REVIEW ARTICLE

THE ANESTHETIC SIGNIFICANCE OF SEROTONIN SECRETING CARCINOID TUMORS

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THE malignant carcinoid syndrome is an addition to the list of endocrine disorders which respond to the stress of anesthesia and operation by releasing into the circulation excessive quantities of a biologically active hormone. This hormone is 5-hydroxy tryptamine or serotonin. It is a normal body constituent which is found in highest concentration in the gastrointestinal tract, blood platelets, spleen and brain. Its precise physiologic role has not been determined. Its synthesis in the normal individual mainly occurs in the chromaffin cells of the intestinal tract and to a lesser degree, in the brain. Some patients who develop malignant carcinoid tumors, may synthesize large amounts of serotonin in the primary and metastatic tumor masses. At varying intervals and in response to various stimuli, these tissue concentrations of serotonin are released into the circulation and produce a characteristic symptom complex or "attack," which is now identified as the malignant carcinoid syndrome. The onset of such an attack during the administration of anesthesia may provoke one of the most fulminating catastrophies encountered in medicine.

HISTORY

Although benign and malignant carcinoid tumors had been identified as a definite pathologic entity as early as 1882, it was not until some 70 years later, in 1953, that it was realized that these tumors were capable of producing bizarre clinical symptoms in addition to the usual changes attributable to a growing intra-abdominal malignancy.

The earliest description of this tumor was made in 1867 by Langhans, who failed to appreciate its correct origin. In 1882, Lubarsch referred to them as "little carcinomas" and in 1907, they were first called "carcinoids" by Oberndorfer because they were rarely malignant, although it was known that liver metastases could occur. The affinity of the cells of carcinoid tumors for silver stains, led Masson to first describe these tumors as argentaffin tumors or argentaffinomas.[1] They also have been designated chromaffin tumors or chromaffinomas because of their derivation from the chromaffin tissues of the body.

In 1952, Biorck, Axen and Thorson, first drew attention to the bizarre clinical symptoms and cardiac changes that may occur with malignant carcinoid tumors.[2] In 1953, Lembeck isolated serotonin from a carcinoid tumor[3] and in the same year, Isler and Hedinger,[4] described the characteristic clinical syndrome which these tumors produce. One year later, Thorson and co-workers brought all these threads of information together by demonstrating that carcinoid tumors do elaborate an active humoral agent, serotonin, which when released into the circulation causes the manifestations of the carcinoid syndrome.[5]

The isolation and synthesis of serotonin preceeded, by many years the appreciation of its importance in the functioning carcinoid syndrome. In 1948, Rapport isolated a potent tryptamine-like substance from serum which was named serotonin.[6] Its structural identification was completed in 1949,[7] and was first successfully synthesized by Hamlin and Fischer[8] in 1951. In another independent investigation, Erspamer and Asero[9] in 1952, identified serotonin as the active principle of enteramine: a substance isolated by them many years previously from the chromaffin cells of the intestine.[10]

The discovery of serotonin has aroused considerable scientific interest. Demonstration of its presence in various body tissues as a normal biologic substance, has stimulated the imagination of the investigator to ascertain its precise physiologic role in normal and pathologic states. The data which have accumulated in recent years have failed to establish

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conclusively this role, although many theories have been postulated. No attempt will be made to discuss these many findings except as they apply to the interests of anesthesia. Several excellent reviews covering all phases of this subject are available.[10-13]

Pathology

Carcinoid tumors arise from the Kultschitzky cells of the crypts of Lieberkuhn of the gastrointestinal tract. Although they may originate from any portion of the gastrointestinal tract, 50 to 90 per cent of them arise from the appendix or in areas immediately adjacent.[14, 15] The primary lesion is usually small and slow in growth. Metastases may develop many years after the appearance of the primary tumor. Appendiceal carcinoids tend to be locally invasive and rarely extend beyond the regional lymph nodes.[14] Primary lesions of the stomach, small intestine and colon are more malignant and metastasize to regional lymph nodes, the liver and less frequently to the lungs, ovaries and bones. Liver metastases enlarge slowly but may, in time, become massive. The presence of liver metastases seems to be essential for the development of the typical carcinoid syndrome. Excessive concentrations of serotonin elaborated in this tumor mass (1 Gm. of tumor may contain 2 to 3 mg. of 5-hydroxy tryptamine) are released into the hepatic vein and hence into the lesser circulation. The exposure of the right heart and the pulmonary structures to chronically high titres of serotonin eventually produce the characteristic cardiac and pulmonary changes of this syndrome.[16]

It is estimated that only 25 per cent of all malignant carcinoid tumors produce and secrete serotonin.[17] Others behave like any other intra-abdominal neoplasm, causing intestinal obstruction and eventual cachexia as the tumor mass continues to enlarge.

Metabolism of Serotonin (Fig. 1)

The dietary precursor of serotonin is the amino acid tryptophan.[18, 19] In the normal individual, less than 1 per cent of ingested tryptophan is utilized in serotonin synthesis.[18-20] In patients with secreting carcinoid tumors however, as much as 60 per cent of the daily intake of tryptophan may be diverted into this process.[20, 21] The hydroxylation of tryptophan yields 5-hydroxy tryptophan, the immediate precursor of serotonin.[22] This conversion has never been observed in mammalian tissues. Decarboxylation of 5-hydroxy tryptophan by the specific enzyme, 5-hydroxy tryptophan decarboxylase, yields 5-hydroxy tryptamine or serotonin.[22] This decarboxylase is found in most body tissues and in all tissues containing serotonin with the exception of blood.[22] Its distribution closely parallels that of serotonin especially within the central nervous system. The greatest concentration is found within the hypothalamus.[23, 24] Studies indicate that most serotonin synthesis occurs in the enterochromaffin cells of the intestine.[12] However, the wide distribution of 5-hydroxy tryptophan decarboxylase throughout the body suggests other sites of serotonin synthesis as well.[12] This view is supported by the fact that serotonin, which cannot pass the blood-brain barrier, is still a normal constituent of brain tissue. The demonstration of increased brain concentrations of serotonin following the intravenous infusion of the serotonin precursor 5-hydroxy tryptophan, is further proof of the extra-intestinal synthesis of this amine.[25]

The metabolic destruction of serotonin in

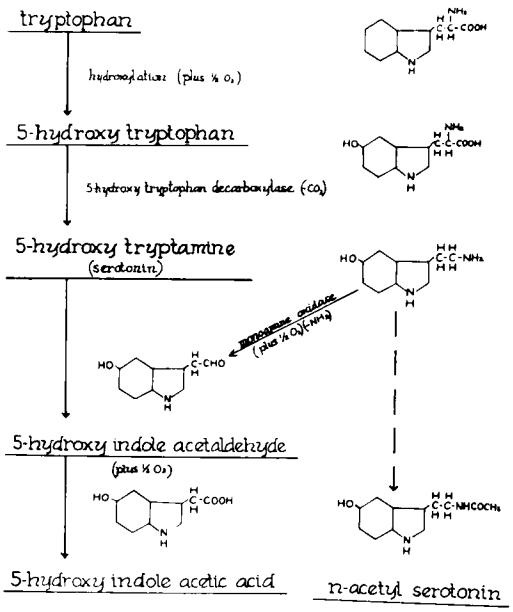

Fig. 1. Biogenesis and metabolism of serotonin.

man is chiefly accomplished by oxidative deamination through the action of the enzyme monoamine oxidase.[18, 26] Serotonin is thus first converted to relatively inert 5-hydroxy indole acetaldehyde and finally to 5-hydroxy indole acetic acid [26] which is excreted in the urine. Normally, 5-hydroxy indole acetic acid is the only serotonin metabolite found in the urine.[26, 13] Thus, increased urinary concentrations indicate an increased synthesis and destruction of body serotonin.[13] Monoamine oxidase, like 5-hydroxy tryptophan decarboxylase, is present in most body tissues and is found in high concentration in all portions of the brain.[18, 21] Inactivation of this enzyme by one of the monoamine oxidase inhibitors such as iproniazid, results in a decreased urinary excretion of 5-hydroxy indole acetic acid.[13]

Distribution of Serotonin

Normally approximately 90 to 95 per cent of body serotonin is contained within the Kultschitzky cells of the gastrointestinal mucosa.[13] Tissue values vary from 2 to 15 μg. per gram of intestine.[13] Carcinoid tumors which are composed of these cells may contain as much as 2 to 3 mg. of serotonin per gram of tumor.[25]

The remainder of serotonin is distributed in the blood platelets spleen and brain. Minimal concentrations are present in other tissues. Normally each milliliter of blood contains between 0.1 and 0.2 μg. of serotonin, all of which is bound to blood platelets. Little if any free serotonin exists in the serum.[27, 28] Platelet values of serotonin in carcinoid patients may reach 10 to 20 times this amount, while serum levels may rise above 5 μg. per milliliter.[20]

Concentrations of serotonin within the brain have received considerable attention because of their possible importance in normal and abnormal mental functions.[24] The largest amounts are found in the most primitive areas of the mesencephalon and diencephalon,[29] where similarly high concentrations of norepinephrine and 5-hydroxy tryptophan decarboxylase exist. Of the many theories proposed for establishing the physiologic role of serotonin in the brain, that of Brodie and Shore has aroused the greatest attention.[30] As a working concept, serotonin has been suggested as the chemical transmitter of central parasympathetic impulses, with norepinephrine as the central sympathetic transmitter. Arguments for and against the concept continue to be inconclusive.

The Malignant Carcinoid Syndrome

The attack is typified by a peculiar cutaneous flushing which involves the head, neck, thorax, arms and less commonly, the entire body. The skin first becomes fiery red and somewhat blotchy and then progressively assumes a cyanotic, dusky appearance. This cyanosis is first a bluish purple and finally becomes an intense bluish black. It may persist for hours after the other symptoms of the attack have subsided. Normal skin color first returns in the center of the cyanotic areas and progresses peripherally. Profuse perspiration and warmth accompany the attack. During the flush, nausea, vomiting, abdominal distension and cramps, anorexia and a watery diarrhea may develop. Some patients become dyspneic and develop respiratory stridor with the typical wheezing of an asthmatic attack. A dry, nonproductive cough may follow. A marked fall in blood pressure and tachycardia may occur during the attack and cause syncope.

With repeated exacerbations, various permanent tissue changes may occur. These include a rheumatoid type of arthritis, sclerodermic changes of the skin especially in areas of flushing, prominent telangiectasia about the face, chronic elevation of central venous pressure, engorgement of the external jugular veins, dependent edema and fibrosis of the tricuspid and pulmonic valves which may cause tricuspid insufficiency and pulmonic stenosis.

There is great variability in the number of symptoms and permanent changes manifested by the patient with carcinoid disease.[20] In some, these will be minimal; in others, all may appear simultaneously. Little direct correlation exists between the blood concentration of serotonin and the severity of the attack or the multiplicity of manifestations. It is possible to have high serotonin blood levels with few if any symptoms and even those present may be mild.

The release of bound serotonin from its sites of synthesis is precipitated by stimuli such

as palpation of an enlarged liver or intra-abdominal mass, hypotension, fear, anxiety, anger, alcoholic beverages, hot drinks, eating and defecation. Except for direct palpation of the tumor, hypotension is probably the most important stimulus for the release of serotonin just as it has been recognized to be for the release of catechol amines from an adrenal medullary tumor.[31] The degree of hypotension necessary to precipitate an attack is variable. Similar variations have also been observed in the frequency and duration of attacks. Typical symptoms may appear weeks, days or minutes apart and may last for a few minutes or a few days.

Diagnosis

Diagnosis of the functioning carcinoid syndrome is made from the characteristic history, the presence of an abdominal mass, the demonstration of elevated blood levels of serotonin during an attack and most consistently, an increased urinary excretion of 5-hydroxy indole acetic acid.[32] The normal 24-hour urinary excretion of this serotonin metabolite is between 2 and 9 mg. Values slightly greater than these are suggestive and those greater than 25 mg. 24 hours are diagnostic of a secreting carcinoid tumor. Carcinoid patients may excrete as much as 1,000 mg. of 5-hydroxy indole acetic acid per 24 hour period.[13]

Pharmacology of Serotonin

Serotonin is a potent smooth muscle stimulant [13] capable of producing vasoconstriction, contraction of the estrus uterus,[33] increased peristalsis [34, 35] and bronchoconstriction.[12, 13] Many factors such as dose, frequency of administration, species, individual response and site of action alter the pharmacologic properties of the drug.

The vasoconstrictor effects of serotonin are not consistent and are dependent to a great degree, upon the pre-existing neurogenic tone of the blood vessels.[12, 36] In the presence of increased vascular tone, serotonin may produce dilatation and hypotension; when initial tone is low, the drug produces vascular constriction and hypertension. In many instances, no effect on blood pressure will be noted.[36] The vasoconstrictor effect of serotonin on the pulmonary vasculature is far more constant. It is a powerful constrictor of the pulmonary vessels.[13, 37] In the dog and cat, it is more active in this respect than epinephrine or norepinephrine.[38] Infusions of as little as 10 μg. of serotonin per kilogram of body weight per minute in the dog, increases pulmonary artery pressure ten times.[39] It appears that serotonin is one of the few drugs with greater effect on the pulmonary vasculature than on the systemic circulation. Small doses of serotonin insufficient to cause systemic circulatory effects, are capable of producing pulmonary vascular constriction.[12] In the human patient, intravenous infusions of serotonin produce an increase in venous, right atrial and pulmonary arterial pressures [40] and as much as 50 per cent increase in cardiac output.[41, 42] In the patient with carcinoid, serotonin by direct effect, may produce intense pulmonary vascular constriction, pulmonary hypertension, a rise in central venous pressure and a fall in cardiac output. Some investigators feel that this response is not common.[13] Obviously, the variability of change in cardiac output is dependent upon the degree of pulmonary vasoconstriction which serotonin produces. Slight increases in pulmonary vascular resistance enhance cardiac output while marked increases will reduce it.

Serotonin produces arteriolar constriction and dilatation of the smaller blood vessels of the skin.[43] These changes account for the peculiar flushing responses of the carcinoid syndrome.

The bronchoconstrictor effect of serotonin is frequently observed in functioning carcinoids.[12] Asthmatic attacks with the characteristic wheezing, respiratory stridor and rhonchi, may be a prominent feature of the syndrome although all patients do not manifest it.[31] Some reports indicate that asthmatic symptoms respond well to routine medical measures; others report no benefit no matter what treatment is used.

Nausea, vomiting, diarrhea and abdominal cramps result from the contraction of the intestinal masculature by serotonin. These symptoms are often the first to appear and prompt the patient to seek medical advice.[44]

The right-sided cardiac lesions which appear with this syndrome are supposedly produced by the high titres of serotonin to which the tricuspid and pulmonic valves are chronically exposed. The absence of left-sided cardiac lesions is attributed to the metabolism of about two thirds of the serotonin in venous blood as it passes through the lung. Thus, the right heart is exposed to maximum serotonin concentrations while the left heart is not.[16]

Serotonin is an antidiuretic but the mechanism by which it produces this effect is unknown.[12, 13]

Anesthesia and the Carcinoid Syndrome

The administration of anesthesia to patients with serotonin secreting carcinoid tumors may be completely uneventful or it may be complicated by an exacerbation of symptoms of variable severity. A severe attack may produce death before surgery has begun. Less severe responses may cause many apprehensive moments. In the last five years, four patients with secreting carcinoid tumors received general anesthesia in this institution. Two of these patients, both females, had uncomplicated operative periods without active symptoms of the syndrome and no increase in the 24-hour excretion of 5-hydroxy indole acetic acid. The course of the other two patients, both male, will be described since they illustrate the anesthetic problems which arise.

Case 1—White Male, 51 Years Old. This patient entered the hospital on 1/22/59 with a chief complaint of abdominal distension, diarrhea and flushes. He first noted a change in bowel habits with distension, abdominal cramps and diarrhea early in 1957. Later that year he began having "flushes" involving the face and shoulders. These came on 4 or 5 times each day and lasted 2 to 3 minutes. A chronic cough developed and was accompanied by wheezing which was worse during the flushes. He noticed a loss of libido. His weight decreased from 216 to 183 pounds in a period of one and one-half years. Prior to his illness, he had been a heavy drinker. His positive physical findings included: flushes of the head and shoulders, conjunctival injection, mild emphysematous changes, mass in the RUQ with a palpable liver, erythematous areas of the skin with multiple small telangiectasia, thickening of the skin with eczematoid patches of the flush areas of the face and neck and the popliteal surfaces.

Positive Laboratory Findings

	Normal Value	Pre-operative 1/26/59	At Surgery 1/29/59	Post-operative
Uric acid (mg./%)	2.5–5.8	6.4		
Thymol turbidity (units)	Less than 5.5	12.3		
Whole blood serotonin (μg./ml. blood)	0.1–0.3	1.6	2.6	1.4
Platelet serotonin (μg. mg. platelet protein)	0.2–0.7	2.8	3.8	2.6
Urinary 5-OH indole acetic acid (mg. 24 hour sample)	2–9	160/825 ml. urine		186/1,635 ml. urine

Pre-operative diagnosis: Malignant Carcinoid Tumor with Liver Metastases Chronic Cholecystitis with Cholelithiasis.

On 1/29/59, an exploratory laparotomy was performed under spinal anesthesia (tetracaine 18 mg., phenylephrine 5 mg. and 10 per cent dextrose 1.2 ml.) with thiopental, endotracheal cyclopropane and ether supplementation. Premedication consisted of pentobarbital 100 mgs., meperidine 75 mg. and atropine sulfate 0.4 mg. Twelve minutes after the administration of the spinal anesthetic, the blood pressure fell from 134/80 to 80/60. With pressor treatment it rose to 120/80 within 10 minutes and remained stable. However, with the onset of the hypotension, the patient developed moderate flushing of the face, neck and shoulders, profuse perspiration and evidence of moderate bronchospasm. Respiratory exchange was maintained by controlled respiration. Inflation of the chest was slightly impaired and was accompanied by moderate wheezing. The patient had received thiopental 500 mg. by intermittent injection and topical 5 per cent cocaine spray to permit endotracheal intubation immediately following the administration of spinal anesthesia. We did not believe that the thiopental had initiated the bronchospasm. These changes did not require special therapy and in no way interfered with the conduct of the anesthesia or operation.

A primary malignant carcinoid tumor was found in the ileum which had spread to the regional lymph nodes and liver. The patient continued to have several flushing episodes with asthmatic symptoms each day. He was discharged unimproved.

Case 2—White Male, 52 Years Old. This patient entered the hospital on 1/13/55 with a chief complaint of painful swelling of the hands and lower legs of one month duration. Some change in bowel habits had developed with a tendency toward diarrhea of 3 to 6 watery movements per day. A weight loss of 10 to 15 pounds had occurred in the previous 3 weeks. Clinical findings included a well-nourished, well-developed white male weighing 180 pounds. The skin had a peculiar dusky color. The face was polycy-

themic with a strange plethoric hue. The hands and legs appeared grossly cyanotic. There was 2 plus pitting edema of the ankles but hard induration of the arms and upper legs. The skin changes were similar to those of advanced scleroderma. The chest was emphysematous with decreased breath sounds over the right thorax. Heart sounds were distant. A rough systolic grade 3 murmur was best heard at the apex. There was marked venous engorgement of the neck veins in the recumbent position. The liver was enlarged, firm and tender and protruded three fingers breadths below the costal margin.

Positive laboratory studies included a Bromsulfalein retention of 22.8 per cent after 1 hour; thymol turbidity of 7.2 units and a positive serology. All other routine studies were within normal limits.

Roentgenographic study of the gastrointestinal tract revealed a filling defect in the caecum. A provisional diagnosis of carcinoma of the caecum was made. Blood and urine determinations of serotonin and its metabolites were not performed since knowledge of the significance of secreting carcinoid tumors was not appreciated in 1955 at this institution.

The patient was scheduled for exploratory laparotomy on 2/7/55. Premedication consisted of morphine sulfate 10 mg. and atropine sulfate 0.4 mg. intramuscularly one hour prior to surgery. The patient was slightly apprehensive but in no acute distress; blood pressure 100/70 mm. Hg; pulse 76 and respirations 20. After the rapid intravenous injection of 400 mg. of 5 per cent thiopental and 4 mg. of decamethonium and manual pulmonary ventilation with 100 per cent oxygen, a no. 38 cuffed orotracheal tube was inserted under direct vision. A closed, to-and-fro, carbon dioxide absorption system was connected to the endotracheal tube and controlled respiration initiated. Anesthesia was to have been maintained using cyclopropane and ether. However, within 10 seconds following endotracheal intubation, the color of the entire body became fiery red. This bright redness soon began to disappear and the skin took on a progressively darker, purplish, cyanotic hue. Within minutes, the patient became intensely cyanotic: at first, bluish-black and then a death like grayish black. The nailbeds were completely black. Attempts to infiltrate the lungs were unsuccessful and it felt as though a clamp had been placed across the trachea. Only with tremendous positive pressure was it possible to force a small amount of oxygen into the lungs. This exchange produced no improvement in skin color. Blood pressure and pulse were absent, the pupils widely dilated and the venous distension of the neck veins tremendous. The patient appeared to be dead except for the presence of an active pupillary light reflex.

An electrocardiogram revealed a functioning, electrically intact heart with serious T-wave changes suggesting acute anoxia and evidence of cor pulmonale. The pulse rate was 36 per minute. Vigorous resuscitative measures (positive pressure oxygen and intravenous infusion of vasopressors) were instituted immediately. An intravenous injection of a therapeutic dose of diphenhydramine failed to improve the respiratory difficulty. Atropine 0.4 mg. intravenously did not increase pulse rate.

After 15 minutes of almost complete respiratory obstruction, inflation of the chest gradually became easier and after 25 minutes, adequate spontaneous respirations ensued. By this time, the intravenous infusion of 5 per cent dextrose in water containing 20 mg. of phenylephrine per 1,000 ml., had finally produced a detectable blood pressure of 50/20. After one hour, blood pressure returned to its preanesthetic level and stabilized without support. The deep cyanosis persisted for 6 to 7 hours before it improved. The patient had fully recovered consciousness and complained of headache. Obviously, operation was cancelled.

A few days later, a skin and muscle biopsy done under local anesthesia revealed scleroderma.

One week after the first episode, another attempt was made to administer general anesthesia to this patient. The same premedication was used. Induction of anesthesia was accomplished slowly by the injection of 100 mg. of thiopental. The larynx was cocainized thoroughly and endotracheal intubation easily accomplished. A to-and-fro closed, absorption system was used to administer cyclopropane and ether. Again the same changes occurred as previously observed but they came on less rapidly and were not as intense. Cyclopropane appeared to intensify the bronchospasm and its use was discontinued. Anesthesia was maintained by ether and oxygen. All curare preparations were omitted. Exploratory laparotomy revealed widespread metastatic malignancy which proved to be carcinoid tumor on histologic section. The patient made an uneventful recovery. He did not have similar attacks in the postoperative period. He was discharged from the hospital with no change in his original complaints.

Discussion

Although blood levels of serotonin or urine concentrations of 5-hydroxy indole acetic acid were not obtained in this last patient, there is little doubt that hyperserotonemia was the cause of the intense reaction which developed. The clear recognition of the difficulty remained obscure for years, until the classic changes of the syndrome were better documented in the literature. In retrospect, it was obvious that the most extreme type of response to serotonin

had been observed. Hypotension incident to the induction of anesthesia, caused the release of serotonin. Severe bronchial and pulmonary vascular obstruction resulted. In addition, intense cutaneous arteriolar constriction with cutaneous capillary dilatation produced the unusual flush phenomenon. The decrease and absence of systemic blood pressure was caused by pulmonary vascular obstruction with secondary reduction in left heart filling and left ventricular output. The severe degree of anoxia produced by the bronchospasm was evident in the T-wave changes of the ECG and the pronounced bradycardia. The rise in venous pressure and right heart preponderance were further indications of pulmonary arterial constriction.

The striking changes observed in the second patient are identical to the cardial changes of fatal pulmonary embolism. Efforts have been made to implicate serotonin in the pathogenesis of pulmonary embolism.[15, 16, 17] Although in the human a true cause and effect relationship remains to be demonstrated, the events of this case indicate that serotonin, in certain patients, may produce lethal pulmonary effects identical to those of fatal pulmonary embolism.

These two cases clearly demonstrate the variable responses produced by serotonin in the patient with carcinoid disease. In the first patient, minimal effects were noted during the attack which occurred during operation even though the highest blood serotonin level recorded during his hospitalization, was attained at that time. In the second case a fulminating response to serotonin developed in a patient who preoperatively had only vague symptoms of carcinoid disease. Similar responses with fatalities have occurred in patients during the anesthesia induction period and prior to the operative manipulation of the tumor.[18]

The preoperative recognition and diagnosis of carcinoid disease can help immeasurably in preventing a typical seizure during anesthesia or in ensuring effective resuscitative measures once the attack occurs. The variable manifestations of the syndrome may easily mask its correct diagnosis. It should be suspected if any or all of the previously mentioned signs or symptoms are present. The clinical suspicion may be confirmed by demonstrating increased blood titres of serotonin and increased concentrations of 5-hydroxy indole acetic acid in a 24 hour urine specimen. Exploratory laparotomy with tissue biopsy will supply the conclusive evidence. Surgical treatment consists of relieving intestinal obstruction if it be present and the excision of as much of the tumor mass as possible including liver metastases. Thus, operating time may be long and blood loss excessive. In most instances, only a biopsy is taken with no attempt at definite resection.

The choice of anesthetic agents and method should be made after due consideration to the following unique features of this syndrome: First, since hypotension is known to initiate attacks possibly through the liberation of catechol amines,[48] anesthetic agents and methods with the greatest potential for hypotension are perhaps poor choices. Thus an agent such as halothane or a method such as spinal or epidural anesthesia might be contraindicated for the patient with carcinoid. This is at best a relative contraindication since it is well appreciated that all general anesthetic agents have hypotensive properties. It appears that the abruptness of the fall in blood pressure is of relatively greater importance both in initiating the attack and patterning its severity, than the magnitude of the fall. Therefore the rapid injection of 350 or 400 mg. of thiopental intravenously, as in case 2, could produce a sudden fall in systemic blood pressure which would be a greater stimulus for the release of serotonin than a greater or more gradual fall produced by spinal anesthesia.

The onset of a severe attack producing marked hypotension during operation when employing spinal or epidural anesthesia may create a hypotension refractory to treatment. With both a decreased cardiac output due to pulmonary arterial constriction and a decreased peripheral resistance due to sympathetic block, all resuscitative efforts could be but weakly effective. While a decreased cardiac output during hyperserotonemia is rare and indicates an extreme response, nevertheless, it is impossible to know in whom it will develop. For this reason, the use of spinal or epidural anesthesia for patients with the carcinoid syndrome is not as safe as general anesthesia, even

though, in some patients the amount of general anesthesia required to produce comparably equal operating conditions will cause as great a fall in blood pressure. The factor of prolonged sympathetic block is absent with general anesthesia.

Second, since bronchoconstriction is the most common complication which develops during a carcinoid attack in the anesthetized patient, it is essential that a cuffed endotracheal tube be inserted at induction of anesthesia regardless of agents or method used. This will permit effective positive pressure ventilation in the event of a severe response. Neither the anesthetic nor technic used should induce changes which further augment the bronchospasm which may result. The use of thiopental or cyclopropane is perhaps unwise because of their bronchoconstricting tendency which is most commonly manifested in allergic states. Even though no evidence is available to indicate an allergic component in the bronchial response of the patient with carcinoid, these agents have in some degree contributed to the bronchospasm incident to an attack and therefore, must be used with caution and moderation.

Third, the precise physiologic function of serotonin within the body has not as yet, been identified with certainty. Numerous reports of specific effects of this amine have appeared in the literature but their significance remains obscure. Perhaps some have an importance in anesthesia. The ability of serotonin to potentiate hypnotics,[49] antagonize acetyl choline[50, 51] and tubocurarine,[52] release bound histamine,[53] produce mental sedation[30] and evoke parasympathetic responses[30] in addition to its direct smooth muscle stimulatory effects, are but a few of the areas to which future thinking in anesthesia should be directed. How these factors might influence choice of agents or method for the anesthetic management of the carcinoid patient remains to be seen.

The treatment of patients with this syndrome has been disappointing. The use of various serotonin antagonists such as BAS (benzyl analogue of serotonin), *d*-lysergic acid diethylamide, BOL-148 (2-bromo lysergic acid diethylamide)[54] and UML-491 (1-methyl-*d*-lysergic acid butanolamide tartrate)[55] has been generally ineffective. Chlorpromazine has provided some symptomatic relief chiefly by improving mental state rather than directly antagonizing serotonin.

Severe pulmonary vascular spasm is fortunately a rare reaction to a carcinoid attack. It has proven refractory to all types of treatment. The outcome for the patient depends upon the degree of obstruction of the lesser circulation and its duration.

Vasopressor agents used to treat the hypotension of a severe attack are relatively ineffective in restoring blood pressure when a marked decrease in left heart output is the primary deficiency. Lacking more effective therapy they deserve trial. Norepinephrine is perhaps contraindicated if it (as postulated) causes the release of serotonin.[48] Fluid therapy to combat hypotension is not without danger. Excessive fluid administration may further increase right heart pressure. Its elimination may be prevented or slowed by the antidiuretic property of serotonin.[54, 55]

Bronchospasm which develops during surgery has not been significantly reduced by the conventional bronchodilators. The antihistaminics have been used with equivocal results. They were not effective in the cases previously reported. Divided parenteral doses of epinephrine have not provided the relief anticipated. The additional release of serotonin and increased pulmonary vascular constriction following administration of epinephrine, perhaps contraindicate its use. Cyclopropane and thiopental increased the severity of the bronchospasm in case 2, while diethyl ether, though not providing appreciable improvement, at least did not accentuate it. The only reliable treatment of severe serotonin induced bronchospasm is vigorous, manual, positive-pressure respiration, utilizing pressures that prove effective. Resuscitation should be continued until spontaneous, adequate ventilation returns.

Summary

Primary tumors of the chromaffin cells of the intestine which undergo malignant change, may synthesize a biologically active substance, 5-hydroxy tryptamine or serotonin, which, when released into the circulation in high concentration, produces a bizarre symptom

complex known as the malignant carcinoid syndrome. Serotonin is a normal body constituent and is found in highest concentration in the chromaffin or Kultschitsky cells of the intestine, the blood platelets, brain and spleen. Normally its synthesis chiefly occurs in the intestinal wall and to a lesser degree, in the brain. It is derived from the amino acid tryptophan.

Patients with carcinoid tumors may develop an exacerbation of their symptoms or "attack" while receiving anesthesia. The severity of the symptoms is quite variable. Rarely, the attack may be extreme. The anesthetic management of these cases requires great skill and an understanding of the basic pathophysiologic changes induced by serotonin.

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