SEROTONIN AND THE CARCINOID SYNDROME

W. P. G JONES, M.B , CH.B [1]

WHEN BLOOD clots, a vasoconstrictor substance is released from the disintegrating platelets The isolation of this principle from beef serum was described in 1948 by Rapport, Green and Page (1) who later identified it as 5-hydroxytryptamine. For this vasoconstrictor principle, Corcoran coined the word serotonin. Many years previously Erspamer studied a vasoconstrictor substance associated with the enterochromaffin system of the gastro-intestinal tract which he called enteramine This he later identified as identical with 5-hydroxytryptamine or serotonin.

The presence of large amounts of serotonin in carcinoid tumours, the description by Biorck (2) of a bizarre syndrome associated with metastatic malignant carcinoid and attributable to excessive serotonin production, and the discovery of this substance in the brain (3) stimulated much research to elucidate the functions of the amine in health and disease

Although the precise functions of serotonin are still obscure there can be little doubt that it is a substance of great physiological importance The anaesthesiologist in his role as the applied physiologist of the surgical team should be aware of how this compound, especially when present in excessive amounts as in the carcinoid syndrome, can effect the homeostasis of his patient and modify the actions of the agents he uses to produce anaesthesia. In this paper some of the actions of serotonin will be described, with particular reference to the carcinoid syndrome, and an attempt made to indicate how these may modify the choice and conduct of anaesthesia in patients suffering from that condition

SOURCE, SYNTHESIS, AND DISTRIBUTION (4, 5)

Serotonin is widely distributed in the body. Large amounts are found in the brain, blood platelets, and gastro-intestinal tract. Smaller quantities are present in the liver and bone marrow while little occurs in the lungs, thyroid, pancreas, and diaphragm None is present in skeletal muscle, the peripheral nerves, or the adrenal glands.

The dietary precursor of serotonin is the amino-acid tryptophan This becomes hydroxylated, probably in the liver, to 5-hydroxytryptophan (5-H-T-P) which then undergoes decarboxylation to form 5-hydroxytryptamine or serotonin. The specific decarboxylase for 5-H-T-P is found in most tissues, particularly in the brain, lungs, liver, kidneys, and sympathetic ganglia. Serotonin is mainly broken down and excreted in the urine as 5-hydroxyindole acetic acid (5-H-I-A-A), the enzyme responsible being the widely distributed monamine oxidase. The quantitative excretion of 5-H-I-A-A may, therefore, be used as an index of serotonin metabolism.

[1]Fellow in the Department of Anesthesiology, Cleveland Clinic, and the Frank E Bunts Educational Institute, Cleveland. Ohio

Functions of Serotonin in the Maintenance of Homeostasis

Serotonin-buffering System

In experiments to determine the effect of injections of serotonin on the cardiovascular system conflicting results were often obtained. For example, in a given series of patients, following injection of the amine, the blood pressure may be raised, lowered, or undergo a biphasic response. In order to try and explain these findings the concept of a serotonin-buffering system was advanced (6). This ascribes to serotonin the role of humoral antagonist to neurogenic vasomotor tone, the vascular response to the amine being largely determined by the degree of tone present. When this is high, the response is hypotensive and when low a pressor effect is seen. There is probably both a central and a peripheral inhibitory effect of the hormone on neurogenic tone

Blood

Nearly all the serotonin of the blood is found in the platelets and is released when these disintegrate When applied directly to blood vessels, serotonin exerts a vasoconstrictor effect and it is tempting to ascribe to it some role in the haemostatic mechanisms This assumption is not confirmed experimentally, however. It is possible in man by administration of reserpine to cause marked and prolonged depletion of the serotonin content of the platelets, brain, and gastro-intestinal tract without influencing the clotting mechanism or haemostasis (7) However, some workers have suggested that serotonin might be an antagonist of antithrombin, thus facilitating the conversion of fibrinogen to fibrin (8).

The observations that the platelets in the carcinoid syndrome contain excessive amounts of serotonin, and that ordinary platelets are capable of absorbing large amounts of this amine, indicate the possibility that platelets may be concerned in the fixation and inactivation of this potent humoral agent by binding to the platelet constituents in an inactive form (4). Conversely, of course, it can be argued that when stored in platelets serotonin is protected from destruction by amine-oxidase, to be available for release when required

Gastro-intestinal Tract

A large proportion of the body serotonin occurs in the gastro-intestinal tract where it is formed by the enterochromaffin cells Its physiological function in the alimentary canal is unknown, but it probably serves as a local hormone to regulate smooth muscle function. The increased intestinal motility produced by injection of serotonin and the diarrhoea and colic characteristic of the carcinoid syndrome tend to support this theory.

The Brain (4, 5)

The brain contains relatively large amounts of serotonin, the greatest quantities being located in the hypothalamus and other areas concerned with autonomic activity. Parenterally administered serotonin does not readily cross the blood-brain barrier, the brain probably synthesizing its own serotonin from 5-H-T-P and metabolizing it with monamine oxidase.

Interest was aroused concerning the possible functions of serotonin in the

brain by the discovery that administration of the tranquillizer reserpine caused release of serotonin from the body depots with a marked increase in the excretion of 5-H-I-A-A. The brain serotonin is especially susceptible to reserpine release and naturally some connection between the ataractic effect of this drug and its ability to release serotonin was postulated. However, the distribution of norepinephrine in the brain closely parallels that of serotonin and reserpine reduces its concentration at about the same rate. This tranquillizer also stimulates release of catechol amines from the innervated adrenal medulla and norepinephrine from the cervical sympathetic ganglia. Thus reserpine brings about changes in the distribution of three very active amines so that a simple explanation for its tranquillizing action is unlikely.

The precise functions of serotonin in the central nervous system remain obscure though many theories have been advanced Brodie and Shore (30) suggest that it may be the transmitter substance for stimulation of subcortical parasympathetic centres or inhibition of sympathetic centres Marrazzi and Hart (31) report that the hormone is a potent inhibitor of central sympatic transmission while Dobkin (9) suggests that optimum nerve function depends on the ratio of intracellular to extracellular serotonin. With a relative increase in intracellular serotonin there is increased tension, alertness, irritability, and a tendency towards convulsive behaviour. Conversely, an excess of extracellular serotonin results in depression and withdrawal.

Respiratory System

Serotonin is a potent bronchoconstrictor Herxheimer (10) has reported that inhalation of serotonin aerosol in four normal subjects had no effect, while in three of six people with asthma severe asthmatic attacks were precipitated, which responded to isopropylnoradrenalin. In retrospect, he believes this effect was due to the acidity of the aerosol solution used When a buffered, neutral solution was used no attacks were seen However, inhalation of serotonin aerosol in guinea pigs produced a shock-like syndrome with dyspnoea, cyanosis, and often convulsions. Some relief was obtained with atropine It is noteworthy that "asthmatic" attacks are characteristic of the carcinoid syndrome and are probably induced by release of serotonin from the tumour.

A constant decrease in tidal air occurs following injection of serotonin intravenously (11). This reduction is probably by bronchoconstriction, the effect being partly antagonized by atropine

When injected, serotonin produces a rise in venous, right atrial, and pulmonary artery pressures with a fall in systemic blood pressure (12). The mechanism is probably by pulmonary vasoconstriction. These findings have led Smith and Smith (13) to implicate serotonin release from blood clot and infarcted lung as a factor in the production of the systemic effects of pulmonary embolism.

Potentiation of Choline Compounds and Inhibition of Cholinesterase

Fried and Antopol (14) found that very low concentrations of serotonin augmented the effect of human pseudo-cholinesterase, while higher concentrations caused marked inhibition They comment that the potentiating effect at low

concentrations may be of greater significance than inhibition at higher concentrations as these low levels probably more nearly correspond to physiological values for the amine. This raises the possibility of cholinesterase inhibition by serotonin in conditions where its circulating level is above physiological limits, as in the carcinoid syndrome

The work of Pick (15) showed that pre-treatment with small doses of serotonin strongly potentiated the effect of acetylcholine on the guinea-pig ileum. Serotonin also enhanced, but to a lesser extent, the effect of the more stable choline compounds. He does not believe that this potentiation can be explained solely on the basis of simple cholinesterase inhibition.

These findings are of significance to the anaesthesiologist concerned with the use of muscle relaxants. Consider neuromuscular blockade produced by a non-depolarizing relaxant such as tubo-curare Serotonin would be expected to potentiate the effect of acetylcholine at the motor end-plate leading to its accumulation in this region. This would result in displacement of the curare from the cholinergic receptors of the end-plate and a reversal of the blockade. This hypothesis receives some support from the work of Philippot and Dallemagne (16). These workers found that in cats partial neuromuscular blockade produced by tubo-curare was rapidly reversed by injection of serotonin. No effect was seen in blockade produced by the depolarizing relaxant decamethonium iodide. With more intense blockade by curare, repeated injections of serotonin were necessary to produce reversal

This reversal of neuromuscular blockade was independent of any variations in arterial pressure produced by the injection of serotonin They do not believe that release of adrenalin following the injection of serotonin is a factor in producing reversal as this occurs too rapidly for any but a direct action and is also seen when injection of the hormone produces a fall in systemic blood pressure.

Since the introduction of succinylcholine as a depolarizing muscle relaxant, many cases of prolonged apnoea following its use have been reported. Though this apnoea can be caused by many mechanisms (17), the following may be relevant to this discussion.

Restoration of neuromuscular conduction following succinylcholine block is due to enzymatic hydrolysis, by plasma cholinesterase, of the succinylcholine to succinylmonocholine and then to succinic acid and choline If cholinesterase activity is inhibited by serotonin, the rate of breakdown will be decreased, and the duration of blockade prolonged. With the slowing of the rate of breakdown of the relaxant, accumulation of the primary breakdown product succinylmonocholine will also occur. This compound has some neuromuscular blocking action, being about a twentieth as active as succinylcholine.

Thus, in conditions associated with an increased level of circulating serotonin, it may be postulated that the use of depolarizing muscle relaxants, especially succinylcholine, carries a risk of prolonged neuromuscular blockade due to cholinesterase inhibition.

Prolongation of Hypnosis by Serotonin

Correll and co-workers (18) noted that rats rendered unconscious with a variety of barbiturates often succumbed to minute quantities (often as little as

0.1 mg.) of serotonin given intravenously. Unanaesthetized animals tolerated up to 50 mg./kg. Similar results were obtained with light ether anaesthesia, 0.1 mg. of serotonin given intravenously killing four out of ten rats. It is interesting to note that with light cyclopropane anaesthesia, 0.1 mg. intravenously did not kill any of the rats, 0.5 mg. being necessary to kill five out of ten. They conclude that the intravenous injection of serotonin into an anaesthetized animal enhances the respiratory depression produced by the anaesthetic agent so that death appears to be the result of respiratory failure

In view of the greater sensitivity to serotonin under light ether anaesthesia, which stimulates respiration, than under cyclopropane, which is a marked respiratory depressant, this explanation seems unlikely.

Brodie (19) showed that reserpine markedly potentiates the hypnotic effects of hexobarbitone and ethyl alcohol in mice, probably by causing release of serotonin. Reserpine does not increase the rate of bio-transformation or affect the rate of uptake by the brain of the two hypnotics It presumably acts by increasing the sensitivity of the nervous system to these agents

The same workers found that the sleeping times of mice under hexobarbitone (20) and pre-treated with serotonin were some 300 per cent longer than in mice given the barbiturate alone. This effect was substantially diminished by the prior administration of a serotonin antagonist (L.S.D.).

In confirming the hypnosis-prolonging properties of serotonin in mice anaesthetized with cyclobarbitone and chloral hydrate, Fastier (21) suggests that the ability of this hormone to prolong narcosis may be due to a relatively unspecific vascular effect, rather than to a more specific action on the nervous system. As he points out, this potentiating action of serotonin extends to several different kinds of hypnotics—barbiturates, alcohol, and chloral hydrate—which are metabolized in different ways. Thus, any explanation of its action on the basis of the inhibition of a specific enzyme system in the brain is unlikely

Later work by Fastier (22) revealed that the potentiation of hypnosis by serotonin in mice anaesthetized with chloral hydrate was related to the hypothermic action of this hormone This is enhanced in the presence of the hypnotic The sleep-prolonging effect is much reduced when the environmental temperature is raised to make heat loss minimal. This hypothermic effect may be mediated centrally via the hypothalamus or peripherally by a direct action on the blood vessels.

Other workers (23) have shown that the injection of very small amounts of serotonin intravenously will exert a marked inhibitory effect on the brain-wave rhythms as seen under thiopentone anaesthesia. Paradoxically, under ether anaesthesia or unanaesthetized, the effect is excitatory, tending to increase the frequencies of these waves.

That these observations find clinical application will be shown in the discussion on anaesthesia in the carcinoid syndrome. Purely in the realms of conjecture, it is fascinating to speculate as to the possible part serotonin may play in the prolonged unconsciousness seen after some head injuries; the excessive somnolence associated with certain hypothalamic disorders and the narcoleptic state. Of more direct interest to the anaesthesiologist, what is its role, if any, in the phenomenon

of artificial hibernation? Is its metabolism altered in those patients who show abnormal sensitivity to the barbiturates? The field is indeed fascinating and the possibilities seem legion.

The Pituitary-Adrenal System

Moussatche and Pereira (24) have shown that the administration of serotonin to rats decreases the ascorbic acid content of the adrenal glands. This did not occur in hypophysectomized animals, indicating that the mechanism is through release of A.C T.H This action is blocked by the serotonin antagonist B.O.L Others (25) have demonstrated an increase in platelets and decrease in eosinophils following injection of a large dose of serotonin in rats. Munson (26) has shown that reserpine can stimulate the secretion of A C T H and, after administration of this drug, other stressful agents no longer have their usual effect on A C T H production. These findings have stimulated interest in the possibility that serotonin may be the hypothalamic neuro-humor responsible for stimulating A C T.H secretion

In patients with the carcinoid syndrome there is an increased incidence of adrenocortical hyperplasia and adenomas (27), indicating possible persistent stimulation by A.C.T H. They are also more susceptible to overwhelming bacterial infections which may be anticipated if long-continued adrenal stimulation has resulted in their inability to respond to additional stress by increased output of steroids

Apparently, then, these patients might be expected to have a poor adrenal response to the stress of anaesthesia and surgery so that supplemental steroid therapy may become necessary.

Additional Functions

Evidence is accumulating that serotonin may be concerned in many other vital functions. This has been reviewed by Page (5) and will only be briefly mentioned The hormone may be involved in the vascular changes and pain produced in the early phases of inflammation. The amine is released in anaphylactic shock and certain antigen-antibody reactions, it may also be concerned in the regulation of sodium metabolism

These actions of serotonin may be related to its ability to produce a selective alteration in the permeability of the cell membrane

Intestinal Carcinoid and the Malignant Carcinoid Syndrome

Carcinoid tumours arise in the enterochromaffin cells and comprise (5, 27, 28) about 1 per cent of all neoplasms of the gastro-intestinal tract They can occur anywhere from the stomach to the rectum, but are usually found in the ileo-caecal region. In about 25 per cent of these neoplasms, especially those associated with hepatic metastases, a peculiar syndrome occurs, characterized by all or some of the following features. (1) colicky abdominal pain, borborygmi, hypermotility of the bowel, and watery diarrhoea; (2) a violaceous cyanosis, intermittent flushing of the skin associated with tachycardia and telangiectasia (3) right-sided endo-

cardial fibrosis with pulmonic stenosis and tricuspid regurgitation leading to right-sided heart failure with hepatic congestion and dependent oedema; (4) "asthmatic" attacks associated with cyanosis, flushing, and dyspnoea.

Tumour extracts and the blood of patients with this syndrome contain large amounts of serotonin, while the excretion of 5-H-I-A-A is greatly increased. Many of the features of the syndrome can be reproduced by the administration of exogenous serotonin and it seems reasonable to assume that carcinoids are endocrine tumours producing excessive amounts of the hormone serotonin. About two-thirds of the free circulating serotonin is removed during passage through the lungs.

The flushes of the syndrome are related to falls in blood pressure and are probably mediated through release of serotonin from the tumour and metastases Sudden release of serotonin into the circulation may occur with handling of the tumour or be precipitated by a fall in blood pressure.

The serotonin antagonists are peculiarly ineffective in controlling the symptoms of the syndrome, though some symptomatic relief is usually obtained with chlorpromazine.

With physicians becoming increasingly aware of the existence of the syndrome, improved methods of diagnosis, the relatively slow growth and spread of the tumour, and its frequent association with other surgical conditions, the anaesthesiologist will no doubt be more frequently called upon to anaesthetize patients with this condition in the future Anaesthesia may be required for an exploratory laparotomy, attempted excision of the tumour and metastases, or relief of intestinal obstruction produced by the growth. Also surgical treatment of an associated cholecystitis, cholelithiasis, or peptic ulceration, which show an increased incidence in association with this disease, may become necessary

In deciding which methods and drugs to use in the anaesthetic management of patients with these conditions, there are several factors the anaesthesiologist must consider.

Many of the patients have been taking chlorpromazine over a prolonged period for symptomatic relief of some of the manifestations of the syndrome. This tranquillizer produces peripheral vasodilation, mild hypotension, and tachycardia. There is a well-marked adrenolytic action and orthostatic hypotension readily occurs The drug also potentiates the effects of hypnotics, narcotics, and relaxants so that prolonged apnoea and delayed return of consciousness may complicate the picture.

The avoidance of hypotensive episodes is especially important in these patients as there is evidence that falls in blood pressure can release serotonin into the circulation from the tumour and metastases (29). If hypotension occurs, its reversal by vasopressors may be difficult as the response to these drugs is modified by chlorpromazine. Phenylephrine and L-noradrenalin are the vasopressors of choice, the less potent agents such as ephedrine, methyl amphetamine, and methoxamine being singularly ineffective in the presence of the tranquillizers.

The development, during the course of operation or postoperatively, of a prolonged hypotension refractory to powerful vasopressors and not associated with blood loss is likely to indicate adrenocortical insufficiency. This may be due to

exhaustion of the adrenal cortex following prolonged stimulation by A.C.T.H. released by serotonin. In this state patients react poorly to the stress of anaesthesia and surgery so that hypotension, respiratory depression, and delayed recovery are seen.

Treatment of this complication is by intravenous steroids although if its existence is suspected preoperatively the use of steroids before and after operation may prevent its occurrence.

Small amounts of narcotics and sedatives should be used in the premedication of these patients as marked potentiation of the effects of these agents occurs with both chlorpromazine and serotonin. Atropine should be given in full dosage, in view of the experimental work indicating a protective effect against serotonin-induced bronchoconstriction.

Endotracheal intubation is mandatory to ensure perfect oxygenation at all times, especially if the cardiac lesions sometimes associated with the syndrome are present Intubation also ensures easy access to the tracheobronchial tree so that rapid and efficient treatment of any "asthmatic" attack is possible.

Induction and maintenance with cyclopropane are recommended in light of the finding that rats anaesthetized with this gas are more resistant to the lethal effects of injected serotonin. Also with this agent, high oxygen concentrations can be given and excellent muscular relaxation obtained, if required, with only small amounts of relaxant The slight increase in blood pressure often seen in light cyclopropane anaesthesia is also of benefit in avoiding hypotensive episodes.

The use of barbiturates is contra-indicated because of the potentiation of hypnosis produced by both chlorpromazine and serotonin. Another disadvantage is the frequent occurrence of hypotension during induction. This fall in blood pressure is exaggerated in the presence of chlorpromazine.

If the use of a muscle relaxant becomes necessary, curare is the agent of choice owing to the risk of the prolongation of muscle blockade following the use of depolarizing relaxants.

During the course of the surgical procedure, sudden release of serotonin from the tumour may occur following a period of hypotension or handling of the neoplasm. The increase in circulating serotonin may precipitate an "asthmatic" attack with bronchoconstriction and cyanosis. Treatment is by intravenous atropine, and phenylephrine by nebulization into the anaesthetic circuit.

In the postoperative period, careful watch must be kept to detect any hypotension, shock, and respiratory depression. These may develop suddenly and prove resistant to treatment for reasons already discussed.

Summary

A brief description of some of the main physiological actions of serotonin has been given. Their clinical implications, especially where they pertain to the field of anaesthesia, are presented in some detail.

The malignant carcinoid syndrome is discussed and some of the problems which may confront the anaesthesiologist in dealing with patients suffering from this condition are mentioned.

ACKNOWLEDGMENT

I gratefully acknowledge the advice and assistance given by Dr Donald E Hale, Head of the Department of Anesthesiology, Cleveland Clinic Foundation, in the preparation of this paper.

RÉSUMÉ

La sérotonine (5-hydroxytryptamine) est une hormone que l'on trouve en grande quantité dans le cerveau, les plaquettes sanguines et le tractus gastro-intestinal. L'on ne connait pas précisement son rôle dans le maintien de l'homéostase, mais des travaux de laboratoire nous font croire qu'elle joue un rôle dans le maintien de plusieurs fonctions vitales de l'organisme

En se désagrégeant, les plaquettes sanguines libèrent cette hormone en grande quantité; on ne peut pas affirmer que ce fait influence les mécanismes de l'homéostase. Dans le tractus intestinal, la sérotonine est sécrétée par les cellules entérochomaffines. Il est possible que cette sécrétion locale serve à la régulation de la contraction des muscles lisses.

La découverte que la réserpine provoque une libération de sérotonine dans le cerveau n'a pas manqué de soulever de la curiosité sur son rôle dans le fonctionnement du système nerveux central. C'est un inhibiteur de la transmission synaptique centrale et il est possible que ce soit un véhicule chimique des stimuli destinés aux centres parasympathiques sous-corticaux

Sur l'arbre respiratoire, cette hormone produit de l'hypertension et de la bronchoconstriction.

En laboratoire, on a établi que la sérotonine inhibait la pseudo-cholinestérase humaine. En conséquence, dans les états où il y aurait une augmentation de la sérotonine circulante, il y aurait un risque additionnel, à cause de l'inhibition de la cholinestérase, à employer des agents curarisants du type dépolarisant de crainte d'avoir à faire face à un blocage neuromusculaire prolongé.

La sérotonine potentialise l'action de plusieurs hypnotiques, des barbituriques, de l'alcool et de l'hydrate de chloral. Cet effet dépend de l'action hypothermisante de la sérotonine, effet qui peut être considérablement diminué par l'administration de L.S.D , un antagoniste de la sérotonine.

L'administration de sérotonine provoque une libération d'A.C.T.H, cela ne manque pas d'intérêt si l'on songe à la fréquence accrue des hyperplasies adrénocorticales et des adénomes chez les malades présentant un syndrôme carcinoide.

Le syndrôme carcinoide est causé par la libération de grandes quantités de sérotonine venant de tumeurs carcinoides des cellules entérochromaffines, plus particulièrement quand il existe des métastases hépatiques. Ce qui le caractérise, c'est une douleur abdominale ressemblant à une colique, de la diarrhée, des attaques d'asthme et de la fibrose du cœur droit. Des manipulations de la tumeur ou une chute de tension artérielle peuvent provoquer une libération de sérotonine.

On a souvent besoin d'administrer une anesthésie à ces malades et il s'impose, pour l'anesthésiste, d'apporter une attention spéciale. Un grand nombre de ces malades prennent de la chlorpromazine pour soulager leurs coliques et leur

diarrhée. Comme prémédication, on peut prescrire de petites quantités de narcotiques et de sédatifs, mais il faut avoir recours à l'atropine à hautes doses. Nous conseillons une induction et un maintien de l'anesthésie au cyclopropane et déconseillons l'usage des barbituriques. Le myorésolutif de choix demeure le curare puisque les dépolarisants sont contrindiqués. Il faut éviter l'hypotension car elle peut entraîner la libération de sérotonine S'il faut avoir recours à des vasopresseurs, il faudrait employer de la phenylephrine et de la L-noradrénaline car il peut arriver que, avec des agents moins puissants, on éprouve de la difficulté à corriger l'hypotension à cause des effets adrénolytiques de la chlorpromazine.

Si, en l'absence d'hémorragie, on est en face d'une hypotension marquée et prolongée, il faut songer à une insuffisance adrénocorticale et recourir à l'usage des stéroides On peut observer, au cours de l'anesthésie, des crises asthmatiformes avec bronchoconstriction et cyanose. Il faut administrer de l'atropine par voie endoveineuse et nébuliser dans le circuit de la machine à anesthésie de la phenylephrine. Dans les suites opératoires, il faut exercer une surveillance de tous les instants car, soudainement, il peut survenir une hypotension, un état de choc et une dépression respiratoire.

REFERENCES

1 Rapport, M M, Green, A A, & Page, I H Partial Purification of the Vasoconstrictor in Beef Serum J. Biol Chem *174* 735 (1948).

2 Biorck, G, Axen, O, & Thorson, A Unusual Cyanosis in a Boy with Congenital Pulmonary Stenosis and Tricuspid Insufficiency Fatal Outcome after Angiocardiography. Am Heart J *44* 143 (1952)

3 Twarog, B M., & Page, I H. Serotonin Content of Some Mammalian Tissues and Urine and a Method for Its Determination Am J Physiol *175* 157 (1953)

4 Udenfriend, S, Shore, P A, Bogdanski, D F, Weissbach, H, & Brodie, B. B. Biochemical, Physiological and Pharmacological Aspects of Serotonin Recent Progress in Hormone Research *13* 1 (1957)

5 Page, I H. Serotonin (5-Hydroxytryptamine) The Last Four Years Physiol Rev. *38*: 277 (1958)

6 McCubbin, J. W, & Page, I H Editorial Circul Res *2*: 395 (1954)

7 Wiener, S, & Undenfriend, S Relationship of Platelet Serotonin to Disturbances of Clotting and Hemostasis Circul *15* 353 (1957)

8 Milne, W L, & Cohn, S H Role of Serotonin in Blood Coagulation Am J Physiol *189*. 470 (1957).

9. Dobkin, A B. Efficacy of Ataractic Drugs in Clinical Anaesthesia A Review. Canad Anaesth Soc. J. *5*: 178 (1958)

10 Herxheimer, H 5-Hydroxytryptamine Shock in the Guinea Pig J. Physiol *128*. 435 (1955).

11 Konzett, H. The Effects of 5-Hydroxytryptamine and Its Antagonists on Tidal Air Brit. J. Pharmacol. *11*. 289 (1956).

12. Page, I H. Serotonin (5-Hydroxytryptamine) The Last Four Years Physiol Rev. *38*: 279 (1958).

13 Smith, G., & Smith, A. N The Role of Serotonin In Experimental Pulmonary Embolism. Surg, Gynec. & Obst. *101* 691 (1955)

14. Fried, G H, & Antopol, W. Effects of Psychotomimetic Compounds on Human Pseudocholinesterase. J. App. Physiol *11*: 25 (1957).

15. PICK, E. P. Potentiating Action of Serotonin on Choline Compounds J Mount Sinai Hospital, N.Y. *24* 1104 (1957).
16. PHILIPPOT, E., & DALLEMAGNE, M J. L'action anti-curare de la 5-Hydroxytryptamine Arch Internat Pharmacodyn. *105*. 426 (1956).
17 FOLDES, F F., RENDELL-BAKER, L., & BIRCH, J H. Causes and Prevention of Prolonged Apnea with Succinylcholine. Anesth. & Analg. *35* 609 (1956).
18. CORRELL, J. T , LYTH, L F , LONG, S ; & VANDERFOEL, J. C. Some Physiologic Responses to 5-Hydroxytryptamine Creatine Sulphate Am J Physiol *169* 537 (1952)
19. BRODIE, B. B., SHORE, P A , & SILVER, S. L Potentiating Action of Chlorpromazine and Reserpine Nature *175*. 1133 (1955).
20. SHORE, P. A , SILVER, S L , & BRODIE, B. B. Interaction of Serotonin and Lysergic Acid Diethylamide in the Central Nervous System. Experientia *11* 272 (1955)
21. FASTIER, F. N. Prolongation of Hypnosis by 5-Hydroxytryptamine (Serotonin) Experientia *12*: 351 (1956)
22. FASTIER, F N , SPEDEN, R N , & WAAL, H Prolongation of Chloral Hydrate Sleeping Time by 5-Hydroxytryptamine and by Certain Other Drugs Brit J Pharmacol *12* 251 (1957).
23 UDENFRIEND, S., *et al.* Biochemical, Physiological and Pharmacological Aspects of Serotonin. Recent Progress in Hormone Research *13* 14 (1957)
24. MOUSSATCHE, H., & PEREIRA, N. A. Release of Adrenocorticotrophin by 5-Hydroxytryptamine Acta physiol Latino Am 7. 71 (1957)
25. STEINER, F. A., & HEDINGER, C H. R Thrombozytose und Eosinopenie bei Ratten nach Einmaliger 5-Oxytryptaminojection Experientia *12* 109 (1956)
26 UDENFRIEND, S , *et al.* Biochemical, Physiological and Pharmacological Aspects of Serotonin Recent Progress in Hormone Research *13*. 15 (1957)
27. DEBAKEY, M. E. Year Book of General Surgery, 1957–1958 Series, pp. 77–81. Chicago Year Book Publishers.
28. SAPEIKA, N. 5-Hydroxytryptamine A Review South African Med J *30*. 811 (1956)
29. SCHNECKLOTH, R , PAGE, I H , DEL GRECO, F , & CORCORAN, A C Effects of Serotonin Antagonists in Normal Subjects and Patients with Carcinoid Tumors Circul *16* 523 (1957)
30. BRODIE, B B , & SHORE, P A A Concept for a Role of Serotonin and Norepinephrine as Chemical Mediators in the Brain. Ann N Y Acad Sc *66* 631 (3) (1957)
31. MARRAZZI, S , & HART, E R Relationship of Hallucinogens to Adrenergic Cerebral Neuro-humors Science *121* 365 (1955).