Fig. 12. Anterior bissus retractor muscle of *Mytilus edulis*. The interaction of 5-HT and acetylcholine. A, acetylcholine 4×10^{-6} M; W, wash; S^{10}, S^{8}, S^{6}, 5-HT 10^{-10}, 10^{-8}, and 10^{-6} M. It may be noted that 5-HT produces marked relaxation in a muscle tonically contracted by acetylcholine and that after full relaxation responses to acetylcholine are potentiated. [From Fig. 5, TWAROG, B. M., J. cell. comp. Physiol. **44**, 151 (1954).]

this muscle is contracted by acetylcholine (Fig. 12), electric stimulation, or electric stimulation plus adrenaline (TWAROG 1954, 1958, 1960a, 1960b; HOLGATE and CAMBRIDGE 1958; CAMBRIDGE and HOLGATE 1958; LOWY and MILLMAN 1959). In the presence of 5-HT, tension development by electrical stimulation or acetylcholine is not blocked, but potentiated, while the prolonged phase of contraction which usually may be seen after washing of the stimulating agent is abolished. Moreover, in the presence of 5-HT acetylcholine evokes a succession of spike-like electrical discharges. 5-HT itself, up to 10 μg/ml, does not interfere with neural excitation (TWAROG 1960a, 1960b). LSD (1 μg/ml) is ineffective as an antagonist of 5-HT on this muscle (CAMBRIDGE 1959).

It has been suggested that the relaxing effect of 5-HT involves an alteration of membrane properties which is expressed variously as increased synchronization and recruiting of previously non-spiking elements in response to stimulation (TWAROG 1960a). TWAROG maintains that acetylcholine and 5-HT should be considered as mediators released by the nerve supplying the bissal retractor muscle, with 5-HT being the transmitter involved in neurally-induced relaxation. This opinion, which is shared by others (HOLGATE and CAMBRIDGE 1958, LOWY and MILLMAN 1959), is strongly supported by the presence in the muscle of 5-HT and acetylcholine, as well as of cholinesterase and monoamine oxidase. LOWY

and MILLMAN think that the kind of response, tonic or phasic, given by the retractor muscle on nervous stimulation is determined by the amount of 5-HT-like substance present.

Anodonta cygnea. The application of 5-HT (threshold 1 μg/ml) to the cerebral ganglia of this mollusc is followed, within 1 min, by relaxation of the tonically contracted adductor muscle. At the same time there is a considerable increase in the rhythmic activity of the muscle, the duration of which varies according to the concentration of 5-HT (up to $2^1/_2$ hr after 10 μg). The same effect is exerted by adrenaline, noradrenaline, LSD, tryptamine, 5-HTP and tryptophan. Surprisingly enough, there is no difference between the time elapsing between administration of 5-HT and the administration of the other indoles and the time of relaxation and similarly there is no difference in the efficacy of these substances. SÁLANKI and KOSCHTOJANZ (1962) and SÁLANKI (1963) suggest that indolealkylamines and phenylalkylamines may play an important part in the regulation of the periodic activity of *Anodonta.*

5-HT, 5-HTP, tryptophan and tryptamine all increase the rhythmic activity in the glochidia of fresh-water mussel. Tryptamine is the most effective agent (threshold 0.01 μg/ml water), and the increase of activity produced by it is long lasting, keeping on for over 30 min. It is suggested that in the early ontogenetic stage of *Anodonta cignea* tryptamine plays the role of a local hormone in the regulation of the "spontaneous" rhythmic activity (LABOS et al. 1964).

Busycon canaliculatum. The radula protractor muscle of this mollusc can be contracted by acetylcholine and can then be relaxed rhythmically by 5-HT and, even more effectively, by tryptamine. It is probable that indolealkylamines act, like acetylcholine, on the muscle rather than on the nerve (HILL 1958).

Strophocheilos oblongus. 5-HT 10^{-7} induces rhythmic contractions or "beating" of the penis retractor muscle. Graded responses may be obtained with increasing concentrations of 5-HT. Bufotenine and LSD cause irreversible rhythmic contraction (JAEGER 1963).

13. Muscles of worms

Leech dorsal muscle. According to POLONI (1955) the dorsal muscle of the leech responds to 5-HT with a relaxation which is proportional to the dose within astonishingly wide limits (from 0.001 ng to 1 mg/ml!). Relaxation is even more pronounced and proportional if the muscle has been previously contracted by acetylcholine (0.1—10 ng/ml). The effect of 5-HT is inhibited by LSD.

The above results have been generally confirmed by SCHAIN (1961), who similarly observed that 5-HT diminishes the size of acetylcholine contraction and accelerates relaxation of the muscle after washing out acetylcholine. The threshold concentration of 5-HT necessary to reduce the size of contraction produced by 3—5 ng/ml acetylcholine is 25—50 ng/ml. The relaxing effect is also seen in a muscle not contracted by acetylcholine but the effect is less pronounced and it has not been found suitable for the assay of 5-HT because of the difficulty of establishing a stable base line for comparison of relaxations. The nicotine contractions of the leech muscle are inhibited by 5-HT in the same way as acetylcholine contractions are, but potassium contractions are affected to a much lesser degree.

Liver fluke musculature

5-HT and related indolealkylamines, as well as LSD have a stimulatory effect on the rate and amplitude of contractions and on the tone of the musculature of the liver fluke *(Fasciola hepatica).* The effect is peripheral and not media-

ted through the central ganglion; it persists, in fact, after removal of the ganglion. LSD is more than 100 times as active as 5-HT (threshold concentration of the amine 10 μg/ml), and this in its turn is 5—10 times more active than tryptamine or bufotenine and 100 times more active than 5-HTP.

BOL, yohimbine, harmine and dopamine depress rhythmical movements and antagonize the stimulant action of 5-HT and LSD.

On the basis of the above effects and on the occurrence of 5-HT in the organism of *Fasciola hepatica*, MANSOUR (1956, 1957) suggests that 5-HT or a related compound may be the humoral transmitter for the peripheral receptors of this worm.

14. Muscles of sea anemones

Column preparations. 5-HT has no significant effects on the tone, activity or responses of column preparations from *Calliactis parasitica* or *Metridium senile.* Tryptamine, on the contrary, causes, at concentrations of 100 μg/ml, direct contractions, high tonus and enhanced responses to stimulation. 5-Methoxytryptamine has similar effects. Treatment must be applied directly to the contractile part of the preparation; applying the active drugs to attached strips of column has no effect (ROSS 1957, 1960a).

Sphincter preparations. 5-HT has no effect on either quick or slow contractions. Tryptamine (10—100 μg/ml) causes direct quick contraction of the sphincter and somewhat enhances both quick and slow responses to stimuli (ROSS 1960b).

XI. Action on respiration

It is commonly observed that the intravenous injection of adequate doses of 5-HT and other indolealkylamines provokes transient respiratory effects in the experimental animal and in man. These effects may be different in different animal species. In spite of careful and extensive studies there is as yet no complete accordance of opinion in regard to the site and mechanism of action of 5-HT.

Cat. REID and RAND (1952a, 1952b) and REID (1952b) first found that intravenous injections, as well as direct introduction into the right heart of crude serotonin preparations and of pure 5-HT (10—200 μg) caused in the cat under chloralose anaesthesia and with intact vagi, a brief period of apnoea, lasting up to 30 seconds. This was frequently followed by tachypnoea and simultaneous bronchoconstriction, as shown by remarkable fluctuation in intrapleural pressure, reduced amplitude of the respiratory movements, and increase in the chest volume. The observations of the Australian investigators have been regularly confirmed (Fig. 13).

SCHNEIDER and YONKMAN (1953, 1954) have analyzed the frequency of the vagal afferent impulses during the respiratory responses provoked by 5-HT in the normal cat and in the cat treated with ganglion-blocking agents and local anaesthetics. Following intravenous administration of 20—40 μg/kg 5-HT base there was at first respiratory arrest in expiratory position, then tachypnoea. In both conditions an increase in the frequency of afferent vagal impulses was recorded. Ganglion blockade (3 mg/kg hexamethonium) prolonged the period of respiratory arrest; local anaesthetics (procaine 10 mg/kg, nupercaine 0.5—0.7 mg/kg) shortened it. SCHNEIDER and YONKMAN concluded that 5-HT has a peripheral point of attack on autonomic sensory nerve endings in the cardio-pulmonary region, including the pulmonary stretch receptors.

These conclusions have been accepted in part by other research workers.

COMROE and collaborators (COMROE 1952, COMROE et al. 1953) found that in the cat under slight chloralose anaesthesia, introduction of 20—40 μg 5-HT base directly into the right heart produced vehement circulatory and respiratory changes, including apnoea and both direct and reflex bronchospasm. With larger doses apnoea was persistent. They suggest that apnoea is due to stimulation of receptors situated in the ascending aorta, which are probably different from veratridine-sensitive receptors.

MOTT and co-workers (MOTT and PAINTAL 1953, KOTTEGODA and MOTT 1955) observed that reflex apnoea produced by intravenous injection of 20—40 μg 5-HT base was usually abolished by cooling the vagi to 1.5—2° or by vagotomy.

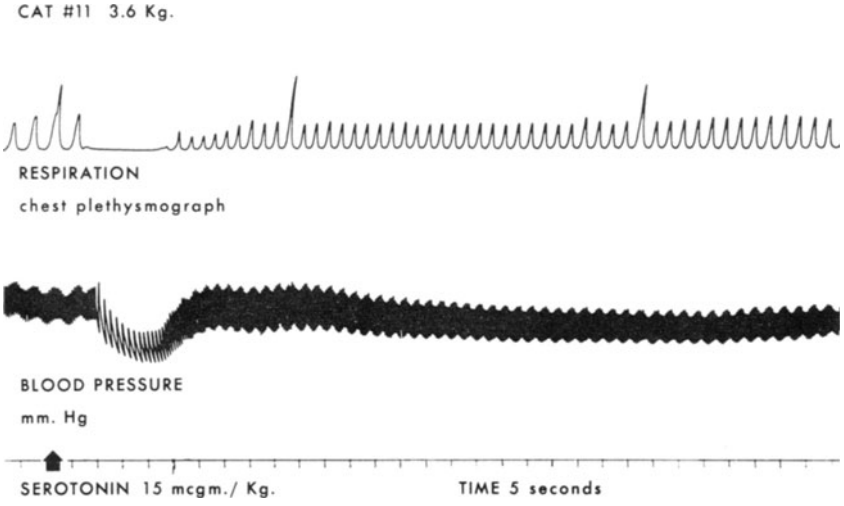


Fig. 13. Effect of a single intravenous injection of 15 μg/kg 5-HT on respiration and blood pressure of a cat anaesthetized with chloralose. The initial brief period of respiratory arrest is followed by a period of moderate tachypnoea (Courtesy Dr. D. C. KROEGER)

However, in some cases a brief apnoea was still produced after vagotomy. Respiratory arrest is interpreted by MOTT and co-workers as being caused by stimulation of receptors situated in the circulation between the large veins and the left atrium (pulmonary pain receptors?). These receptors are thought to give origin to afferent vagal fibres having a conduction velocity of 5—6 m/sec. There is no evidence that doses of 5-HT less than 40 μg/kg stimulate or sensitize pulmonary stretch endings, nor right or left atrial or depressor nerve endings. However, intravenous injection of 40—85 μg/kg 5-HT base into vagotomized cats given artificial positive-pressure ventilation at constant stroke-volume caused a small increase in peak intra-tracheal pressure accompanied by changes in the rate of discharge of pulmonary stretch fibres. It is suggested by KOTTEGODA and MOTT (1955) that these changes are secondary to direct broncho-constriction caused by 5-HT.

The above results give an explanation of the finding of WEIDMANN and CERLETTI (1955) that vagotomy and cooling of the vagi reduced but did not abolish apnoea produced by 5-HT, and justifies the statement of WESTERMANN (1958) that apneic reactions produced by large doses of 5-HT are due to stimulation of both intrapulmonary receptors with vagal afferencies and the bulbo-inhibitory system of the reticular formation.

Ginzel and Kottegoda (1954) have investigated more closely the action of 5-HT on aortic and carotid sinus receptors. They observed that small amounts of 5-HT (2—10 μg) injected into the carotid sinus region caused fall of blood pressure and stimulation of respiration usually preceded by a short period of apnoea. After section of the sinus nerves only the apneic response remained. The same stimulant action, but no apnoea, was noted following introduction of 5-HT into the aortic body region. The effect was abolished after section of the vagus nerves, but remained unaffected after hexamethonium and atropine. Both 5-HT and tryptamine produced temporary desensitization to their own actions. Ginzel and Kottegoda believe that the excitation of respiration is due to

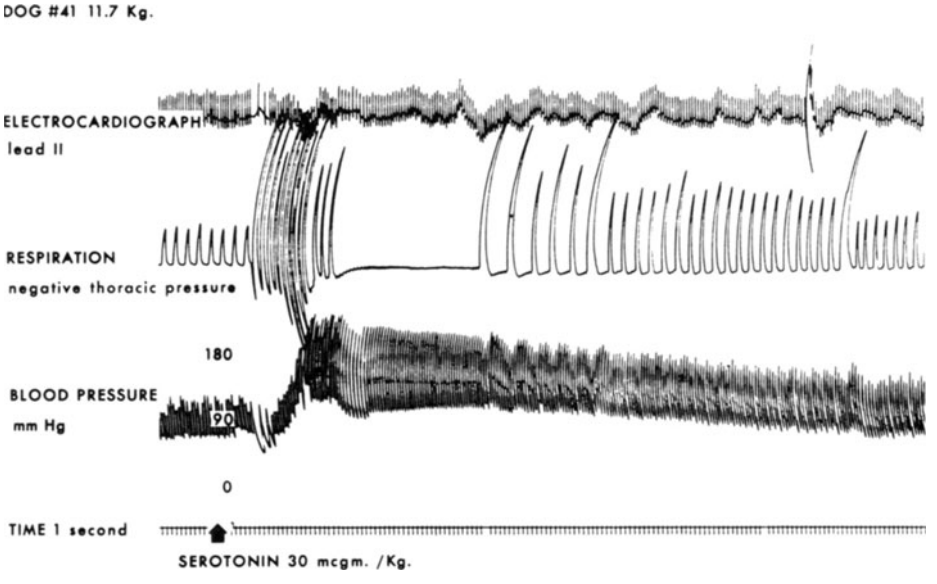


Fig. 14. Effect of a single intravenous injection of 30 μg/kg 5-HT on electrocardiogram, respiration and blood pressure of a dog anaesthetized with pentobarbital-morphine. Note the initial brief period of extreme respiratory effort (hyperpnoea and tachypnoea) followed by a period of respiratory arrest in the expiratory stage, followed in its turn by another period of inspiratory stimulation. [From Fig. 1, Kroeger, D. C., and L. J. Lucco, J. Amer. pharm. Ass., sci. ed. **49**, 171 (1960).]

chemoreceptor stimulation, and that the apnoea, a phenomenon quite independent of the preceding one, is probably of central origin.

Tryptamine (Ginzel and Kottegoda 1954, Reid 1952a), bufotenine and bufotenidine (Raymond-Hamet 1953a, 1954) act on respiration like 5-HT. Tryptamine is however about 20 times less active than 5-HT (Reid 1952a).

Dog. Numerous concordant observations demonstrate that the predominant respiratory response of the anaesthetized dog to single intravenous injections of 5-HT (5—100 μg/kg) is transient hyperpnoea followed in the majority of the animals by a period of apnoea (Douglas and Toh 1952, 1953, Page 1952b, Heymans and van den Heuvel-Heymans 1953, Schneider and Yonkman 1954, MacCanon and Horvath 1954, McCubbin et al. 1956, Westermann 1958). There are, however, also more or less divergent results. Kroeger and Lucco (1960), for example, found that most frequently three respiratory events were obtained with intravenous 5-HT: transient gasping and a slower developing hyperpnoea which was generally interrupted by apnoea (Fig. 14). Schmid, Waltz and Freund (1956) noted that whereas small doses of 5-HT displayed in the waking dog a prevalent depressive effect on respiration, quickly injected large

doses produced respiratory stimulation. An initial decrease in respiratory movements resulting in marked tachypnoea was also observed by BEN, BOXILL and WINBURY (1962).

HARASAWA and RODBARD (1961) injected 4 μg/kg 5-HT base, or more, into the pulmonary artery of the anaesthetized dog. The respiratory cycle began to shorten about 10 seconds after the injection and became shortest in 15 to 45 seconds. The respiratory cycle then lengthened gradually to control values over the course of about 5 min. The effects on the respiratory cycle were reduced but not entirely abolished by vagotomy even though changes in heart rate were eliminated.

When 5-HT is infused into the right atrium at a rate of 4 μg/kg/min there is an increase in respiratory volume associated with a significant reduction in CO_2 content of arterial, mixed venous and coronary sinus blood (MAXWELL et al. 1957, CRUMPTON et al. 1959). Similarly, 5-HT produces in the intact dog a rise in the arterial oxygen saturation, as measured by the cuvette oximeter (NIDEN and BARKLAY 1959). Concerning the interpretation of the mechanism and sites of action of 5-HT in producing the above respiratory changes, there are still some obscure and controversial points.

On the basis of the observations a) that respiratory stimulation elicited by the introduction of 5-HT into the common carotid artery remains unchanged after ligation of the internal carotid, the external carotid and the occipital arteries but is abolished by section of the carotid sinus nerves and of the IX cranic nerve, and b) that respiratory effects produced by intravenous 5-HT are reduced or abolished by vagotomy and by bilateral ablation of carotid sinus and glomus, DOUGLAS and TOH (1952, 1953) believe that 5-HT exerts its respiratory effects mainly through stimulation of afferent fibres in the vagus and sinus nerves. A direct stimulation of the respiratory centre is not completely excluded, but it is considered of secondary importance. This view has not been accepted by HEYMANS and VAN DEN HEUVEL-HEYMANS (1953), who failed to confirm that denervation of the carotid sinus and section of the sinus-carotid and vago-aortic nerves caused a reduction in the respiratory response to 5-HT. Accordingly, they consider 5-HT hyperpnoea predominantly due to central stimulation. Another opinion is held by SCHNEIDER and YONKMAN (1953) who maintain that the initial respiratory stimulation in the dog is primarily due to a cardio-pulmonary reflex, since it is greatly diminished or abolished after bilateral vagotomy and only a short period of respiratory depression is observed when the spinal cord is sectioned at C_6. Again stimulation of vago-aortic and carotid sinus afferents appears to be of minor importance.

MCCUBBIN et al. (1956) seem to have resolved the problem by showing that small doses of 5-HT fail to stimulate respiration unless the drug reaches chemoreceptors. In fact, whereas 5 μg 5-HT given into the common carotid artery causes pronounced increase in chemoreceptor impulse traffic in the carotid sinus nerve, the same dose of the amine is ineffective when injected into a perfusion system permitting chemoreceptors to be excluded from the natural circulation. Much larger doses (100—220 μg 5-HT base) cause the reappearance of some respiratory stimulation, which persists after cervical section of the spinal cord with section of the vagus-aortic and sinus nerves. The mechanism of this residual effect is assumed to be central. On a weight basis, 5-HT appears to be a much more powerful chemoreceptor stimulant than lobeline, tryptamine or 1,1-dimethyl-4-phenylpiperazinium iodide.

The theory of a double or treble point of attack of 5-HT (carotid body chemoreceptors, respiratory centre and, eventually, cardiopulmonary receptors) is shared by WESTERMANN (1958) and by KROEGER and LUCCO (1960).

The above explanations, however, apply only to the stimulant action of 5-HT on respiration. Origin of secondary apnoea is largely obscure. KROEGER and LUCCO have called attention to the direct bronchoconstrictor effect possessed by 5-HT and have presented evidence that preventing bronchoconstriction reduced the occurrence of apnoea in the dog.

What has been said for 5-HT applies also to 7-HT and to tryptamine, administered in large doses. Initial hyperpnoea is always the most prominent response, sometimes followed or interrupted by periods of apnoea or reduced respiration (PAGE 1952b, REID 1952a). Psilocybin (0.5 mg/kg, i.v.) given to dogs premedicated with morphine and anaesthetized with a dial-urethane-nembutal mixture decreases respiratory volume from 2.7 to 2.1 l/min and respiratory rate from 19 to 17 movements per minute. There is a definite decrease in arterial oxygen content and arterial saturation also falls (MAXWELL et al. 1962). Little is known about gramine, which seems however to increase depth and rate of respiratory movements and to cause bronchoconstriction (SUPNIEWSKI and SERAFINOWNA 1938).

In marked contrast to the normal dog, but like the cat, the dog with neurogenic hypertension responds to 5-HT and tryptamine with a period of apnoea, followed by deep, forced breathing (PAGE 1962b).

Man. 0.5—1.5 mg 5-HT given by rapid intravenous administration produces in normal subjects a short-lasting (20—40 seconds) increase in depth and rate of respiration with elevation of the mid position of the chest. There are no signs of bronchial obstruction. The respiratory response is potentiated by pyrilamine maleate (25 mg), inhibited by BAS (50—100 mg, i.v.) and left unchanged by anticholinergic drugs, and by ganglionic or adrenergic blockade (HOLLANDER et al. 1957, MICHELSON et al. 1958).

The effect of 5-HT given by intravenous infusion in doses of 1—3 mg/minute is essentially the same. Stimulation of respiration is most marked in the first 5 min but persists to a lesser degree throughout the remainder of the 10- or 20-min infusion. Tidal air always increases but respiratory rate shows a variable change. Apnoea is not seen. On repeated infusion tachyphylaxis of the hyperpnoea is observed. Neither release of adrenaline nor increased metabolic rate seems to be responsible for the stimulatory effect of 5-HT (PARKS et al. 1960).

In asthmatic patients aerosolized 5-HT produces a prompt fall in vital capacity and a decrease in respiratory flow rate (MICHELSON et al. 1958).

Whereas MICHELSON and co-workers think that it is probable that the respiratory effect of 5-HT is due to direct stimulation of the central nervous system, PARKS et al. believe that 5-HT stimulates receptors situated in the systemic arterial circulation. This is based on the observation that the onset of hyperpnoea corresponds in time with the initial effect on the forearm blood flow.

Bufotenine produces, when blown into the nostrils (10 mg) or given intravenously by quick injection (10 mg in 50 seconds), hyperventilation eventually followed by apnoea (TURNER and MERLIS 1959). Given by slow intravenous injection (0.06—0.25 mg/kg over 3 to 20 min) it causes only slight variation in respiration with a tendency to increase (FABING et al. 1956).

Rabbit. The injection of 5-HT (50—100 μg/kg, i.v.) into the anaesthetized animal causes a marked immediate stimulation of breathing, followed in 50% of the animals by respiratory arrest in inspiratory position. A diminution of the respiratory response is evident after spinal cord section (SCHNEIDER and YONKMAN 1954). Respiratory arrest is not due to bronchospasm, since 5-HT has little or no effect on the bronchi of rabbits in doses up to 2.5 mg/kg given intravenously or endobronchially (JÄNKÄLÄ and VIRTAMA 1961). Like 5-HT, psilocybin (thresh-

old dose 20 μg/kg, i.v.) and bufotenidine (threshold 5 μg/kg, i.v.) produce predominant respiratory stimulation (CERLETTI 1959, UEDA et al. 1957).

Guinea-pig. An analysis of the respiratory effects of 5-HT in the guinea-pig is made very difficult by the potent direct bronchoconstrictor action of the amine (HERXHEIMER 1955, 1957; BHATTACHARYA 1955; BALZER et al. 1956; JÄNKÄLÄ and VIRTAMA 1961). Intravenous 5-HT generally provokes hyperpnoea over a wide dosage range (WESTERMANN 1958). Tidal air, however, is decreased at constant stroke volume, both in anaesthetized and in spinal guinea-pigs. Threshold dose is 3 to 22 μg/kg (KONZETT 1956). 0.5—0.7% 5-HT aerosols administered to unanaesthetized animals provoke tachypnoea followed in 30—40% of the animals by an asthmatic attack, succeeded, in its turn, by deep and frequent respiration and then, in spite of continuous inhalation of aerosol, by normal breathing (FRAHM 1957). 1% 5-HT aerosols given to urethane-anaesthetized

Table 1. *Action on respiration of indolealkylamines administered intravenously to different animal species*

	5-HT	Bufotenine	Psilocybine	Bufotenidine	Tryptamine	Gramine
Man	+	+ (—)				
Dog normal	+ —		—		+ (—)	—
hypertensive	— (+)				— (+)	
Cat	— (+)	— (+)		— (+)	— (+)	
Rabbit	+ (—)		+	+		
Guinea-pig	+					
Rat	+ — +					
Chicken	—				—	

\+ indicates respiratory stimulation,
— indicates reduced respiratory rate or apnoea.
Occasional or minor effects are given in brackets.

guinea-pigs induce characteristic changes in the expiratory reflexes and inspiratory dispnoea. Vagotomy largely reduces this response suggesting that 5-HT affects respiration not only through a direct peripheral action on the bronchi but also through vagal reflexes (MEIER et al. 1956).

Rat. The respiratory response of the rat to intravenous 5-HT shows remarkable individual variations (WESTERMANN 1958). Generally a brief initial stimulation is followed by apnoea in the expiratory position and then, sometimes, by moderate tachypnoea. The respiratory stimulant effect of 5-HT (4—10 μg/kg, i.v.) is abolished by inactivation of the carotid sinuses but not by vagus section or ganglionic blockade. It seems to depend on stimulation of carotid and probably aortic chemoreceptors, as well as, with larger doses, on a central mechanism (SALMOIRAGHI et al. 1956).

Chicken. 5-HT (5—50 μg/kg, i.v.) and tryptamine (25—500 μg/kg, i.v.) decrease both rate and amplitude of breathing. Antihistaminic drugs or atropine do not alter these respiratory effects (BUÑAG and WALASZEK 1961c).

It clearly appears from the preceding data that respiratory changes elicited by 5-HT and other indolealkylamines are consistently different in different animal species, and even, to some degree, in the same species according to experimental conditions. Table 1 summarizes the most common features of the respiratory effects of indolealkylamines.

According to WESTERMANN (1958) animal species whose respiratory centre possesses an elevated activity of its own, largely independent of vagal afferent impulses (e.g. cat) respond to 5-HT with predominant apnoea; animal species,

on the contrary, with a respiratory centre largely dependent on vagal afferent impulses (e.g. guinea-pig) respond to the amine with hyperpnoea and/or tachypnoea.

There is no evidence that 5-HT participates in the physiological control of respiration. Hence, all actions described in this chapter should be considered pharmacological actions.

XII. Action on external secretions

1. Salivary secretion

Dog submaxillary gland. According to PETRUCELLI et al. (1961) single injections of 50—100 μg 5-HT into the common carotid artery via the cranial thyroid artery produce potentiation of salivation caused by continuous electrical stimulation of the chorda tympani. 5-HT in this dose range causes no salivation by itself. The intravenous administration of iproniazid further increases the potentiation observed with identical doses of 5-HT. The intravenous administration of reserpine in single doses which by itself produce salivation also further potentiates 5-HT after cessation of reserpine-induced salivation. Moreover, it appears that 5-HT by subminimal infusion potentiates the sialagogue effect of acetylcholine. PETRUCELLI and co-workers suggest that 5-HT, while not strictly necessary for neural transmission, may facilitate transmission at parasympathetic ganglia and/or neuroeffectors.

At complete variance with the above results are those of CALDARERA et al. (1961a, 1961b), who found that both the intravenous injection of 20—120 μg/kg 5-HT base and the intravenous infusion of 5—20 μg/kg/min 5-HT caused a complete or partial inhibition of the secretory response of the dog submaxillary gland to electrical stimulation of the chorda tympani as well as to intravenous infusion of pilocarpine. The inhibitory effect lasted 3—15 min and was sometimes preceded by transient potentiation of salivation. Enervation of the gland did not alter the effect of 5-HT. There was no definite correlation between reduction of salivation and the observed decrease in blood flow through the gland.

Posterior salivary glands of octopoda. Perfusion of the isolated posterior salivary glands of *Octopus vulgaris* and *Octopus macropus* with sea water containing 1—10 μg/ml 5-HT produces, together with a decrease in the perfusion rate and a conspicuous increase in the rhythmic movements of the gland and the ducts, the secretion of a liquid which greatly differs from that obtained by electrical stimulation of the gland. In fact, the secretion is clear, limpid, not viscous, rich in chlorides, poor in proteolytic enzymes and lacking any toxicity towards the crab. GHIRETTI (1953a, 1953b) suggests that 5-HT may act through changes in the permeability of the cellular elements of the gland.

2. Gastric secretion

Man. At variance with CALÌ and CORDOVA (1956a, 1956b) who found that intravenous 5-HT (2 mg) displayed in man a stimulant action on gastric secretion, which was inhibited by antihistaminic drugs and therefore did not appear to be mediated through liberation of histamine, all other research workers (ROSA et al. 1957—1958; SCHMID et al. 1959, 1960; PICHEL WARNER et al. 1959; HAVERBACK and DAVIDSON 1958) observed that 5-HT and 5-HTP inhibited the volume and acidity of both spontaneous and histamine-induced gastric secretion while at the same time increasing production of mucus. Following the intravenous infusion of 1.5—15 μg/kg/min 5-HT maximum effects (rise of pH values by 0.5 to

1.5) appear after 5—25 min and the secretory response wears off within 15—20 min after the infusion has been discontinued (SCHMID et al. 1959); 5-HTP infused intravenously for 5 min at a rate of 10—80 μg/kg/min produces a more intense and sustained reduction of gastric secretion. The pH of the gastric juice rises by 3.5 and the inhibitory effect lasts up to 60 min (SCHMID et al. 1960).

Dog. BLACK et al. (1956, 1958) and SMITH (1957) examined the effect of 5-HT on gastric secretion in dogs anaesthetized with chloralose and urethane, starved for al least 12—24 hours and prepared with a stomach fistula and a ligature at the pylorus-duodenal junction. They found that intravenous infusions of 5-HT, at a rate of 2.5—20 μg/kg/min for 45—90 min did not stimulate any gastric secretion whatever, but caused the production of an alkaline juice rich in mucus. During this infusion the arterial plasma pH fell, unlike the plasma pH during histamine infusion. When an acid gastric secretion was stimulated by a continuous intravenous infusion of histamine (e.g. 5 μg/kg/min) concurrent infusion of 5-HT (15 μg/kg/min) for 30 minutes was found to inhibit the secretion. Recovery from the inhibition usually began within 60 min after stopping the 5-HT infusion. Infusion of 5-HT at the start of histamine-stimulated gastric secretion failed to prevent the onset of secretion due to infusion of histamine.

However, the effect of 5-HT on histamine-induced gastric secretion was greatly influenced by the previous dietary history of the animals. In dogs which were not starved completely but were given a fatty meal in the 12 hours preceding the experiment, 5-HT elicited a much more striking inhibitory response and all acid secretion was abolished, whereas in dogs in which the period of starvation was prolonged to 36 hours, 5-HT did not inhibit and in several cases stimulated the acid secretion.

When 5-HT was given after bilateral cervical vagotomy it was found to be ineffective in inhibiting histamine-stimulated secretion. This has been considered evidence in favour of the suggestion that 5-HT might exert its effects on gastric secretion reflexly, through stimulation of vagal receptors in the stomach wall.

The above observations were, on the whole, confirmed by several research workers.

HAMMOND (1956) observed that in dogs receiving 5-HT intravenously in doses which stimulated intestinal motility, no gastric secretion ensued and that stimulation of gastric secretion by reserpine was not affected by the simultaneous injection of 5-HT.

WHITE and MAGEE (1958) found that intravenous infusion of 10—30 μg/kg/min 5-HT increased by 200% the secretion of mucin from the pyloric mucosa of the dog and that this effect was regularly reduced by the administration of 1 mg atropine intravenously. The action of 5-HT was not dependent on increased motility since it was present in the everted pouch and was not abolished by hexamethonium, which decreased motility.

Finally, HAVERBACK et al. (1957, 1958) noted that whereas 5-HT base in a dose up to 4 μg/kg/min had no marked transient or sustained effect on the volume and pH of gastric secretion from the denervated Heidenhain pouch, a dose of 16 μg/kg/min produced a rise of the pH of the reduced volume of gastric juice.

In acute observations on dogs anaesthetized with pentobarbital, bearing a tube in the stomach introduced through a duodenostomy, 3 subcutaneous doses of 10 μg/kg 5-HT base given every 15 min, single intravenous doses of 25 μg/kg and intravenous infusions of 13 μg/kg/min for 45 min failed to cause any appreciable change in the gastric secretion (HAVERBACK and WIRTSCHAFTLER 1962).

The variable effect of 5-HT on histamine-stimulated gastric secretion is again emphasized in recent experiments by SOSIN et al. (1962). They observed that

whereas significant elevation of free HCl (177% of controls) occurred in Heidenhain pouches of dogs receiving an intravenous infusion of 4 μg/kg/min histamine plus 8 μg/kg/min 5-HT base, no significant changes in free HCl were noted in dogs receiving the same dose of histamine plus 16, 25 and 32 μg/kg/min 5-HT. Dogs receiving 5-HT alone produced virtually no free HCl. The volume of gastric juice paralleled free HCl, and pepsin activity was not altered in any test group.

Results obtained with the precursor aminoacid 5-HTP were on the whole in accordance with those obtained with 5-HT, with an important partial discrepancy, however, concerning the effect of 5-HTP on the histamine-induced gastric secretion.

SMITH et al. (1957) and BLACK et al. (1958, 1959) found that the intravenous infusion of doses of 5-HTP as low as 5—20 μg/kg/min produced, after a latent

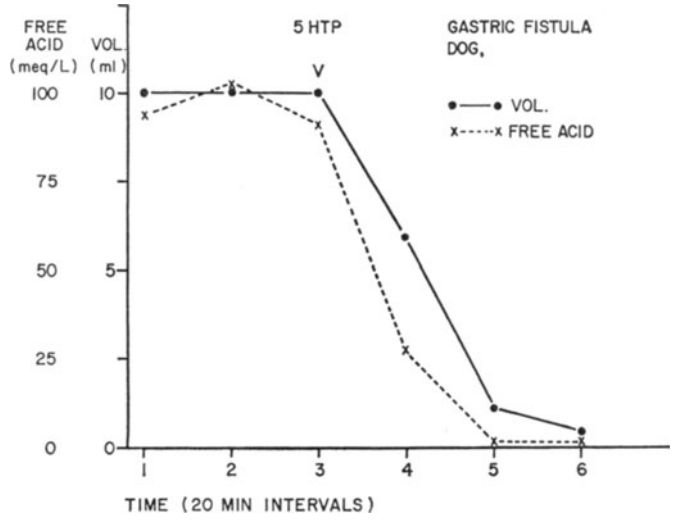


Fig. 15. The inhibitory effect of 5-HTP (25 mg/kg, i.v.) on spontaneous gastric secretion in a dog with gastric fistula and intact vagal nerves. Each value represents the mean of three studies on different days. [From Fig. 6, HAVERBACK, B. J., and S. K. WIRTSCHAFTLER, Advanc. Pharmacol. **1**, 323 (1962).]

period of 15—30 min, a marked fall in secretory acid output elicited by histamine. Occasionally 5-HTP stimulated gastric acid secretion for a short time as the first action. The effect was maximal when 5-HTP was given 2 hours after histamine stimulation. Bilateral cervical vagotomy markedly reduced the inhibitory effect of 5-HTP.

HAVERBACK and co-workers (HAVERBACK 1958, HAVERBACK et al. 1958, HAVERBACK and WIRTSCHAFTLER 1962) observed that 5-HTP in a single intravenous dose of 25 mg/kg inhibited spontaneous gastric secretion in dogs with Heidenhain pouches and with simple gastric fistulae and intact vagal nerves (Fig. 15). Volume of gastric juice fell from 10 to 1.5 ml/20 min, and free acid from 93 to 0 meq/litre within 40 min after 5-HTP administration. The aminoacid was equally effective in inhibiting gastric acid secretion stimulated by insulin-induced hypoglycaemia and by urecholine infusion (3.5 μg/kg/min) (Fig. 16). However, it did not inhibit gastric secretion stimulated by reserpine or histamine (2 μg/kg/min). In each instance, following inhibition of gastric acid secretion, there was a marked increase in the quantity of mucus secreted by the stomach.

It is suggested that 5-HTP does not directly affect the mechanism of acid formation, but probably interrupts the pathway for the transmission of stimuli to gastric secretion.

Of considerable interest is the observation of BLACK et al. (1959) that in previously starved anaesthetized dogs, feeding of tryptophan (300—1000 mg)

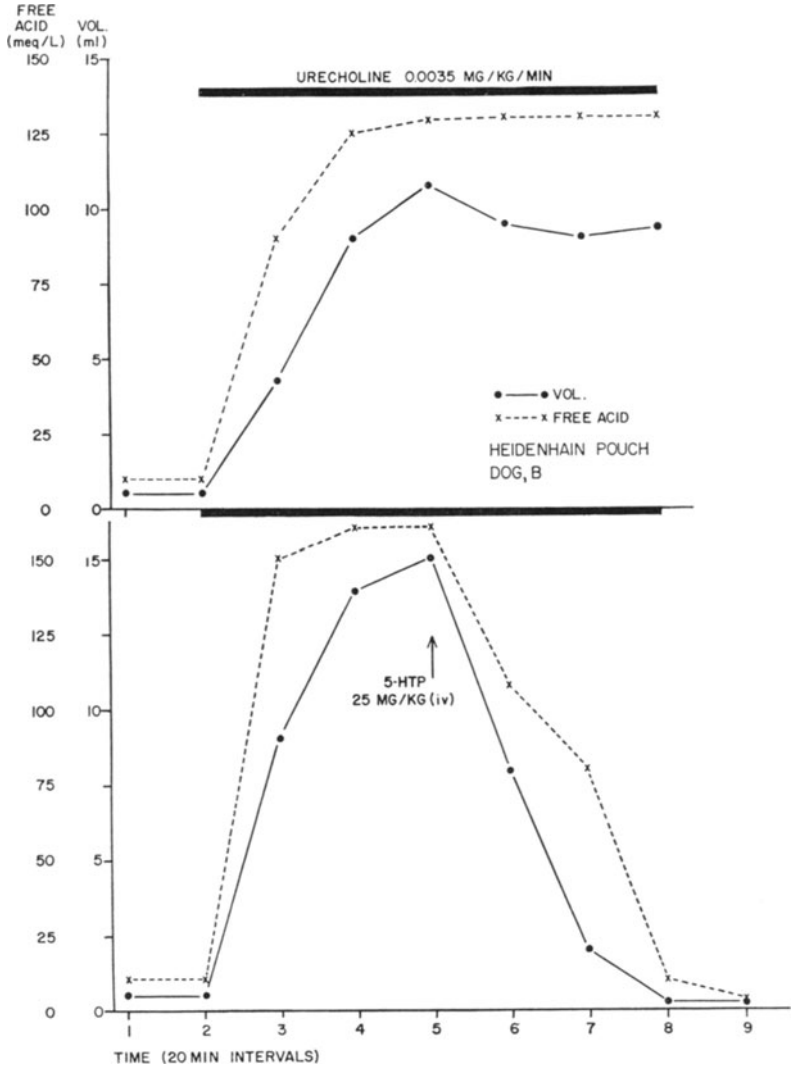


Fig. 16. (Above) Stimulus of urecholine to gastric secretion in a dog with a Heidenhain pouch. (Below) Inhibition of this secretion in the same dog by 5-HTP (25 mg/kg, i.v.) [From Fig. 7, HAVERBACK, B.J., and S. K. WIRTSCHAFTLER, Advanc. Pharmacol. **1**, 324 (1962).]

before the start of an experiment led to a fall in acid output between 1 and 3 hours after the onset of histamine-stimulated secretion.

Guinea-pig. Given to unanaesthetized guinea-pigs in intraperitoneal doses of 1 to 20 mg/kg, 5-HT reduces the concentration of free acid and raises the concentration of Na in the gastric secretion induced by histamine. Like other inhibitors of gastric secretion, 5-HT causes the replacement of Cl ions with Na

ions, leaving unaffected the concentration of potassium. Small doses of 5-HT increase and larger doses decrease the peptic activity of the juice (WILSON 1957).

Rat. Both 5-HT (4—8 mg/kg of the base, subcutaneously) and 5-HTP (10 to 20 mg/kg) produce a significant depression in volume, acid and pepsin output of the interdigestive gastric secretion in the Shay-rat, as well as a depression of gastric secretion stimulated by urecholine. Doses of 5-HT lower than 10 mg/kg are ineffective. Following 5-HTP, inhibition of gastric secretion occurs after a considerable latency (SHAY et al. 1957, 1958; HAVERBACK and DAVIDSON 1958; HAVERBACK et al. 1958).

These results were confirmed in chronic gastric fistula rats prepared by implanting stainless steel cannulae in the rumen portion of the stomachs. 5-HT (8 mg/kg, s.c.) significantly reduced, 2 hr after the injection, the volume of gastric juice and the output of free and total acid (MARSHALL et al. 1962).

To explore whether inhibition of gastric secretion observed following HCl perfusion of the small intestine was due to release of 5-HT by the upper intestine, gastric secretion in the pyloric-ligated rat was studied by RESNICK and GRAY (1961) after the administration of varying quantities of 5-HT through the rat portal vein. It was found that infusion of 5-HT (2—20 μg 5-HT base in 1-hr experiments, and 4—180 μg in 3-hr studies) did not alter either gastric pH or secretory volume. Similarly, neither partial depletion of intestinal 5-HT by reserpine nor use of 5-HT antagonists prevented the suppression of gastric secretory function caused by HCl perfusion of the small intestine.

The above experiments are more than ever pertinent since RESNICK and GRAY (1962) demonstrated that perfusion of 0.1 N HCl (3 ml for a period of 15 min) through the upper intestine of the rat or introduction of HCl into an obstructed intestinal loop, produced a decrease in the 5-HT concentration from 2.4 to 1.8 μg/g and from 3.4 to 1 μg/g, respectively.

At intraperitoneal doses of 15 mg/kg, 5-HT does not produce any significant increase in plasma pepsinogen, i.e. it does not stimulate gastric endocrine function (KOWALEWSKI 1960).

Cat. The effect of intravenous 5-HT (1—6 mg base/cat) on the secretion of gastric pouches is variable, in part depending upon the integrity of the vagus nerves. With intact vagi, spontaneous secretion is but little affected by 5-HT (production of a small amount of non-acid juice), and histamine-induced secretion (40 μg histamine/min) is generally reduced in both volume and acidity. With cut vagus nerves non-acid spontaneous secretion is more abundant, for 10 minutes, and reduction of histamine-induced secretion is preceded by an increase of secretion. When vagus nerves are cut at the cardias instead of at the neck, there is always an immediate reduction in both volume and acidity of the histamine-induced secretion (DE CORRAL SALETA 1956, 1960).

3. Pancreatic and biliary secretions

Rats given daily injections of 2 mg/kg 5-HT base for 3 days present a slight decrease in the lipase and protease activity of the pancreatic juice, whereas the amylase activity remains unchanged (MIGLIETTA and SALVADÈ 1959).

No significant changes in bile flow occur during and after 4 to 6 hr of perfusion of 5-HT (2 to 100 μg/min) through the portal vein cannula of an isolated rat liver (LEVINE et al. 1964).

In dogs with total pancreatic fistulae, 5-HT (0.2 mg base/kg, i.v.) reduces both food-stimulated and non-stimulated flow of pancreatic juice. Whereas pH or amylase activity of the juice is not affected, bicarbonate level is decreased. 5-HTP (25 mg/kg, i.v.) produces similar but slower and less pronounced effects

(DRAPANAS and POLLACK 1960). Pancreatic secretion provoked by intravenous infusion of pilocarpine (5—25 μg/kg/min) is reduced both by single intravenous injections (40—60 μg/kg of the base) and by intravenous infusion of 5-HT (10 μg/kg/min). Inhibition of pancreatic flow is sometimes preceded by short-lived stimulation (RIVA SANSEVERINO and URBANO 1961c, 1961d, 1963), Concerning the influence of 5-HT and 5-HTP on flow rate of secretin-stimulated pancreatic juice results are at variance. DRAPANAS and POLLACK observed no action, RIVA SANSEVERINO and URBANO a clear inhibitory effect.

5-HT (0.7—1 mg/kg of the base, i.v.) elicits in the majority of the experiments a temporary diminution of the bile flow in the dog. The effect on bile concentration is variable (SEFERIAN 1962).

In man, intravenous infusion of 4 μg/kg/min 5-HT for 60 min does not affect significantly external pancreatic secretion (volume, bicarbonate and amylase concentration of the duodenal aspirate), but partially inhibits the bile pigment flow (PICHEL WARNER et al. 1959).

Intramuscular injection of 10 mg 5-HT base, repeated after 1 hr, provokes in man a more rapid disappearance of sulfobromophthalein from plasma, i.e a more prompt extraction of the dye by the hepatocytes (TURA et al. 1960)

It appears from the preceding data that 5-HT and 5-HTP display on the secretions of the alimentary canal a prevalently depressive effect. Now, the problem arises as to whether or not this pharmacological action elicited by hexogenous 5-HT or 5-HTP is indicative of a possible physiological function displayed on gastrointestinal secretions by strictly endogenous 5-HT. In other words, considering for the sake of simplicity the stomach only, does the 5-HT produced and stored within the stomach mucosa contribute to a local regulation of the gastric secretion, or does the 5-HT circulating in the blood display the same function ?

In the writer's opinion evidence so far available is insufficient for an answer to the above questions. However, a few considerations can be made:

a) There is no direct proof whatever demonstrating that a *local* release of 5-HT by the enterochromaffin cells of the gastric mucosa occurs at the time of gastric secretion and may exert any influence upon this secretion. In fact, no changes in the 5-HT content of the stomach have been described which could be referred to the phases of the secretory activity of the organ.

The suggestion that reserpine may stimulate gastric secretion through local release of 5-HT is hardly tenable because 5-HT, in contrast to reserpine, inhibits gastric acid secretion, and because reserpine is active even after pretreatment with 5-HTP which is a potent inhibitor of gastric secretion (HAVERBACK et al. 1958, HAVERBACK and WIRTSCHAFTLER 1962, NEČINA and KREJČI 1961).

b) BLACK et al. (1959) affirm that 5-HT levels in portal blood are higher in fed (0.24—0.39 μg/ml) than in starved dogs (0.13 μg/ml). These observations, which would indicate a release of 5-HT by the gastrointestinal mucosa in connection with presence of food in the alimentary canal, await confirmation before they can be accepted. In fact, keeping in mind the rate of blood flow through the portal vein, excess 5-HT liberated by the intestines of fed animals would be enormous, far beyond any reasonable expectation. Caution is more than ever justified since no relationship between meals and the peak in the diurnal variation in 5-HT metabolism, as inferred from the urinary excretion of 5-HIAA, could be demonstrated in man.

It should be added that increased liberation into the blood of 5-HT produced by food would neither prove nor disprove that released 5-HT acts on secretory processes.

c) Although the 5-HT content of the gastric mucosa is generally maximum in the red, glandular portion of the stomach, even the white, non-glandular portion may contain large amounts of the amine. In *Ameiurus catus*, a fish belonging to the Teleostei, enterochromaffin cells are localized only near the pylorus, while completely lacking in the glandular portion of the stomach.

These species differences in the gastric distribution of enterochromaffin cells and 5-HT are not in favour of a direct local action of 5-HT on gastric secretion.

d) Accepting the view that 5-HT may exert its physiological action on the gastric secretion via the blood, then it should be stressed that the intravenous doses of exogenous 5-HT required to produce changes in the gastric secretion are always considerably high [in the rat doses of 5-HT base infused into the portal vein for 1—3 hours at a rate of up to 20—50 μg/rat/hour failed to alter either gastric pH or secretory volume (RESNICK and GRAY 1961)] and that changes in the stomach secretion are accompanied by changes in gastrointestinal motility and by a more or less conspicuous involvement of the vascular system.

So far, information is lacking about the behaviour of gastric secretion following close intraarterial injection or infusion of physiological doses of 5-HT.

e) As already stated, BLACK et al. (1959) observed that feeding of tryptophan to dogs produced, after a latency period, a reduction in histamine-stimulated gastric secretion. The confirmation of these results appears to be of the greatest interest and it would be important to try separately L-tryptophan and D-tryptophan and to follow up the urinary excretion of 5-HIAA during the experiment. It is evident that the demonstration that endogenous 5-HT originating from dietary L-tryptophan is capable of influencing gastric secretion would offer strong support to the hypothesis that 5-HT is involved in the physiological control of this secretion.

4. Sweat secretion

In man intramuscular doses of 2 mg 5-HT are sufficient to depress sweat secretion. The effect, which reaches its maximum during the second hour, wears off within 4 to 5 hours. In 50% of the cases inhibition is preceded by stimulation (MORSIANI and MARTELLI 1955). In mice complete inhibition of plantar transpiration is observed only with doses of 5-HT base as high as 5—6 mg/kg (BLOZOVSKI and SIVADJIAN 1959), which are known to produce conspicuous vascular effects.

XIII. Metabolic effects. Action on enzymes

1. Action on carbohydrate metabolism

Mammals. CORRELL et al. (1952) first found that the intravenous injection of 10 mg/kg 5-HT into non-anaesthetized rats produced an increase of plasma glucose level from 157 to 269 mg per cent, and that the injection of 2.5 mg/kg 5-HT into rabbits brought the level from 120 to 193 mg per cent. The presence of the adrenal medulla was not essential for the hyperglycaemic response. These data have been generally confirmed.

In rats, hyperglycaemia produced by 5-HT (0.4 mg/rat, i.v.) may by preceded by a hypoglycaemic phase which is potentiated by pentobarbital anaesthesia. Insulin-induced hypoglycaemia is enhanced by 5-HT, whereas adrenaline-induced hyperglycaemia is reduced by the amine. Chronic administration of 5-HT for 50 days increases insulin sensitivity and glucose tolerance (KOBAYASHI et al. 1960a).

Furthermore, 0.1—0.4 mg 5-HT base/rat given by intraperitoneal or intravenous route depletes liver glycogen, decreases glycogen levels (by 35—50%)

and phosphorylase activity of uterine smooth muscle, decreases glycogen concentration in the diaphragm (25—30%) and rapidly elevates glycogen in heart muscle (30%), while leaving phosphorylase activity unaltered in both instances (KOBAYASHI et al. 1960b, LEONARD and DAY 1960).

However, when given subcutaneously to adrenodemedullated rats, 5-HT increases the glycogen content of the diaphragm, the effects of 5-HT and insulin being additive when given together (KOBAYASHI 1960).

The intravenous injection of 20—200 μg 5-HT base/rat causes a rapid rise of blood lactate both in intact and adrenodemedullated animals. This is due both to enhancement of extrahepatic production and to retardation of hepatic utilization of lactate (UI et al. 1960a, 1960b).

LEVINE et al. (1964) administered 5-HT into the portal vein cannula of an isolated rat liver, either by rapid injection over a 2-min period (7—700 μg 5-HT base) or by constant infusion (1.6—100 μg/min). They observed that the amine produced glycogenolysis, hyperglycaemia and stimulation of hepatic phosphorylase activity. The increase in blood glucose was not dose-related and was variable. These actions were independent of observed vasomotor effects of 5-HT on hepatic blood flow. Similar effects were produced by 5-HTP (8—26 mg/hr).

A more precise analysis of the effects of 5-HT in stimulating phosphorylase activity in the rat uterus was carried out by LEONARD (1963). He found that 5-HT administered either intraperitoneally (5 mg/kg every 30 min for 6 hr) or by intraluminal uterine injection (0.5 mg/uterine horn) did not increase uterine weight or activity of *a*(active)-phosphorylase. Intraperitoneally-injected 5-HT produced, however, a decrease in total-phosphorylase activity which was similar though smaller than that caused by histamine.

After intraperitoneal injection of 2 mg 5-HT base/rat there is a significant increase in the P^{32} uptake by adrenal cortex and medulla, pancreas, liver and diaphragm, and a significant decrease in the spleen and testis. This signifies that 5-HT, according to different tissues, increase or decreases the rate of metabolic phosphorylation (LINGJAERDE and SKAUG 1957).

5-HT at 10 mM concentrations abolishes the oxidative phosphorylation of guinea-pig liver mitochondria. This can be observed when either L-glutamate or β-hydroxybutyrate is used as substrate. Tryptamine is approximately half as active as 5-HT, IAA possesses the same activity as tryptamine, 5-HTP is inactive (ALIVISATOS et al. 1964).

In rabbits both 5-HT and 5-HTP elicit a predominant hyperglycaemic response. Rise in blood sugar level is by 10, 40 and 60% after 2, 4 and 12 mg/kg 5-HT base, respectively (MAZZONE et al. 1959a, 1959b), and by 40% after 5 to 20 mg/kg 5-HTP (KONZETT 1958). Hyperglycaemia may be preceded by a fleeting hypoglycaemic phase (—10%). Diabetic rabbits behave like normal rabbits (NIAUSSAT et al. 1961). 5-HT-induced hyperglycaemia is antagonized by dihydroergotamine and probital anaesthesia, whereas pretreatment with 5-HT (1 mg/kg) has little influence on hyperglycaemia produced by LSD (MAZZONE et al. 1959b, KONZETT 1956, 1958).

2.5—25 mg/kg 5-HT given intravenously in the rabbit produces an important decrease in the brain consumption of oxygen and glucose, a mobilization of brain glycogen and a reduction in brain production of pyruvate as well as an increase in the consumption of lactate and inorganic phosphate (CAHN et al. 1957, 1958).

Glucose content of the cortex of the perfused cat brain is higher when 25 to 44 mg 5-HTP or 40—300 μg 5-HT are added to the perfusion liquid. However, neither glucose uptake nor oxygen consumption are affected whereas there are

some indications that 5-HTP tends to depress aerobic glycolysis (MAGNES and HESTRIN-LERNER 1960).

In normal dogs intravenous doses of 5-HT base as low as 5 μg/kg fail, as expected, to produce hyperglycaemia. However, when the same or even half the amount of 5-HT is injected into depancreatized dogs, there is a significant rise in blood sugar level during the first 40—60 min. This preliminary observation of SIREK (1957) still awaits confirmation.

Large doses of 5-HT (2 mg/kg of the base, i.v.) produce even in normal dogs a 30% rise in blood glucose, a decrease in liver glycogen and an increase in liver phosphorylase activity. Since 5-HT fails to prevent the progressive decrease in blood sugar and liver glycogen seen in adrenalectomized dogs treated with saline, it is suggested that the changes in carbohydrate metabolism observed in normal dogs are secondary to a release of adrenaline from the adrenal glands and not due to a direct stimulation of liver phosphorylase by 5-HT (COLOMBO et al. 1960).

Intravenous injection of STH, ACTH or deserpidine does not cause any significant rise of catecholamines or 5-HT in the blood of the pancreato-duodenal vein of the dog. Thus, the hyperglycemia which sometimes follows intravenous injection of STH cannot be explained by a release of 5-HT (GALANSINO et al. 1963).

In human subjects, 4 mg 5-HT given intramuscularly or intravenously does not appreciably affect blood sugar level (SCALTRINI 1956).

At least 3 mg/kg of intravenous psilocybin is required to give in rabbits a moderate hyperglycaemic response (CERLETTI 1959, STEINER and SULMAN 1963). Intravenous doses of 50—500 μg/kg tryptamine are inactive on the blood sugar level of the rabbit (WEITZEL et al. 1956). Gramine doses as large as 5—20 mg/kg have no effect on the plasma glucose level of fasting rabbits (POWELL and CHEN 1945).

In thyroid slices or homogenates of beef, pig, sheep and dog, 5-HT (0.2—1 mg/ml) stimulates the oxidation of glucose-1 and 6-^{14}C to $^{14}CO_2$. Tryptamine and 5-methoxytryptamine are approximately half as active as 5-HT. N-acetyl-5-HT, melatonin, 5-HTP and 5-HIAA are inactive. The effects of 5-HT and adrenaline are additive. In a cell-free system fortified with TPNH, 5-HT augments the oxidation of TPNH to TPN (PASTAN and FIELD 1962, HUPKA and DUMONT 1963).

Molluscs. When an excised gill of *Mytilus edulis* or *Modiolus demissus* is incubated in sea water, both the rate of endogenous respiration and the rate of anaerobic glycolysis are stimulated promptly by the addition of 5-HT. Concomitantly there is an increase in lactic acid production. Glucose uptake, on the contrary, is not enhanced by 5-HT. A similar stimulation has been observed to develop slowly in the presence of 5-HTP. In contrast, neither acetylcholine nor adrenaline influence the respiration of excised gill. 5-HT 10^{-5} causes a 75% increase in oxygen consumption, a 30—70% increase in glycolysis and a 50—150% increase in lactic acid production; 5-HT 10^{-7} is completely inactive. 5-HTP is approximately 30—100 times less active than 5-HT and maximal response is not reached until the second hour after addition of the compound. The actions of 5-HT on the carbohydrate metabolism of excised lamellibranch gill cannot be ascribed to an activation of the gill phosphorylase. Similarly, the glycogen that is degraded during incubation of the gill cannot account for all the oxygen that is consumed, indicating that some other substrate within the gill is also oxidized. BOL 10^{-4} M inhibits the effects of 5-HT, while LSD 10^{-4} M mimicks them. It is suggested that the action of 5-HT on carbohydrate metabolism may be responsible for the accelerated ciliary activity that is observed after the addition of the amine (MILTON and GOSSELIN 1960a, 1960b; MOORE et al. 1961; MOORE and GOSSELIN 1962).

The addition of 10^{-6} M 5-HT to the anterior byssus retractor muscle of *Mytilus edulis* produces a gradual increase in the oxygen consumption, which reaches a maximum (40%) after 45 min. It is suggested that the effect is due to an interference of 5-HT in oxydative phosphorylation (BAGUET and GILLIS 1964).

Liver fluke. It has been reported elsewhere that 5-HT stimulates the rhythmical movement of this parasite. This stimulation is accompanied by the following biochemical events when 5-HT is put into contact with *Fasciola hepatica* at concentrations of 10^{-5} M to 10^{-3} M:

a) An increase in the rate of anaerobic glucose uptake.

b) An increase in glycogen breakdown when the organisms are cultured in media containing no glucose. Stimulation of glycolysis also occurs in homogenates of flukes which have previously been incubated with 5-HT when glucose, glucose-6-phosphate or fructose-6-phosphate are used as substrate.

c) A 2- to 10-fold increase in lactic acid production with little or no change in the production of propionic and acetic acids.

d) An increase in phosphorylase activity, with a rapid and specific increase in the formation of adenosine-3′,5′-phosphate or cyclic 3′,5′-AMP.

e) An increase in the activity of phosphofructokinase, the activating effect of 5-HT being dependent upon the presence of a heavy particulate fraction, ATP and Mg^{++} (MANSOUR and LAGO 1958, MANSOUR 1959, MANSOUR and MENARD 1960, MANSOUR et al. 1960, 1961a, 1961b, MANSOUR and MANSOUR 1962).

Stimulation of phosphofructokinase activity can account, at least in part, for the increase in glycolysis by 5-HT in intact flukes (MANSOUR 1962).

It has been suggested that 5-HT may have a direct effect on mechanisms concerned with the uptake and utilization of glucose by flukes (MANSOUR and LAGO 1958, MANSOUR 1959), and that some actions of 5-HT in the liver fluke appear analogous to some actions of catecholamines and glucagon in mammalian liver and to some actions of catecholamines in mammalian skeletal and cardiac muscle (MANSOUR et al. 1960).

2. Action on oxygen consumption

RAPPORT and VIRNO (1952) first observed that 5-HT reduced the rate of oxygen consumption of the rat when injected intraperitoneally in doses of at least 1 mg/kg. The reduction varied in intensity between 24 and 61%, and in duration between 12 and 120 min. A similar effect was obtained with tryptamine and histamine at much higher dose levels. The effect was not observed in other experimental animals, even with enormous amounts of 5-HT. The phenomenon was attributed, at least to a great extent, to the action of the drug on the central nervous system or on the arterial vessels of the brain.

BIANCHI (1957) showed that mice behaved like rats in their response to 5-HT. In fact, 0.85 mg/kg 5-HT given by subcutaneous route lowered the oxygen consumption of the animals by 20—25%.

Similarly, FÖLDES and KOMLÓS (1959) found that 0.4—4 mg/kg 5-HT base, given by the subcutaneous route, produced in rats a significant and prolonged decrease in O_2 consumption and a fall in body temperature when the environmental temperature was 20°, but had no effect when the animals were kept at 30°. Neither adrenalectomy nor previous administration of chlorpyramine, chlorpromazine or reserpine appreciably influenced the action of 5-HT on oxygen consumption while iproniazid pretreatment enhanced it both in normal and adrenalectomized rats. It is suggested that reduction of oxygen consumption is secondary to the vascular effects of 5-HT (FÖLDES and PALINKAS 1960, FÖLDES 1961).

Decrease of oxygen consumption and fall of body temperature produced by 0.8 mg/kg 5-HT at 20° is much more marked in 6-month-old than in 2-year-old rats (FÖLDES et al. 1961, 1962).

DL-5-Iodotryptophan has no significant effect on the oxygen consumption or weight of guinea-pigs (HARVEY 1959).

Results obtained *in vitro* are partly at variance, possibly depending on the different 5-HT dosage. SALGARELLO (1955) and STARBUCK and HEIM (1959) noted an evident depressive action of 5-HT (0.2 mg/ml) on the respiration of liver (—55%) and brain homogenates (—16 to —32%). However, chronic intraperitoneal administration of 5-HT (2 mg/kg daily for 32 days) produced an increase in the oxidative metabolism of liver and brain (SALGARELLO and TURRI 1958). MIETKIEWSKI and JANKOWSKA (1960) found that oxygen consumption of slices of rat brain, kidney, liver and diaphragm was augmented when the animals were killed 15 min after intravenous injection of 4 mg/kg 5-HT base. Similarly, there was an increase in respiration when slices of kidneys or brains taken from untreated rats were incubated with 20—200 μg/ml 5-HT.

3. Action on fat content in peripheral blood

5-HT given subcutaneously to dogs in doses of 0.1 mg/kg increases in peripheral blood neutral fats by 20% after 15 min and decreases phospholipids by 25% over a period of 3 hr. Free cholesterol is slightly above initial levels (MARKIEWICZ 1959).

Oral administration of 0.05—0.2 mg/kg psilocybin produces in human subjects a 100—200% increase in circulating non-esterified fatty acids (KEELER 1963).

4. Action on intestinal absorption of calcium and water

5-HT seems to facilitate the intestinal absorption of calcium. In fact the increase in calcium blood level produced in man by administration of calcium aspartate is further augmented when 40 mg 5-HT base is given by mouth at the same time (TESSARI and PARRINI 1961).

5-HT given to rats intraluminally (2.5 mg) or by i.v. infusion (5 μg/min for 65 min) reduces the speed of tritium-water absorption to about 50%. This effect may be caused by a change in intestinal capillary blood flow or an inhibition of active water transport.

When 5-HT is infused intravenously, but not when it is given into the intestinal lumen, the concentration of tritium-water in blood is found to be higher than in controls. This reduction of the tritium-water space can be explained by concomitant vasoconstriction (LEMBECK et al. 1964).

5. Miscellaneous metabolic effects

5-HT (1 mg/kg), LSD and BOL (0.25 mg/kg), all decrease the incorporation of ^{35}S-methionine into brain proteins. The ATP content of the rat brain is greatly reduced following administration of 5-HT alone, much less reduced in groups of animals receiving 5-HT plus LSD, and is increased in groups given 5-HT plus BOL (KRAWCZYNSKI et al. 1958, KRAWCZYNSKI 1961).

6. Inhibition of lipide peroxide formation in tissues

5-HT is a very powerful inhibitor, as an anti-oxidant, of lipide peroxide formation in tissues. 6—10 μg/ml 5-HT completely blocks the lipide peroxide formation by rat liver mitochondria, and 1 μg/ml still shows appreciable activity.

5-Hydroxyindoleacetaldehyde has approximately the same activity as 5-HT; tryptamine, bufotenine and adrenaline are less active; tyramine, dopa, mescaline and indoleacetic acid are essentially without effect.

According to BERNHEIM et al. (1957) it is not possible to state that the antioxidant activity of 5-HT explains any of its physiological actions. This activity, however, may be of some importance in the radiation protection given by 5-HT injected immediately before exposure.

7. Action on cholinesterases

The hydrolysis of acetylcholine, butyrylcholine, procaine and murexine by plasma cholinesterase is inhibited by high concentrations of 5-HT (50% inhibition of the enzyme is attained at 7.1×10^{-4} M to 3.2×10^{-3} M concentrations of the amine, depending on the substrate), tryptamine (5.6×10^{-4} M to 5×10^{-3} M) and gramine ($1.3—6.3 \times 10^{-4}$ M) (LANGEMANN 1954, ERDÖS et al. 1956, 1957), but markedly potentiated by lower concentrations of 5-HT (31% augmentation at 5×10^{-6} M) (FRIED and ANTOPOL 1957). Bufotenine has been recognized as a strong inhibitor of serum cholinesterase since 1937 by SOBOTKA and ANTOPOL, who called attention to the structural analogy between this indolealkylamine and eserine. ZSIGMOND et al. (1961a) have now shown that bufotenine and psilocybin inhibit plasma cholinesterase more than 5-HT. An inhibitory effect of 5-HT is also seen on hydrolysis of acetylcholine by red cell cholinesterase (LANGEMANN 1954). On this enzyme tryptamine and psilocybin are approximately as active as 5-HT, bufotenine and gramine 20 times more active (ERDÖS et al. 1956, ZSIGMOND et al. 1961a, 1961b).

Surprisingly enough the hydrolysis of benzoylcholine by plasma cholinesterase is conspicuously activated by tryptamine, whereas 5-HT, 5-HTP and N,N-dimethyltryptamine possess no marked activating effect (ERDÖS et al. 1957a, 1957b).

On the cholinesterase from rabbit caudate nucleus homogenates, 5-HT produces at final concentrations of 10^{-3} M, 5×10^{-3} M, and 10^{-2} M an inhibition of 29, 63 and 100%, respectively. Since marked inhibition occurs only at fairly high concentrations of 5-HT, APRISON (1960) suggests that the action of the amine at normal physiological levels might be to compete with acetylcholine for acetylcholine-receptor proteins, whereas at elevated levels, such as after administration of large doses of 5-HTP, the amine would inhibit cholinesterase. Thus the sedative effect seen after moderate doses of 5-HTP might be the result of the block of normal acetylcholine action, whereas the stimulatory effect seen after large doses of 5-HTP might be due to the increased accumulation of acetylcholine after cholinesterase inhibition.

The rat brain cholinesterase is inhibited by large concentrations of 5-HT (0.5 mg/ml and more) when the amine is added to the incubation mixture prior to the substrate, but is activated, with a maximum in the first 5 min (20—150%), when the amine is added at the same time as the substrate (TONINI 1955).

Human grey matter cholinesterase requires a 10^{-2} M concentration of 5-HT for a 50% inhibition (ZSIGMOND 1961b).

5-HT has no inhibitory effect, up to 10^{-3} M concentration, on brain cholinesterases, as evidenced by the KOELLE'S histochemical method (FÖLDES et al. 1959).

The inhibitory effect of psilocybin and 5-HT on grey matter cholinesterase is identical. This indicates that there is no correlation between the *in vitro* anticholinesterase activity of indolealkylamines and their hallucinogenic effekt (ZSIGMOND et al. 1961a).

8. Action on ceruloplasmin

5-HT, 5-HTP, 5-HIAA and bufotenine (0.38 μM/ml), but not tryptamine, indole acetic acid and indole propionic acid are capable of inhibiting the oxidation of N,N-dimethylparaphenylendiamine by purified plasmin and serum oxidase (Aprison et al. 1959).

Like catecholamines, 5-HT (1.5×10^{-4} M) is capable of mediating the oxidation of reduced phosphoridine nucleotides, DPNH and TPNH, in the presence of ceruloplasmin. It is suggested that the free radical semiquinones of the amines formed by the action of ceruloplasmin are the possible electron acceptors during the oxidation of DPNH and TPNH (Walaas and Walaas 1961a, 1961b).

9. Action on phenol oxidases

5-HT and, to a lesser degree, other indolealkylamines, inhibit the phenol oxidases of *Fasciola hepatica* and *Tenebrio molitor* (competitive inhibition) as well as the melanoma phenol oxidase (non-competitive inhibition), but display no effect on mushroom and potato phenol oxidases. For total inhibition of liver fluke phenol oxidase 2 mg/ml 5-HT is required, but partial inhibition is already appreciable with 0.02 mg/ml. 5-HT, 5-HTP and bufotenine are not oxidized by the liver fluke oxidase (Mansour 1957, 1958).

The tyrosinase prepared from mouse melanoma is significantly inhibited by 5-HT, 5-HTP, 5-HIAA and also by 5-hydroxyindole at relatively low concentrations ($< 10^{-4}$ M). Melatonin, indoleacetic acid and other tryptophan metabolites exert some inhibitory effect only at higher concentrations (10^{-2} M) (Seiji 1961).

10. Miscellaneous effects on enzymes

Tryptophan pyrrolase. Many tryptophan analogs effectively block the conversion of tryptophan to kynurenine in the tryptophan pyrrolase reaction. Among the most effective are 5-HT, 5-HTP and tryptamine, which produce 81, 79 and 48% inhibition, respectively, at a 5×10^{-4} M concentration (Frieden et al. 1961).

Tyrosine transaminase. 5-HT and 5-HTP are much more potent inhibitors *in vitro* of tyrosine transaminase of rat liver than catecholamines. Tryptophan, tryptamine and 5-HIAA also have some inhibitory activity but indole is inactive (Jacoby and La Du 1962).

Brain enzymes other than cholinesterase. 5-HT (10 mM) shows no action either on the alkaline phosphatase or on the lactic or malic dehydrogenase of rat brain homogenates (Clark et al. 1956), nor does it inhibit *in vivo* oxidative phosphorylation in the rat brain, as determined by the uptake of ^{32}P (Lingjaerde and Skaug 1957).

However, subcutaneous administration for 7 days of 0.2 mg/kg 5-HT, seems to increase moderately both phosphatase and acetylcholinesterase activity in the hypothalamic magnocellular nuclei of the rat brain, leaving unaffected succinic dehydrogenase activity, as shown by histochemical methods (Kivalo et al. 1958a). Bufotenine slightly inhibits brain lactic dehydrogenase (Clark et al. 1956), while activating alkaline phosphatase. Oxidative phosphorylation in preparations of brain mitochondria is, on the contrary, unaffected by concentrations of bufotenine as high as 10^{-3} M (Bain 1957).

Psilocybin does not display any effect on choline acetylase at a concentration of 10^{-7} M; however, at a 10^{-8} M concentration it potentiates the action of the enzyme. 5-HT is without effect in concentrations of 10^{-7}—10^{-6} M. At the same

concentrations 5-HT inhibits coenzyme A while psilocybin has no effect (Bošković and Pržić 1961).

Thyroxine-degrading enzymes. 5-HT, 5-HTP, 5-HIAA, 3-hydroxyanthranilic acid, xanturenic acid and reserpine (2×10^{-3} M) all depress the degradation of thyroxine to inorganic iodide by homogenates of mammalian and amphibian tissues. In the presence of 5-HT increased amounts of tetraiodothyroacetic acid are formed in certain tissues. Both 5-HT and reserpine also inhibit the formation of iodide from triiodothyronine, whereas the deiodination of mono- and diiodotyrosine by mouse liver homogenate is not altered by the presence of 5-HT. Deiodination *in vitro* is not influenced significantly by the administration of tryptophan derivatives *in vivo* (Galton and Ingbar 1961).

Hyaluronidase. Hyaluronidase effects are inhibited by 5-HT (Ezer and Szporny 1961).

XIV. Action on chromatophores

1. 5-Hydroxytryptamine

Frog skin chromatophores. Both in *Rana esculenta* and in *Rana pipiens* high doses of 5-HT injected into the dorsal lymph espace produce a dispersion of the pigment in the melanocytes, i.e. a darkening of the skin. In *Rana esculenta* doses of 5-HT base above 0.5 mg/frog are required to produce this effect, which reaches its maximum within $1^1/_2$ hr and disappears after 5—6 hr (Kahr and Fischer 1957). In *Rana pipiens* the effect is apparent within 15 min after injection of 0.1—1 mg 5-HT or tryptamine and lasts an additional 15—30 min, then the pigment returns to its normal contracted condition (Davey 1959). According to Kahr (1957) the phenomenon is mediated through release of the melanocyte-stimulating hormone, but Davey has observed darkening of the skin even in hypophysectomized specimens of *Rana pipiens.* Davey (1960) suggests that not 5-HT but rather intermedin may act on the frog skin indirectly, through release of an indolealkylamine.

Van de Veerdonk (1960) and Burgers et al. (1962) have confirmed the pigment-dispersing activity of 5-HT also on the melanophores of *Xenopus laevis.*

Fish cromatophores. The effect of 5-HT on fish chromatophores seems extremely variable depending upon the species. Whereas the drug is completely inactive, both *in vivo* and *in vitro*, on the melanophores of *Lebistes reticulatus* (Cerletti and Berde 1955, Berde and Cerletti 1957) it appears highly active on the chromatophores of other species. Turner (1958), for example, observed that 2—3 μg 5-HT base injected just beneath the scales produced a local constriction lasting half an hour, and that on the dilated chromatophores of the tail fin, which had been cut off, a 5-HT solution of 0.5 μg/ml led to contraction beginning within 10 min.

Although per se inactive, 5-HT and 2,3-dihydro-5-HT are capable, given in high doses, of antagonizing the chromatophore-expanding action of LSD and BOL, as seen in *Lebistes reticulatus* (Cerletti and Berde 1955, Berde and Cerletti 1957, Fellman et al. 1962).

Chromatophores of cephalopoda. Both the chromatophores of *Loligo pealii* (Rosenblum and Zweifach 1959) and those of *Octopus vulgaris* (Kahr 1958) are closed by 5-HT and tryptamine, the threshold concentration for 5-HT and *Octopus* chromatophores being 0.01 μg/ml. The same effect is produced by LSD and by MAO inhibitors. It has therefore been suggested that chromatophore control is achieved in cephalopoda by an amine-amineoxidase system (closure) opposed by an acetylcholine-cholinesterase system (expansion) (Rosenblum and Zweifach 1959).

2. Melatonin

Melatonin, 5-methoxy-N-acetyltryptamine, while apparently devoid of any other important pharmacological activity, possesses a tremendously intense effect of lightening or paling on frog, toad and fish melanocytes.

The most sensitive preparation seems to be the skin of *Rana pipiens*, previously darkened with caffeine or MSH. For measurable lightening of this skin the following concentrations of melatonin and related amines are required, in μg per ml: melatonin 1×10^{-7}, tryptamine 2×10^{-1}, N-acetyltryptamine 5×10^{-2}, 5-HT 1, 5-hydroxy-N-acetyltryptamine 6×10^{-3}, 5-methoxytryptamine 2×10^{-6}, 5-ethoxytryptamine 5×10^{-2}, 5-ethoxy-N-acetyltryptamine 10^{-5}, 5-methoxy-N-methyltryptamine 2×10^{-1}, 5-methoxy-N-formyltryptamine 2×10^{-4}, 5-methoxy-N-propionyltryptamine 1×10^{-7}, 5-methoxy-N-butyryltryptamine 1×10^{-7}, 5-acetoxy-N-acetyltryptamine 5×10^{-3} (LERNER et al. 1958, CASE and WRIGHT 1960, LERNER and CASE 1960). By microscopic bioassay 0.01 ng melatonin can be detected (MORI and LERNER 1960). In lightening the chromatophores of *Rana pipiens* melatonin is far more potent than adrenaline or triiodothyronine.

On the melanophores of *Scardinius erythrophtalmus* pretreated with caffeine the closing effect of melatonin reaches its maximum at concentrations ranging from 1 ng to 1 μg/ml. Melatonin, however, seems to be less potent than adrenaline (MIRA 1962).

Intracutaneous injections of 50 μg melatonin into an adult man produced erythema, which faded within an hour. However, when 100 μg was given a punched-out ulcer appeared at the injection site 2—4 days later. No depigmentation was observed and there was no increase in local sweating. One patient, given 200 mg melatonin intravenously experienced mild sedation. Numerous metabolic tests made before and after the patient received 200 mg melatonin daily for 5 days revealed no change (LERNER and CASE 1960).

The enormous interest in the discovery of melatonin is obvious, and future studies will solve the fascinating problem of whether this hormone is involved in the function of chromatophores in human skin and in the pathogenesis of vitiligo and malignant melanomas (LERNER and CASE 1959, 1960; LERNER et al. 1959).

XV. Action on endocrine glands. Inter-endocrine correlations

1. Anterior hypophysis

ACTH. BERTELLI et al. (1954) first observed that 5-HT given intravenously or injected into the cisterna magna of the dog in doses of 20—40 μg/kg significantly reduced the number of circulating eosinophils, and injected intraperitoneally into the rat in doses of 0.2—0.8 mg/kg moderately reduced the ascorbic acid content of the adrenal glands. The effects were ascribed to a stimulation of the anterior pituitary with ensuing release of ACTH.

The results of BERTELLI and co-workers were generally confirmed. Concerning the ascorbic acid depletion of the adrenal glands, MOUSSATCHÈ and ALVARES PEREIRA (1956) claim to have obtained in the rat a 20% depletion (from 338 to 267 mg/100 g) with intravenous 5-HT doses as low as 10 μg/kg, and a 30—35% depletion with doses of 250 μg/kg, whereas SMELIK and DE WIED (1958a, 1958b) obtained only a 15% reduction with 100 μg/kg 5-HT base. Reduction of the ascorbic acid in the adrenals was missing in hypophysectomized rats, in rats with hypothalamo-hypophysial connections interrupted by electrolytic lesions in the caudal eminence one week previously, and in rats whose hypothalamus was blocked by intraperitoneal injection of 50 mg/kg prednisone 24 hr previously.

FIORE-DONATI, POLLICE and CHIECO-BIANCHI (1959) similarly observed a remarkable decrease in the ascorbic acid content of the adrenal and the preputial glands of rats sacrificed 2 hr after the subcutaneous injection of 4 mg/kg 5-HT base. Decrease in adrenal glands was similar both in intact and ovariectomized rats (23.4 and 23%, respectively), decrease in preputial glands was greater in ovariectomized rats. The weight of the adrenals remained unchanged.

In regard to the eosinopenic action of 5-HT, HALBERG (1954) found that in the mouse 5-HT and cortisone acted reciprocally to potentiate their eosinopenic effects. Indeed, the combined administration of non-eosinopenic doses of cortisone reinforced the eosinopenic effect manifested by 5-HT doses of 0.125, 1.25 and 12.5 mg/kg, and conversely the effect upon the number of eosinophils induced by cortisone in 0.3 and 3 mg/kg doses was strengthened by a non-eosinopenic dose of 5-HT (21.5 μg/kg). HALBERG considers the eosinopenic effect of large doses of 5-HT as a pure pharmacological effect, but believes that the synergism between 5-HT and cortisone may have physiological significance and may be listed among the factors interfering with the production of "eosinophil responses".

MILKOVIĆ and SUPEK (1956) confirmed in the rat the eosinopenic effect of large doses of 5-HT (3 mg/kg) and further stated that LSD (20—120 μg/kg) failed to prevent the eosinopenic action of the amine. 5-HT doses of 150 to 300 μg/kg were completely ineffective.

Finally, reduction in the number of circulating eosinophils following 5-HT administration was observed in the rat also by STEINER and HEDINGER (1956) [from 1000 to 600 per mm^3 after 50 mg/kg 5-HT] and by SERRA and BRUNI (1957) [from 150 to 90—100 eight hours after subcutaneous injection of 2—20 mg 5-HT].

At variance with the above results which, on the whole, are suggestive of a possible "pharmacological" activation of the hypophysary-adrenocortical axis, are the experimental data of GEORGES (1957) and GEORGES and HEROLD (1958). These investigators found that following repeated administration of large doses of 5-HT (2—8 mg/kg daily for 5 successive days, intraperitoneally) there was an inhibition of the reduction of ascorbic acid in the adrenal glands produced by adrenaline, vasopressin, histamine and formalin. They suggest that 5-HT provokes an elective inhibition of the ACTH secretion by the anterior pituitary.

The reason for these strikingly divergent results is not clear. It is possible that it resides in the different dosage schedule of 5-HT. It is perhaps a matter of dosage also that led to the negative finding of SCHEIFFARTH et al. (1961) and of SCHWEMMLE et al. (1961) who could not detect in man any significant change either in the number of eosinophils or in the excretion of 17-ketosteroids following intravenous administration of 10 to 40 mg 5-HTP.

Growth or somatotropic hormone. LABORIT and co-workers (1959a, 1959b, 1959b, 1959d, 1959e) found that growth hormone given subcutaneously to rabbits increased urinary excretion of 5-HIAA, the smaller doses being more effective than the larger ones. With a single injection of 2 Evans u. urinary 5-HIAA rose from the normal 32 ± 16 μg per day and per rabbit to 305 μg (!), with 4 u. to 111 μg, with 20 u. to 161 μg. Isoniazid, administered as a MAO inhibitor (6—12 mg/kg), antagonized the effect of STH. Repeated administration of 2 u. STH on successive days produced effects of decreasing intensity (305 μg 5-HIAA during the first day, 60 μg during the third day).

The above rather surprising observations, together with the observation that 5-HT stimulates the growth of young plants and possesses anti-oxidant properties, are at the root of LABORIT's theory that 5-HT is an essential growth factor favour-

ing anaerobic processes. However, it seems that more evidence must be gathered before LABORIT'S data and conclusions can be accepted.

In dogs the injection of STH into the femoral vein causes no significant rise of 5-HT in the pancreatic blood. This makes it unlikely that the type of hyperglycaemic substance which is released by growth hormone from the area drained by the pancreato-duodenal vein is 5-HT (FOÀ et al. 1962).

Gonadotropins. ROBSON and BOTROS (1960, 1961) found that the administration of 5-HT to immature, 3-weeks-old female mice (1—25 mg/kg 5-HT base, s.c., daily for 18—35 days) produced a marked depression of the growth of the ovaries, uterus and vagina as well as a delay in the opening of the vagina and in the onset of vaginal oestrus. There was little or no effect on body growth. Given to mature female mice, at daily doses of 20—25 mg/kg for 2 weeks, 5-HT produced some inhibition of the oestrus cycle and marked depression of the weight of the sex organs.

ROBSON and BOTROS conclude that the above results strongly suggest that the effect of 5-HT is exerted either on the pituitary itself or on some part of the brain which controls pituitary gonadotropic secretion.

On the other hand, the same group of research workers (BOTROS et al. 1961, LINDSAY et al. 1961, 1962) observed that 5-HT and iproniazid were capable of producing not only interruption of pregnancy, possibly through an action on the placenta, but also marked disorganization of experimental deciduomata in mice. In order to elicit experimental decidual reaction, the females were mated with castrated males implanted with testosterone propionate pellets and on the fourth day after mating the uteri were traumatized by passing a double cotton thread along both horns. 5-HT was given subcutaneously or intraperitoneally at doses of 0.2—0.4 mg base per mouse.

The toxic effects of 5 HT could be prevented by the simultaneous administration of progesterone and, to a lesser extent, of luteotrophin.

ROBSON and co-workers were unable to decide whether 5-HT acted directly on the placenta or the corpus luteum, or indirectly through the pituitary or the centres in the brain responsible for controlling pituitary activity.

However, not all the above experimental results could be duplicated by other investigators. DE MELLO (1957) failed to detect any change in the macroscopic or microscopic aspect of the ovaries or any sign of follicular haemorrhage or follicular increase in the ovaries of rabbits treated, 48 hr previously, with intravenous or intracarotid injections of 0.2—5 mg/kg 5-HT base. He concluded that 5-HT does not play any role in the mechanism of liberation of gonadotropic hormones.

DISCHLER (1960) could not find any influence on the oestrus cycle of the mouse of either 5-HT (20—40 mg/kg, subcutaneously or intramuscularly, daily for 4 weeks) or iproniazid (120 mg/kg per os daily for 8 weeks) alone, or of the combination of the two drugs.

CZYBA and CHIRIS (1962), on the other hand, observed that whereas 5-HT hindered experimental traumatic decidual reaction in rats, it had no effect on rabbits and enhanced decidual reaction in hamsters. The doses of 5-HT base administered daily for 11 days were 10 mg/kg i.p. in rats, 2—5 mg/kg i.v. in rabbits and 4—10 mg/kg i.p. in hamsters.

Prolactin. POLLICE and MAIORANO (1958) first observed that daily subcutaneous administration, for 20 days, of 4 mg/kg 5-HT base displayed in the rat an evident stimulant effect on the growth of mammary glands, with hyperplasia of the duct system and lobulo-alveolar development. Effects were particularly evident in ovariectomized animals.

MEITES and co-workers (MEITES et al. 1959, MEITES and HOPKINS 1960) noted that in mature virgin rats, daily subcutaneous injections of 20 μg reserpine or 0.2 mg 5-HT base/kg for 5 days, preceded by daily injections of 10 μg estradiol for 10 days, initiated milk secretion and induced growth of mammary lobulo-alveolar tissue. When either drug was injected with estradiol for 10 days, mammary growth was greater than with estradiol alone, but there was little evidence of milk secretion. Injections of 5-HT and reserpine alone for 21 days failed to elicit mammary growth or secretion. Injections of 5-HT or reserpine for 10 days following litter removal on 4th day after parturition retarded mammary involution and maintained secretory function. In rats hypophysectomized after estrogen-priming the drugs were inactive in provoking mammary responses.

Induction of mammary growth and lactation is provoked by 5-HT (2 mg 5-HT base once daily, for 5 days, s.c.) also in estrogen-primed rabbits. 5-HT is more active than adrenaline or acetylcholine (MEITES et al. 1960).

Finally, lactation may be induced in normal rabbits by daily intracranial injection, into the hypothalamic region, of 4 mg 5-HT base in 1 ml physiological saline (KEHL et al. 1962).

It is concluded from the above results that 5-HT and reserpine stimulate in rats and rabbits secretion of prolactin and perhaps other factors by the pituitary favourable to mammary growth and lactation.

Effects of hypophysectomy. The influence of lack of all the hormones of the hypophysis, as produced by hypophysectomy, on the level of 5-HT in rat tissues is controversial.

DE MAIO (1959) found a reduction of the 5-HT concentration in serum (from 0.5 to 0.2 μg/ml) and an increase of the 5-HT level in the medulla oblongata (from 0.37 to 0.84 μg/g) and brain stem (from 0.97 to 1.54 μg/g), but these results could not be duplicated by YEH et al. (1959). GHIRINGHELLI et al. (1961 b) observed that both the number of enterochromaffin cells and 5-HT concentration were decreased in the small intestine 28 days after hypophysectomy, and that intraperitoneal administration of STH (15 Evans units in the last 7 days) prevented to some extent the effects of hypophysectomy, but RESNICK et al. (1961) were unable to detect any change in brain or tissue 5-HT, including gastrointestinal 5-HT, either following removal of hypophysis or administration of corticotropin (10 units for 10 days).

2. Supraoptico-hypophyseal tract

Daily subcutaneous doses of 0.2 mg/kg 5-HT base administered for 7 days produce in rats:

a) A decrease of the neurosecretory material in the posterior lobe of the hypophysis as well as in the cells of the supraoptic and paraventricular nuclei, with no change or even increase of the quantity of neurosecretory material going into the portal vessels in the region of the median eminence.

b) An increase in the nucleus and nucleolus volume in the cells of the nucleus supraopticus (KIVALO et al. 1958a, 1958b, HECKMANN et al. 1964).

c) A moderate increase of acetylcholinesterase and phosphatase activity of the hypothalamic magnocellular nuclei (KIVALO and RINNE 1959).

KIVALO and co-workers conclude from the above findings that 5-HT stimulates the activity of the supraoptico-hypophyseal tract, and that 5-HT antidiuresis seen in rats after 5-HT administration is due, at least in part, to an increased release of antidiuretic hormone.

3. Adrenals

ROSENKRANTZ and LAFERTE (1959, 1960) observed that the *in vitro* addition of 5-HT (40—400 μg base per pair of adrenals) produced the release of a blue tetrazolium-reactive reducing material, possibly steroid in nature, from the adrenals of rabbits, guinea-pigs, rats and cows, as well as from a human adrenal tumour which appeared cortical in nature. The releasing-activity of 5-HT, which was protected by iproniazid but completely inhibited by amphenone, appeared to be highly specific, as demonstrated by the failure of several other indolealkylamines, among which were 4-HT and 6-HT, to imitate the effect of 5-HT.

28 to 54% of added exogenous 5-HT was taken up by the adrenal tissue. Rabbit adrenal showed the least uptake in comparison with that of the dog, the cow and the rat, but released the greatest amount of blue-tetrazolium reducing materials. 5-HT was found to elevate oxygen consumption of the adrenals from all species. None of the observations on the uptake of 5-HT, release of reducing material or stimulation of oxygen consumption could be correlated with the dietary habits of the animals. The 5-HT action on the adrenals appeared to be dependent upon a functional oxidative phosphorylating system since the absence of oxygen and the presence of cyanide or dinitrophenol abolished the 5-HT response, whereas adenosine diphosphate augmented it. The optimal concentration for stimulation of adrenals was 80 μg 5-HT base/100 g tissue, and the optimal incubation period for the 5-HT stimulated release of reducing material was 90 min (CONNORS and ROSENKRANTZ 1962).

The above observations have been substantially confirmed and extended by others. CORMIER and JOUAN (1962) found that addition of 5-HT to the incubation liquid of slices of rat adrenals (65 μg 5-HT base per 100 mg adrenal tissue) produced a 30% increase in the secretion of aldosterone and steroid X2, leaving unaffected that of corticosterone, 11-deidrocorticosterone and steroid X3. It is concluded that 5-HT possesses a direct and selective action on corticogenesis. VERDESCA et al. (1961), in their turn, noted that 5-HT given by direct arterial perfusion of the adrenal glands of the hypophysectomized dog (20 μg/min) stimulated the secretion of hydrocortisone to a degree comparable to that seen during ACTH stimulation (1 u/min). Measurable quantities of corticosterone were also secreted. It is suggested that these findings offer a possible explanation of the sodium and chloride retention seen in man and animals following 5-HT administration.

It has been claimed that adrenalectomy produces in rats a decrease of 5-HT in serum (from 0.5 to 0.12 μg/ml) and an increase of 5-HT levels in the hemispheres (from 0.85 to 1.95 μg/g), brain base (from 0.97 to 1.15 μg/g) and medulla oblongata (from 0.37 to 1.4 μg/g) (DE MAIO 1959, SOFER and GUBLER 1962) as well as a progressive increase in the urinary excretion of 5-HIAA, the average 24 hr output being about 70% higher on the 4th and 5th day after adrenalectomy than during the four days before the operation (ENERBACK 1960).

Similarly, HICKS and WEST (1958) found that adrenalectomized rats given water presented a two-fold increase of the 5-HT levels in skin, ears, feet, liver and lung, whereas amine levels in adrenalectomized rats given saline remained normal. Not all the above results could be confirmed. TOWNE and SHERMAN (1960), for example, were unable to detect in rats any influence of acute bilateral adrenalectomy on brain 5-HT level, RESNICK et al. (1961) failed to reveal any change in the 5-HT content of brain and gastrointestinal tract, PFEIFER et al. (1963) found 3—7 days after adrenalectomy a decrease in the rat brain 5-HT from 0.69 to 0.31 μg/g.

PUT and MEDUSKI (1962b) observed in rats subjected to acute bilateral adrenalectomy a biphasic change in the metabolism of 5-HT. In the first post-operative phase (up to 24 hr after surgery) there was an immediate increase in urinary 5-HIAA excretion (up to 200%) with unchanged brain 5-HT level; in the second post-operative phase 5-HIAA returned, more or less promptly, towards normal whilst brain 5-HT level appeared reduced to 12—15% of that of control rats. On the basis of these results PUT and MEDUSKI put forward a questionable theory on probable mechanism of binding and release of 5-HT by tissues.

Daily intramuscular injections of cortisone, prednisolone, triamcinolone, dexamethasone, fludrocortisone and 2-methylfludrocortisone are found to lower the 5-HT level in the skin and small intestine of normal rats (in spleen no 5-HT depletion is noted and the stomach presents, instead of a decrease, an increase in the amine content), to retard the recovery of 5-HT in the skin depleted of the amine by prolonged treatment with polymyxin or with compound 48/80, and to restore to normal the increased 5-HT concentration seen in the skin of adrenalectomized rats. Sex hormones are weaker in these effects, while mineralocorticoids and corticotrophin are inactive. Corticosteroids have no effect on the dopa-decarboxylase activity either of kidney or of liver (HICKS and WEST 1958; WEST 1959; TELFORD and WEST 1960, 1961; CASS and MARSHALL 1962). On the basis of all these results, TELFORD and WEST (1961) suggest that the tissue reserves of 5-HT, like those of histamine, may be in part regulated in rats by the secretion of the adrenal cortex.

Adrenalectomized rats given saline and DOCA show after 10 days a 45% increase of the 5-HT content of the small intestine, accompanied by a similar increase in the number and granular charge of the enterochromaffin cells of the duodenum (GHIRINGHELLI et al. 1961a).

In man glucocorticoids produce an increase in the urinary excretion of 5-HIAA, both following single and repeated doses (SCHWEMMLE et al. 1961).

It is well known that large doses of subcutaneous 5-HT are capable of eliciting in rats acral swelling. BOIS and SELYE (1956) observed that oedema produced by 5-HT (10 mg/kg, s.c.) in adrenalectomized animals was most pronounced after administration of DOCA, 100 μg/day, slightly less so after maintenance on 1% NaCl only or administration of DOCA plus cortisol, and almost completely absent after administration of cortisol acetate, 400 μg/day.

The report of DAVIS and KENNEDY (1962) concerning a case of carcinoid syndrome associated with adrenal hyperplasia is of interest.

4. Thyroid

ZIZINE (1959) and D'ADDARIO et al. (1963) found that single or repeated injections of 5-HT (e.g. 1—2 mg/kg 5-HT base s.c. every second day for 20 days) produced in rats a decrease of thyroid activity, as studied by means of radioactive iodine, and histological signs of atrophy of the parenchymal cells. SALABE' et al. (1963), on the contrary, were unable to detect any significant difference in the ^{131}I uptake by the thyroid gland of rats given 5-HT (3 mg/kg i.m. for 7 days) and of control rats.

In the rabbit, daily intramuscular administration for 4 months of 2 mg/kg 5-HT produces, according to CARLIER et al. (1960) increase in weight and vascularity of the thyroid gland with histological signs of hyperactivity. Similar, but less pronounced results, may be obtained with 5-HTP.

40 μg 5-HT base put onto the surface of a chicken embryo on the 3rd or 9th day of incubation causes a significant increase in the uptake of radioactive iodine

by the thyroid tissue, eventually preceded by a decrease. MARAUD et al. (1962) suggest that this effect may be secondary to the vascular changes produced by the amine.

All research workers agree that thyroidectomy does not change the 5-HT content of brain and other tissues of the rat (TOWNE et al. 1959, RESNICK et al. 1961, PUT and HOGENHUIS 1962). On the other hand, administration of thyroid hormone or antithyroid compounds seems to produce different results in different tissues.

The 5-HT level in the rat brain, for example, is significantly increased (from 0.56 to 1.01 and 0.92 μg/g, respectively) both after subcutaneous injection of L-thyroxine (500 μg/kg daily for 14 days) and after administration ad libitum, for 14 days, of a 0.075% solution of propylthiouracil (TOWNE et al. 1959, PUT and HOGENHUIS 1962). However, feeding for 21 days a meal containing 0.15% strong desiccated thyroid produces a decrease of heart 5-HT only in female rats (from 0.8 to 0.54 μg/g) with no significant effect in males, and feeding a meal containing 0.15% propylthiouracil causes no significant change of heart 5-HT either in male or female rats (SKILLEN et al. 1962).

Similar ambiguous results have been reported in man. In fact, the increased urinary excretion of 5-HIAA seen in thyrotoxic patients by SKANSE and HANSON (1962) has not been observed by KUSCHKE et al. (1962).

The subcutaneous administration of 1 mg/kg melatonin, every day for 10 days, produces in the rat a 20% reduction in thyroid weight, a decrease of nearly 50% in cell height, a prevention of thyroid hyperplasia by methylthiouracil and finally a drastic reduction (from 42.2 to 2%) in the uptake of radioactive iodine by the thyroid gland. This inhibitory effect of melatonin on thyroid function is ascribed by BASCHIERI et al. (1963) to an inhibition of either the secretion of the thyrotropic hormone or the action of this hormone on the thyroid gland.

5. Pineal gland

It has been suggested by JOUAN (1963), without any persuasive evidence, that the factor secreted by the pineal gland which induces secretion of aldosterone is closely related to 5-HT.

6. Testes

5-HT (3—6 mg/kg, s.c.) and histamine (100—200 mg/kg) when administered either separately or in combination, cause weight increase of the mouse prostate gland (from 33.4 to 68.3 mg/100 g) and histological changes indicative of edema or vascular defect. Pathological changes in testes of treated mice include degenerating seminiferous tubules that contain spermatogonial cells with pyknotic nuclei and giant multinucleate cells. O'STEEN (1963) suggests that the above histological changes are not necessarily dependent upon vascular effects of the two amines.

Rats subjected to orchidectomy or injected with testosterone cyclopentylpropionate (three 7 mg doses, one dose every three weeks) show no change in tissue 5-HT (RESNICK et al. 1961).

Male specimens of *Rana esculenta* present in 73% of cases an ejaculation when 5 mg 5-HT is injected into the dorsal lymphatic sac. Maximum response is observed after 5 hr. This gametokinetic activity is ascribed to pituitary stimulation (SALVADORI et al. 1962).

7. Ovary

Daily injections, for 28 days, of microgram amounts of melatonin (20 to 200 μg/kg, i.p.) in rats decrease the incidence of oestrus and reduce ovarian weight. This effect is reduced by exposure of the rats to constant light. Circulating exogenous melatonin is selectively taken up and retained by the ovary and pineal gland. On the basis of these and other experimental results (cf. pag. 152—153) WURTMAN et al. (1963, 1964) and AXELROD et al. (1964) suggest that it is possible that some of the effects of the pineal gland on gonad function of rats are mediated by melatonin, and similarly that some of the effects of lighting on bird gonads are mediated by alterations in the rate of synthesis of melatonin in the pineal gland.

This may certainly be true, but it should be pointed out, however, that in spite of all appearance, the doses of melatonin injected into the rat by WURTMAN and his colleagues are very high, if compared with the content of endogenous melatonin in the rat pineal gland [1—3 ng/pineal, according to QUAY (1964)], and with the melatonin-synthesizing capacity of the rat pineal gland [2.5—5 ng/hr/pineal, according to WURTMAN et al. (1964)].

8. Pancreas

On the basis of experiments carried out *in vitro* on the rat diaphragm, UI (1962b) suggests that 5-HT is a physiological "accelerator" of insulin secretion in the organism.

The concentration of 5-HT in the dog blood is not affected by total pancreasectomy (LOUBATIÈRES et al. 1963).

It is highly probable that endocrine glands, neurohormones and tissue hormones interfere in the biosynthesis, release and metabolism of 5-HT, as well as in the physiological actions of the amine. However, up to the present time, meagre information is available on the most intimate biochemical and functional correlations existing between 5-HT and other hormones or active tissue products. In fact, very often doses of 5-HT which have been found to elicit responses by endocrine glands are far beyond physiological limits and, on the other hand, removal of endocrine glands or administration of hormones have frequently given conflicting or ambiguous results.

XVI. Protective action of indolealkylamines in experimental tissue injury

1. Radiation injury

Since the first communication by GRAY et al. (1962) a considerable number of research papers has been devoted to the description of the protective effects of 5-HT and related indolealkylamines against ionizing radiations. In addition to the authors quoted in the text see also, for complete information on the topic, BRAUN et al. (1960), HIETBRINK et al. (1961), PANASEWICZ et al. (1961), TRICOU and DOULL (1960b, 1961), WANG et al. (1961), VENINGA and BRINKMAN (1962). FRANZEN (1962), VITTORIO et al. (1963), DOULL et al. (1963), ZHEREBCHENKO et al, (1963).

a) Reduction of radiation lethality

Mouse. The most extensive investigation on the protective effect of indolealkylamines has been carried out in the mouse.

Protection afforded by different intraperitoneal doses of 5-HT against whole-body irradiation with 810 r is as follows, according to LANGENDORFF et al. (1958):

5-HT dose	Survival rate (%) after 30 days
Nil (controls)	2
0.2 mg/mouse	31
0.4 mg/mouse	80
0.6 mg/mouse	53
0.8 mg/mouse	72
1.0 mg/mouse	82
1.5 mg/mouse	58

Essentially similar results have been obtained by BACQ (1954), TRICOU and DOULL (1960a, 1960c), PANASEWICZ and LOPACIUK (1960), LEITSCH (1961), WANG and KEREIAKES (1962) and COHEN and COHEN (1962).

Protection is maximal when 5-HT is administered 0—5 min before irradiation, negligible when the amine is given more than 30 min before irradiation or after irradiation (MELCHING et al. 1958, LANGENDORFF et al. 1958, DUKOR 1962).

Table 2. *Radioprotective action of indolealkylamines* (DUKOR and SCHÜPPLI 1961)

Compound (50 mg/kg, i.p.)	Survival rate (%) after 30 days	
	900 r	1050 r
5-HT and creatinine sulphate	100	65
N-methyl-5-HT dioxalate	100	
N,N-dimethyl-5-HT dioxalate	5	
1-methyl-5-HT and creatinine sulphate	0	
5-methoxytryptamine base	80	60
5-methoxy-N-acetyltryptamine base	0	
4-HT oxalate	12.5	5
N-methyl-4-HT oxalate	0	
N,N-dimethyl-4-HT base	0	
α-methyl-4-HT dimaleinate	0	
Controls	2.5	0

5-HT is active not only against a single exposure to X-irradiation, but also against repeated whole-body irradiation with lethal doses (LANGENDORFF et al. 1959a).

The protective effect of 5-HT is reinforced by simultaneous administration of adenosine triphosphate or adenosine monophosphate (LANGENDORFF et al. 1960). Similarly, survival rate from radiation is increased by combination of 5-HT with either AET (aminoethylisothiouronium) or MEA (mercaptoethylamine) (MAISIN and DOHERTY 1960, LEITCH 1961, WANG and KEREIAKES 1962, LANDAHL and HASEGAWA 1962, 1963). For example, whereas at 1100 r no protection is afforded by 88 mg/kg of 5-HT alone, the same dose of 5-HT administered together with AET or MEA gives 70—80% protections (WANG and KEREIAKES 1962).

However, combined treatment with AET (8.8 mg/mouse, i.p.) and 5-HT (0.4 mg/mouse, i.p.) while providing better protection to the bone marrow than either alone, does not increase intestinal protection beyond that of AET alone (MAISIN and DOHERTY 1963, MAISIN et al. 1963).

Combination of 5-HT with MAO inhibitors causes a significant increase in the survival time of irradiated mice (DUKOR 1962), combination with LSD, BOL, BOL + LSD or UML (Deseril) strongly reduces or even completely abolishes the protective effect of 5-HT (LANGENDORFF et al. 1959, VAN DEN BRENK and HAAS 1961, DUKOR 1962).

The radioprotective activity of a number of indolealkylamines related to 5-HT is summarized in Table 2. The drugs were given intraperitoneally, in doses of 50 mg/kg, 5 min before exposure to whole-body irradiation with 900 and 1050 r.

In other experiments N-ethyl-5-HT proved to be as effective as 5-HT and 5-benzyloxytryptamine as effective as 4-HT. N-acetyl-5-HT, β-methyl-5-HT, β-dimethyl-5-HT, 6-HT and 7-HT showed no radioprotective activity (DUKOR 1962). Protection afforded by 100 mg/kg tryptophan and 20 mg/kg 5-HTP given 60—90 min prior to irradiation was moderate (LANGENDORFF 1959). The combination of 5-HTP with either pyridoxal-5-phosphate or adenosinetriphosphate, or of 5-HTP and tranylcypromine, a MAO inhibitor, was more active than 5-HTP alone (LANGENDORFF and MELCHING 1959, COEN and WHITEHEAD 1962).

On examination of the blood and tissues of protected animals, eventually in comparison with the tissues of non-protected animals, it emerged that: a) none of the 5-HT-protected mice developed leucaemia, b) lymphocytosis and leucocytosis seen soon after irradiation showed complete regression later on, c) whereas the red blood count was only slightly decreased 7—9 months after irradiation, haemoglobin was significantly reduced (MIYATA et al. 1960), d) whereas the decrease of reticulocytes in the peripheral blood produced by whole-body irradiation with 75 r was to a great extent prevented by 5-HT, the disturbance in the incorporation of ^{59}Fe into young erythrocytes was not corrected by the amine (ELTGEN et al. 1961), e) whereas radiation injury seen in spleen and thymus was the same during the first few days both in protected and non-protected mice, later on the organs of the protected animals showed faster recovery, and finally f) there was an immediate partial protection of the bone marrow, as shown by a smaller reduction of the cell count in the marrow of protected animals (LANGENDORFF and HAGEN 1962, HAGEN and FLEMMING 1963).

Besides increasing survival time, large doses of 5-HT and tryptamine (6 to 200 mg) are capable of protecting mice effectively against epilation caused by X-irradiation (RADIVOJEVIĆ et al. 1960).

It has been demonstrated that splenectomy increases the survival rate of irradiated mice. Surprisingly, this protective effect is reduced by administration of 5-HT (MELCHING et al. 1961).

Rat. GRAY et al. (1952) first observed that the survival rate of rats exposed to lethal X-ray dosage is significantly increased after intraperitoneal pretreatment with 9 mg/kg 5-HT. This observation was soon confirmed by others.

Following intraperitoneal injection of 8 mg/kg 5-HT base 5 min prior to whole-body irradiation with 690 and 800 r, survival rate after 30 days increases from 4—16 to 57—58%, and from 0 to 13—33%, respectively (KRIEGEL and MELCHING 1959). At the same time a reduction of incidence of diarrhoea may be observed in the survivors (VAN DEN BRENK and ELLIOTT 1958).

Intraperitoneal administration of 8 mg/kg 5-HT base 30 min prior to whole body irradiation with 1000 r displays an evident protective effect against depletion of Gomori-positive neurosecretory material in the posterior lobe of the hypophysis produced by irradiation (HECKMANN et al. 1964).

The radioprotective action of 5-methoxytryptamine (10 mg/kg, i.p., 5 min before exposure to 900 r) seems to be greater than that of 5-HT. 5-Benzyloxytryptamine, 4-hydroxy-N,N-dimethytryptamine and tryptamine, on the contrary, do not show any protective effect (SUPEK et al. 1961).

Guinea-pig. 6 mg/kg of 5-HT base given by intraperitoneal route 5 min before irradiation of a guinea-pig flank completely prevents the temporary epilation produced by 800 r and changes into temporary the persistent epilation produced

by 1600 r. On histological examination carried out 23—35 days after irradiation the skin of protected animals shows well-preserved hair bulbs together with numerous mitoses. Acanthosis is less pronounced (MAGGIORA 1960, 1962a).

The protective effect of 5-HT is manifested only if the amine is administered not more than 3 hr before irradiation (MAGGIORA 1962b).

Following administration of 5-HT by ionophoresis (2 mg 5-HT, 20 min) it may be observed, surprisingly enough, that the treated flank is less protected against the epilatory effect of X-rays than the opposite flank, where 5-HT arrives via the blood (MAGGIORA 1963).

Bufotenine, like 5-HT, shows a strong protective action. Feeble protection is afforded by 5-HTP and tryptophan and no protection by 5-HIAA, IAA, psilocine, psilocybine, tryptamine and 5-indoleacetamide (15 mg/animal, i.p.). Surprisingly enough, UML (10 mg, s.c.) does not counteract the protective effect of 5-HT (MAGGIORA and BRUN 1963).

Dog. Chemical mixtures including 5-HT reduce radiation lethality in dogs also (WANG and DAVIDSON 1961).

b) Effects of 5-HT on response of tumours to in vivo irradiation

5-HT (0.4 mg/mouse, i.p., 8—10 min before irradiation) has been found by COHEN and COHEN (1962) to inhibit the response of the isogenic mammary carcinoma to doses of radiation which are normally curative in non-medicated controls, reducing the cure-rate to about half of its control level. On the other hand, whereas direct transthoracic irradiation of both tumour and host tissues with the standard test dose of 7500 r was uniformly lethal to unprotected controls, 5-HT appeared to protect mice from the early mortality associated with the visceral phase of the postirradiation syndrome.

A similar reduction of the radiosensitivity of tumours was produced by 5-HT in the case of Ehrlich ascites and of Ehrlich solid carcinoma. The irradiated Crocker sarcoma, on the contrary, was not protected by 5-HT (KOCH 1962).

It seems pertinent to remember here that 5-HT produces a much greater fall of oxygen tension in tumoral tissue, as followed by a polarographic method, than in bone marrow and muscle (CATER 1962).

c) Radioprotective action of 5-HT in vegetables

When seeds of *Vicia faba* are exposed to an X-ray dose of 400 r the growth of accessory roots is completely inhibited. However, seeds plunged into a 5-HT solution (concentration ?) for 30 min and then irradiated develop accessory roots, at least to a certain extent, after an inhibitory phase of 6 to 8 days (LOZERON et al. 1964).

d) Effect of 5-HT on irradiation-induced mutation rate of bacteria

Following addition of 5-HT, up to 0.01 M concentrations, to a suspension of *E. coli* (strain B/r and its leucine-dependent mutant) irradiated with 40000 r (800 r/min) survival rate increases from 6.5 to 17.7% and irradiation-induced back-mutation to prototrophy is halved (KÜNKEL and TRAMS 1963).

e) Mechanism of the radioprotective action of 5-HT

According to GRAY et al. (1952), VAN DEN BRENK and MOORE (1958), VAN DEN MEER et al. (1961) and BOOZ and BETZ (1961), protection afforded by 5-HT against ionizing radiation is mainly due to vasoconstriction with ensuing temporary tissue anoxia. This view is strongly supported by the experimental results of VAN DEN BRENK and MOORE (1958) showing that increase in respired oxygen

pressure to 4 or 5 atmospheres absolute pressure almost completely reverses the protective action of 5-HT, and by the observation of Booz and Betz (1961) that 5-HT and tryptamine do not protect thymocytes *in vitro* against radiation injury.

However, other investigators maintain that the anoxic mechanism is insufficient to explain the protective effect of 5-HT and suggest that the amine may also act via the central nervous system (Langendorff and Koch 1957), through neutralization of free radicals of water (Alexander et al. 1955) or through a more specific protection of the radio-sensitive substrate against reactive radicals (Dukor 1962). Langendorff and Melching (1959) further suggest that exogenous 5-HT may compensate for lack of endogenous 5-HT due to hindered decarboxylation of 5-HTP (Langendorff and Hagen 1963).

Dukor (1962) affirms that there is no parallelism between the pharmacological effects of indolealkylamines and radioprotection. In the writer's opinion rather the opposite is true, unless a strictly quantitative parallelism is demanded. Furthermore, no comparative data are available on the pharmacological effects (vasoconstriction!) of the different indolealkylamines on the most radiosensitive tissues, such as, for example, intestines and bone marrow.

For description of the effects of X-irradiation on 5-HT levels in tissues and 5-HIAA excretion see pages 373—375.

2. Liver cirrhosis

5-HT administered subcutaneously every other day in doses of 4 mg/kg during the early phase of cirrhogenic treatment, inhibits liver cirrhosis induced by carbon tetrachloride. No comparable effect is observed in rats treated with 5-HT at a more advanced stage of CCl_4 administration. Combined administration of 5-HT and CCl_4 results in 50% reduction of hepatic cellular damage (Fiore-Donati et al. 1958, 1959b; Fiore-Donati and Chieco-Bianchi 1960).

Similarly, 5-HT (13 mg/kg of the base, i.p.) affords considerable protection against liver damage provoked in rats by allyl alcohol, provided that it is administered 15—30 min prior to the poison. No protection is seen when 5-HT is given 2 hr before allyl alcohol (Eger 1958).

5-HT does not influence fatty liver, leading to cirrhosis, when produced with a choline-deficient, high-fat, high-caloric diet (MacDonald et al. 1958).

Fiore-Donati et al. (1959b) suggest that the hepatoprotective effect of 5-HT may be due to liberation of ACTH or adrenocortical steroids rather than to any vascular effect of 5-HT.

3. Cardiac and renal necroses

5-HT injected subcutaneously at a dose of 0.4 to 0.6 mg/animal twice daily, prevents renal and cardiac calcifications induced in rats by dihydrotachysterol administered per os at a dose of 0.25 mg for 5 consecutive days. This preventive action is also demonstrable with regard to cardiac calcifications produced by plasmocid and coronary vein ligature, as well as to skeletal muscle calcifications produced by paraphenylendiamine. 5-HT diminishes but does not prevent degenerative and necrotic lesions associated with these calcifications. On the other hand, the development of massive cardiac infarcts that follows the occlusion of the left main coronary artery cannot be influenced by 5-HT.

Similar protection is afforded by 5-HTP and nialamide, in daily doses of 200 and 30 mg/kg, respectively.

The mode of action of these agents is obscure because 5-HT prevents the deposition of calcium salts without changing calcium blood level. It may be that 5-HT acts through vasoconstriction or through decrease of the oxygen requirements of the myocardium (BAJUSZ and JASMIN 1962, JASMIN and BAJUSZ 1962).

XVII. Miscellaneous effects

1. Action on striated muscle

a) *Crustaceans.* The injection of 1 μg 5-HT into the musculature of the pincers of *Potamoebius*, through the tip of the propodite, causes, after a short latency, an abrupt powerful closing of the pincers which lasts for several minutes. An exactly similar result is produced by extracts of nervous tissue of cephalopods and decapod crustaceans, extracts which like 5-HT are also active on the heart (FLOREY and FLOREY 1954).

b) *Insects.* The effect of tryptamine analogues on the neuromuscular transmission of impulses in the jumping leg of the locust *Schnistocerca gregaria* has been studied by recording action potentials and active membrane responses with intracellular micro-electrodes, and by recording tension with a mechano-electronic transducer.

High concentrations of 5-HT and tryptamine (10^{-2} to 10^{-3} M) block the development of an action potential and of tension in fibres of the metathoracic extensor tibialis and flexor tibialis muscles, but do not block the action potential in the fibres of the crural nerve which supplies "fast" motor axons to the extensor and flexor tibialis. Tryptamine analogues do not inhibit the active membrane response in the fibres of the extensor or flexor tibialis, or alter their membrane resistance. It is concluded by HILL and USHERWOOD (1961) that 5-HT and tryptamine block neuromuscular transmission in the locust.

LSD and BOL do not antagonize 5-HT but, on the contrary, have effects similar to those of the amine and in similar concentrations.

c) *Mammals.* The statement of PHILIPPOT and DALLEMAGNE (1956) and of SALA and PERRIS (1958) that 5-HT (25—400 μg/kg, i.v.) is caprable of moderately antagonizing, in the cat and in the rabbit, the neuro-muscula block produced by tubocurarine, but not that produced by decamethonium was not confirmed in man by FROSALI et al. (1961).

Artificial actomyosin threads are poorly sensitive to 5-HT. In fact, the threshold dose for actomyosin prepared from ox heart is 50 μg/ml, that for actomyosin obtained from bovine striated muscle 250 μg/ml (KURIAKI and INOUE 1955, INOUE 1956).

2. Action on the gill cilia of molluscs

Both 5-HT (threshold concentration 0.1 μg/ml, optimum concentration 10 μg/ml) and 5-HTP (5—100 μg/ml) stimulate the activity of lateral gill cilia of *Mytilus edulis* and of other lamellibranchiates.

Beat frequency of the cilia and velocity of the metachronal wave increase, while the average wave length remains unchanged (AIELLO 1957, 1960a, 1960b; GOSSELIN and ERNST 1958; GOSSELIN 1961). The acceleration, as measured in stroboscopic light, is prompt, sustained, and graded over a wide range of drug concentrations. Maximal frequencies, however, are not greater than those sometimes encountered in untreated gills. Different gill preparations may vary widely in sensitivity and summer *Mytilus* is more sensitive to 5-HT than winter *Mytilus*. In summer *Mytilus* high concentrations of 5-HT inhibit the ciliary activity, instead of increasing it (GOSSELIN 1961).

The action of 5-HTP is less prompt than that of 5-HT but lasts longer, up to several hours (MILTON and GOSSELIN 1960b). LSD and BOL block the action of 5-HT, but at the same time are effective accelerators of gill cilia (GOSSELIN and ERNST 1958). According to AIELLO (1963), 5-HT affects ciliary activity by some action at or near the cell surface.

Since the gills of lamellibranchiates contain detectable amounts of 5-HT, it has been suggested that this endogenous 5-HT is concerned in the physiological regulation of ciliary activity (AIELLO 1960b, 1962; MILTON and GOSSELIN 1960b; GOSSELIN et al. 1962).

Similarly, it is possible that 5-HT plays a role in the motor activity of embryos of some marine gastropods, through stimulation of their cilia (KOSHTOYANTS et al. 1961).

3. Action on lymph flow

5-HT infused intravenously into unanaesthetized dogs at a rate of 20 μg/kg/min produces a 115% increase in lymph flow from the thoracic duct cannulated with a polyethylene catheter, with a 20% decrease in total protein concentration. According to SHIM et al. (1961) these effects are brought about by a probable selective alteration of capillary permeability rather than by increasing intestinal motility.

4. Action on intra-ocular pressure

The intravenous injection of 7 μg/kg 5-HT base produces in the dog an evident reduction of intra-ocular pressure which does not parallel systemic hypotension.

Intra-ocular pressure of the rabbit is not affected by the introduction of 5-HT into the conjunctival sac but is consistently reduced following subconjunctival or retrobulbar injection of 90—450 μg 5-HT. This effect is not changed by antihistamine compounds and is only slightly increased following pretreatment with iproniazid (SCHUMACHER and CLASSEN 1962b).

5. Histamine-releasing activity

Tryptamine and 5-HT, according to FELDBERG and SMITH (1953), are to be listed among the drugs able to release histamine. This property of the indolealkylamines has been shown experimentally on perfused isolated skin flaps and gastrocnemius muscles of the cat and the dog after arterial injections of 1 to 5 mg of the substance (estimation of histamine in the venous effluent), as well as on rat tissues after subcutaneous or intraperitoneal injections of 2 mg 5-HT or 13 mg tryptamine (estimation of tissue histamine). The activity of the indolealkylamines is somewhat greater than that of propamidine, but about 100 times less than that of compound 48/80. FELDBERG and SMITH suggest that histamine release may be at the root of certain phenomena resembling effects of histamine which are seen in the intact animal after injection of tryptamine compounds. This opinion is shared by several research workers. SCARINCI (1955b, 1955c) and BUÑAG and WALASZAK (1962b), for example, believe that hypotension seen in dogs and chickens following intravenous injection of 5-HT is largely due to liberation of histamine.

6. Action on phagocytosis

LUDÁNY et al. (1958) observed that 5-HT enhanced phagocytosis by rat leucocytes obtained from the peritoneal cavity by injection of bouillon, and by circulating rabbit leucocytes. Increase in phagocytosis was 25% at 100 μg/ml concentration of 5-HT, and 13% at 10 μg/ml concentration. Lower concentrations

were ineffective and so was tryptamine at concentrations up to 1 mg/ml. LSD (1 μg/ml) did not inhibit the stimulant action of 5-HT.

These observations were confirmed and extended by NORTHOVER (1961), who found that, at concentrations as low as 1—10 μg/ml, 5-HT stimulated phagocytosis both by rabbit neutrophil polymorphonuclear leucocytes (obtained from the peritoneal cavity by injection of sterile isotonic saline solution) and by rabbit macrophages (obtained by intraperitoneal injection of a mixture of liquid paraffin, peptone water and acacia solution). 5-HTP acted similarly in somewhat higher concentrations and 1 μg/ml appeared to stimulate significantly only phagocytosis by macrophages. BOL was not found capable of preventing the phagocytosis-stimulating action of 5-HT and 5-HTP.

7. Action on tumour growth

When 1.3 mg of 5-HT or 1.1 mg histamine is administered to rats daily, starting 2 days prior to sarcoma implantation, the animals have larger tumours than their controls (0.4 g as compared to 0.3 g). 5-HT depletion with reserpine decreases tumour growth and/or the percentage of takes. Lysergic acid derivatives (LSD, BOL and MLD) antagonize the action of 5-HT. These results suggest that 5-HT and histamine are beneficial to tumour growth (SCOTT et al. 1958, SCOTT and STONE 1959).

In sharp contrast to the above observations, PURKHALSKAIA et al. (1961), SOKOLOFF et al. (1961) and PURKHALSKAIA (1962) found that large doses of 5-HT (3—200 mg/kg, i.p. or s.c.) inhibited by 42 to 97% the growth of 7 out of 9 varieties of tumour in mice and rats. The tumours, however, did not resolve completely in any instance, and oral administration of 5-HT produced no effect.

Similarly, 1 mg 5-HT injected directly into S-91 melanoma or S-180 sarcoma implanted on the feet of mice immediately before exposure of the feet to heat (44^0 for from 30 to 40 min) increased the "curative" effect of heating. Moreover, 1 mg 5-HT injected daily into tumours for from 2 to 3 weeks and accompanied by no heating "cured" 7 out of 55 mice with S-91 melanoma, as compared with one "cure" in 46 mice given injections of saline. If the tumour did not disappear, the rate of growth was greatly reduced (CRILE 1963).

Indoleacetic acid inhibits mitotic activity in LIEBERKÜHN's crypts, as studied by the DUSTIN's colchicine method, when injected intraperitoneally to mice in doses of 2—10 mg/kg (LEAHU 1961).

8. Action on pigment formation

Coats of yellow Ay/a mice given subcutaneous injections of 1 mg/g of DL-5-methyltryptophan daily for a period of 7—10 days, starting at 3—4 days of age, appear darker in colour than those of controls. These results support the idea that tryptophan or a derivative may be utilized for pigment formation by these mice (NACHMIAS 1961).

Utilization of 5-HT in the synthesis of plant pigments is indirectly suggested by the distribution of 5-HT in the vegetable kingdom, and more directly proved by the observation of BROWN and NICHOLS (1958) that addition of 5-HT to an aqueous medium (10—250 μg/ml) results in increased pigmentation of surviving slices of potato tuber.

9. Action on bioluminescence

5-HT introduced into sea water to give a concentration of 20 μg free base/ml initiates prolonged luminescence of the euphausiid crustacean *Meganyctiphanes norvegica* without apparently damaging the creature. Lower concentrations

stimulate no luminescence. However, 5-HT concentrations insufficient to initiate luminescence facilitate the luminescent glow following exposure to room light or to electronic flash. There is reduction in the delay of response and increase in duration and/or intensity of the luminescent response. According to KAY (1963) it is possible that the third step in the chain retina → nervous system → transmitter → photophore luminescence is represented by 5-HT.

10. Action on growth of plant tissues

5-HT (1—100 μg/ml) seems slightly to enhance the growth of plant tissues (NIAUSSAT and DUBOIS 1962, PILET 1962). It may be that the amine acts upon water uptake, by regulating cellular permeability (PILET 1962).

On the elongation of the coleoptiles of *Triticum sativum*, 5-HT is the least active of the four examined indole derivatives, the most active being IAA, followed in order by tryptamine and 5-HIAA. PILET (1963) suggests that indoles other than IAA may act after partial transformation in vivo into IAA.

11. Action on food intake

5-HT injected subcutaneously in daily doses of 1.2 mg/kg for 10 days, decreases food and caloric intake, but not glucose intake in the rat (SOULAIRAC and SOULAIRAC 1960).

12. Action on metamorphosis in amphibians

Tadpoles of *Rana temporaria* injected every other day with 40 μg 5-HT base grow and overcome the metamorphosis crisis exactly as the controls do. Larger doses of the amine (200 μg) are, on the contrary, fatal to the larvae (KEHL et al. 1961).

13. Inhibition of mitochondria swelling

The observation of CASU (1960) that 5-HT has a protective action on liver mitochondria swelling in 0.25 M sucrose is apparently of only slight interest, owing to the enormous concentrations of 5-HT required to elicit the effect (200 μg/ml).

14. Action on brain microsomes

AGHAJANIAN (1963) observed that ascorbic acid produces in specially prepared rat brain microsomes (membrane fragments) a gradual decrease of light scattering and protein fluorescence, and that 5-HT is a powerful inhibitor of these structural changes. There is complete inhibition at about 4×10^{-4}, with graded lesser effects down to 5×10^{-6} or lower.

15. Action on cerebro-spinal fluid pressure

Small doses of 5-HT (2—10 μg/kg, i.v.) initially cause a drop, later on an increase in cerebro-spinal fluid pressure (animal species not indicated!). This biphasic reaction is still more obvious in the case of greater doses (100—1000 μg/kg). The initial phase is very short (10—20 seconds), the second one lasts longer (20—35 min) and occurs when the blood pressure is about to return to its original level (KELENTEY 1963).

16. Action on collagen

5-HT consistently reduces the shrinkage temperature of normal human collagen obtained from the tendo Achillis of people who had died in accidents. With 0.02 M 5-HT reduction is by 1.5—4° from the normal shrinkage temperature

of 60°, with 0.08 M by 7 to 12°, with 0.32 M by up to 30°. 5-Methoxytryptamine and tryptamine produce only a slight reduction; 5-HTP and 5-HIAA, on the contrary, raise the shrinkage temperature. The electron-microscopic appearances of specimens of collagen affected by 5-HT show progressive disorganization. These results suggest that 5-HT may have a direct and important effect on collagen in some disorders, such as rheumatoid arthritis and carcinoid syndrome (HIGHTON and GARRETT 1963).

17. Teratogenic effect

The subcutaneous injection of single doses of 5-HT (0.2—0.8 mg 5-HT base/animal) into pregnant mice produces a large number of foetal abnormalities, mostly of the eyes (absence of one or both eyes, absence of eyelids, one cyclops), limbs (polydactily and syndactily, phocomelia) and tail (absence of tail). The skull and the central nervous system are also sometimes affected (exencephaly, exomphalos). The incidence of abnormalities reaches a maximum of about 30% of surviving foetuses when the injection is given on the 9th to 10th day of pregnancy. The teratogenic effect of 5-HT is inhibited by the administration of 5-HT antagonists, but not by the simultaneous administration of progesterone (POULSON et al. 1963a, 1963b; ROBSON and SULLIVAN 1964).

Similar results have been obtained, again in the mouse, by SELLER (1964), and in the rat by REDDY et al. (1963) following subcutaneous administration of 5-HT during pregnancy, in daily doses of 1.5—15 mg/kg. REDDY and co-workers briefly describe also two cases of carcinoid syndrome in human beings, in which pregnancy resulted in abortion, in infants who died within a few hours after birth, and in an infant presenting multiple congenital malformations.

According to ROBSON and SULLIVAN (1964) there is quite clear evidence that 5-HT interferes with the blood supply to the placenta and with the nutrition of the foetus and it seems likely that this effect is responsible for the development of abnormalities. Thus, as the majority of teratogens, also 5-HT acts on some point in the uterus or the placenta or the umbilical vessels.

(For References see at the end of Chapter 8)

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