1967

# Serotonin and the carcinoid syndrome

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The Senior Thesis

University of Nebraska College of Medicine

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## History

The past ten to fifteen years has brought about the widespread recognition of a relationship between a newly discovered biochemical substance, an unusual type of tumor which produces this substance and a group of symptoms which results in a peculiar syndrome - the malignant carcinoid syndrome. The literature dating back one and a half centuries is filled with reports of cases compatible with this syndrome but not recognized as such until the 1950's. In 1808 Merling[1] recorded the first case of a tumor compatible with the carcinoid tumor and Langhans[1] in 1867 reported a case of a gastrointestinal carcinoid tumor but failed to recognize it as such. Berger[1] in 1882 described a case of carcinoid of the appendix. In 1888 Lubarsch[2] used the term "little carcinoma" and gave the first detailed description of a case having multiple submucosal carcinoids of the ileum with distant metastases, and in 1890 Ransom[1] reported a similar case. Kultschitzky[3] in 1897 described chromaffin cells in the intestine capable of reducing silver compounds. In was in 1907 that Oberndorfer[2] coined the term "carcinoid" to differentiate between the malignant adenocarcinoma-like appearance but benign nature of this neoplasm from the more malignant behaving carcinomas of the bowel. Saltykow[2] in 1912 reported the first case of rectal carcinoid. Two years later Gossett and Masson[2] in 1914 found

histologic evidence which showed that carcinoid tumors arise from the Kultschitzky cells of the intestinal epithelium. In 1928 Masson and Martin[3] applied the name argentaffinoma to this group of tumors since they had cytoplasmic granules in the cells which reduced silver salts. One of the first recognizable cases of the carcinoid syndrome, secondary to a rectal primary, was reported by Cassidy[1] in 1930 although he did not recognize the syndrome as such.

Ersparmer and Vialli[3] in 1933 began the work on a substance which they called enteramine, and in 1948 Rapport[1] designated the vasoconstrictor substance, found to be high in the serum of patients with carcinoid tumors, as serotonin. One year later the structural formula of 5-hydroxytryptamine was proposed for this pressor substance. Ersparmer and Asero[1] demonstrated that Kultschitzky cells secrete serotonin in 1952. That same year Thorson et al[4] reported a case with flushing, pulmonary stenosis and tricuspid insufficiency who at autopsy had a carcinoid tumor of the ileum with liver metastases. The following year, 1952, Lembeck[1] reported the presence of excessive 5-hydroxytryptamine in carcinoid tumors and so established the probable relationship between serotonin and the carcinoid syndrome reported by Thorson. In 1955 Page[1] discovered that the urine of patients with the carcinoid syndrome contained excessive amounts of 5-hydroxyindoleacetic acid.

Metabolism of Serotonin

Serotonin (5-hydroxytryptamine or 5-HT) is a relatively newly discovered product of human protein biosynthesis, and it is now known that it is made from the parent amino acid tryptophan. Tryptophan's primary role in intermediary metabolism is the production of nicotinic acid (niacin). Under normal circumstances only 1 per cent of this absorbed amino acid is converted to serotonin along a secondary pathway in tryptophan metabolism (Figure 1).

Serotonin synthesis begins with the hydroxylation of tryptophan to 5-hydroxytryptophan (5HTP) by a hydroxylating enzyme known to be present in the liver and which is probably present in other tissues as well. Up to 60 per cent of the dietary tryptophan versus 1 per cent normally may be hydroxylated and shunted toward serotonin in the patient with the carcinoid syndrome.[6] Next 5-hydroxytryptophan decarboxylase, an enzyme which is present throughout the body and especially in the Kultschitzky cells lining the crypts of Lieberkuhn of the intestine, decarboxylates 5-hydroxytryptophan to 5-hydroxytryptamine, (serotonin) and $CO_2$. The serotonin produced is then released into the blood where most of it is absorbed by the platelets and transported in the platelet granules; although a small, often immeasurable fraction, may remain free in the blood. Most of the serotonin produced has a short lifespan as a large percentage, especially in patients with

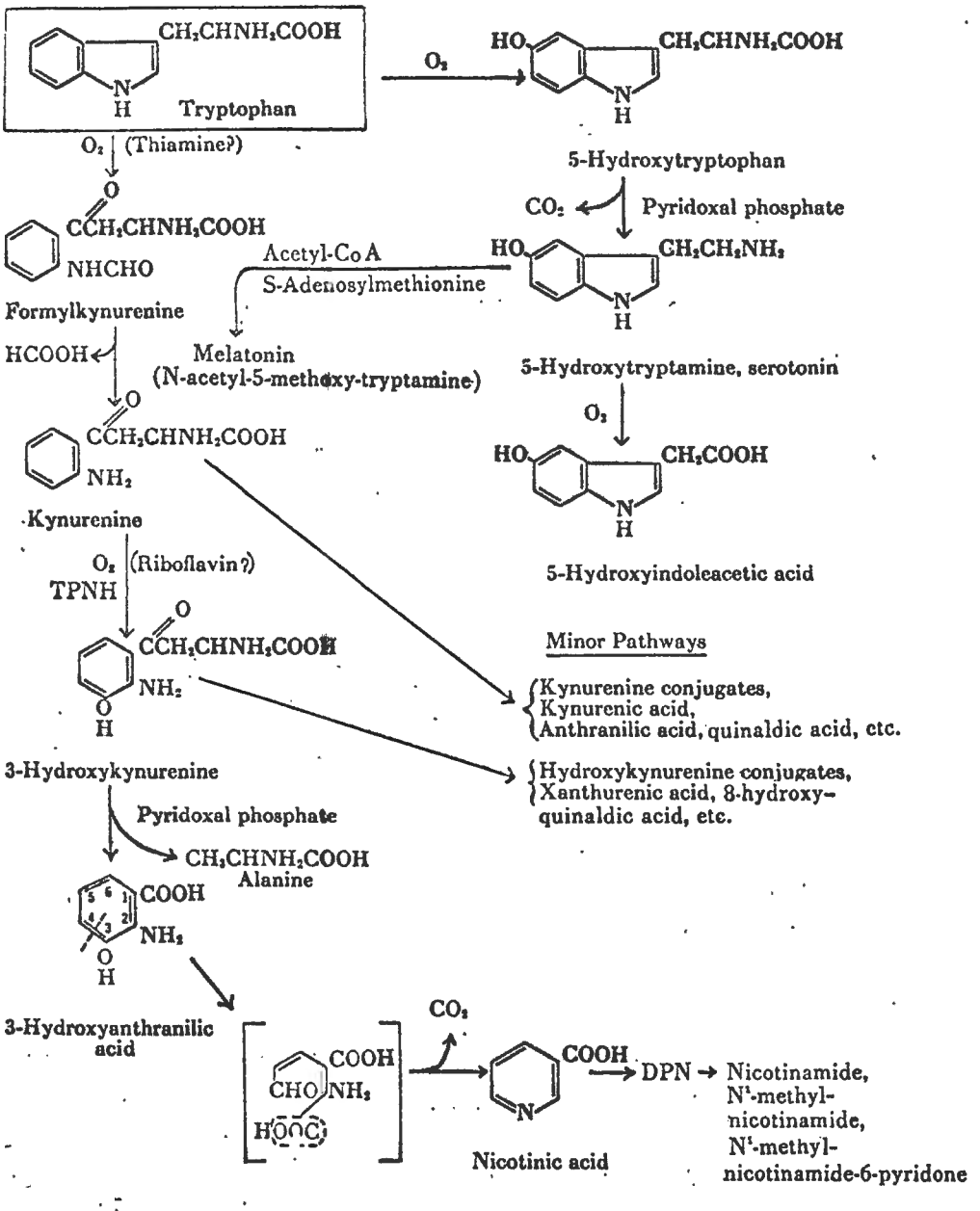
Tryptophan
5-Hydroxytryptophan
Pyridoxal phosphate
(Thiamine?)
Acetyl-Co A
S-Adenosylmethionine
Formylkynurenine
Melatonin
(N-acetyl-5-methoxy-tryptamine)
5-Hydroxytryptamine, serotonin
Kynurenine
5-Hydroxyindoleacetic acid
(Riboflavin?)
TPNH
Minor Pathways
Kynurenine conjugates,
Kynurenic acid,
Anthranilic acid, quinaldic acid, etc.
3-Hydroxykynurenine
Hydroxykynurenine conjugates,
Xanthurenic acid, 8-hydroxy-quinaldic acid, etc.
Pyridoxal phosphate
Alanine
3-Hydroxyanthranilic acid
Nicotinic acid
DPN
Nicotinamide,
N¹-methyl-nicotinamide,
N¹-methyl-nicotinamide-6-pyridone

Figure 1.[5]

the carcinoid syndrome, is deaminated to 5-hydroxyindoleacetic acid (5-HIAA) by monamine oxidase abundantly present in the liver and lungs. This final product of serotonin metabolism, 5-HIAA, is then readily excreted in the urine.

Location of Serotonin

Serotonin is normally present in many tissues and fluids of the body but there are three main sites where large deposits are known to exist: gastrointestinal mucosa, platelets and in the central nervous system. Of these the largest concentrations are in the mucosal enterochromaffin cells of the gastrointestinal tract, but not the muscle layers. These cells are found everywhere from the esophagocardiac junction to the anus with the highest concentration of these argentaffin cells in the duodenal mucosa[7] and pylorus of the stomach.[6] That the intestinal tract is the major site for serotonin production was shown by Haverback et al;[8] when 5-hydroxytryptophan was given to patients with extensive gastrointestinal resections and the same dose given to a normal control group. In the group with resections the blood serotonin and urinary 5-HIAA levels never became elevated so that these levels could be measured; whereas in the controls or patients with various other gastrointestinal diseases the blood serotonin and urinary 5-HIAA level both were significantly elevated.

The platelets are second only to the gastrointestinal tract as a depot for serotonin. The platelets carry and store

5-HT, but they are unable to synthesize it and so must instead pick it up already synthesized by enterochromaffin cells of the gut. As the platelets have a great affinity for 5-HT only negligible amounts are normally present free in the plasma.[8] The third major source of body serotonin is the brain, especially the hypothalmus and midbrain with very little in the cerebral cortex or cerebellum.[7] Unlike the platelets, the CNS is apparently able to synthesize its own serotonin. It has been shown that only 5-hydroxytryptophan and not 5-hydroxytryptamine (serotonin) can cross the blood-brain barrier, and so the serotonin so abundantly present in the midbrain must be synthesized somewhere within this barrier.[6]

Lesser amounts of serotonin have been found in the liver, kidney, spleen, lung and heart where in most of these sites it is stored in mast cells. In man all body fluids contain serotonin with concentrations ranging from 0.15 to 0.70 micrograms/ml. of platelet protein in blood to the lowest serotonin concentration in cerebral spinal fluid of 0.006 micrograms/ml.[7]

Physiopharmacologic Action of Serotonin

Numerous physiologic and pharmacologic actions have been proposed for serotonin but many are still widely debated. The actual normal physiologic functions of serotonin in the human body are still largely speculative. Its effects on certain systems of the body are, however, now more than theory

and have been repeated over and over again in the laboratory. Basically serotonin has been found to cause contraction of smooth muscle at numerous sites in the body. These include its effects on the gastrointestinal, cardiovascular, and respiratory systems whereas its role in the nervous system and hemostasis is still questionable.

Serotonin has a stimulating effect on intestinal motility which is very sensitive to doses of either 5-HTP or 5-HT, so low that respiration, blood pressure, pulse or mental activity is not affected in any way.[8] The increase in peristalsis seen after serotonin administration is probably illicited by several mechanisms:[5] 1) by direct stimulation of smooth muscle of bowel and 2) by lowering the threshold of stretch receptors in the mucosa which trigger the reflex. Hence serotonin probably does have a neuroendocrine role of importance in the regulation of intestinal motility, and the proximity of the enterochromaffin cells to the terminal fibers of the submucosal plexes of Meissner is for a purpose.[8] It has been shown in guinea pig experiments that serotonin does act on the postganglionic cholinergic fibers of the intramural nervous system of the ileum.[9] It is of interest that lysergic acid diethylamide, although it inhibits the properties of serotonin elsewhere, potentiates the intestinal motility stimulated by 5-HT.[8] Also bromylsergic acid diethylamide, which lacks the hallucinogenic properties of LSD, inhibits the intestinal motility induced by 5-HT.[8] The effects

of serotonin on gastrointestinal secretions is still controversial. Page[9] reported in 1958 that serotonin sharply increased gastric acid secretion but not water secretion, whereas histamine would increase both acid and water release. He showed that rats given large doses of 5-hydroxytryptophan developed hemorrhagic mucosal erosions in their stomachs but that when pre-treated with atropine the number and size of these lesions decreased. About this time others reported that both 5-HT and 5-HTP would seem to decrease acid secretion, but it would stimulate mucus secretions of the stomach.[8] More recently Bochus[10] has stated that 5-HT has no effect on gastric acidity following IV administration, but that a patient given 5-HTP prior to testing their secretory responses to insulin or urechole responds with less gastric acidity and less gastric secretions than would normally be anticipated.

Effects on Cardiovascular System

Rapidly injected IV serotonin results in a biphasic blood-pressure response with transient initial rise in blood-pressure followed by a longer phase with hypotension.[1] The initial hypertensive episode is the result of direct vasoconstriction action of serotonin on vascular smooth muscle as is seen when vessels are lacerated at the time of an injury. This contributes to the hemostasis of the body. The receptor sites along the smooth muscle of vessels are not known but as the action of serotonin on smooth muscle is blocked by LSD, a

serotonin antagonist, which has no effect on the action of either acetylcholine or epinephine on the same smooth muscle; it is assumed that each works at a specific receptor site.[11] Likewise promethazine and cyproheptadine, other 5-HT antagonists, block the action of serotonin but not that of either acetylcholine or norepinephrine.[11] The secondary prolonged drop in blood pressure cause by IV serotonin may be due to the Bezold-Jarisch reflex with bradycardia, apnea and hypotension or it may be due to histamine being released.[11] Page has suggested that serotonin may cause a secondary release of endogenous histamine causing a peripheral inhibition of neurogenic vasoconstriction.

In addition serotonin has been shown to have other affects on the cardiovascular system. It causes constriction of the vessels concerned with peripheral resistance while dilating the minute vessels of the skin causing a cutaneous flush with blotchy cyanosis.[1] Peskin et al[6] have pointed out four other probable effects of serotonin on blood hemodynamics. First, the pulmonary circulation, although not responsive to most of the agents which affect the systemic vasculature, does undergo vasoconstriction of the pulmonary vessels with pulmonary hypertension and so serotonin released by tissues and platelets at the time of pulmonary embolism may play major role in the vascular changes noted in the lungs after embolic damage. Next it has been noted that 5-HT is a powerful stimulant of

the carotid body chemoreceptors. Likewise 5-HT has a local effect on the carotid sinus causing a reflex fall in arterial pressure with secondary baroreceptor stimulation and local vasoconstriction. Fourth and finally, Peskin et all reported that serotonin effects kidney function by decreasing both renal blood flow and glomerular filtration rate with a slight rise in mean pressure, hence the antidiuretic effect of serotonin seen in laboratory animal stories.

Effects on Respiratory System

Serotonin also acts on the smooth muscle in the lungs most notable as a bronchoconstricting agent. Serotonin has been suggested as a partial explanation for the frequent asthmatic attacks seen in otherwise normal people because it can precipitate a severe episode of dyspnea in the asthmatic. The syndrome which it causes when given IV resembles that caused by anaphylaxis and histamine. Serotonin also acts on vagal afferent fibers in the lungs to cause rapid shallow breathing with eventual decline in spontaneous respiration.[6]

Effects on Central Nervous System

The importance of central nervous system serotonin is perhaps the least well understood area in serotonin physiopharmacology. Its concentration is highest in the hypothalmus and midbrain where most of it is bound to mitochondria. It

is believed to be involved in mental function as changes in cerebral serotonin have been noted to cause behavioral changes in man. Pfeiffer et al[12] suggest "that serotonin is a vestigial neurohumor which benefits mental patients by its absence". Elevated cerebral serotonin levels are achieved slowly even with high blood serotonin levels since 5-HT passes through the blood brain barrier slowly but 5-HTP passes into CNS rapidly (where it is converted to 5-HT). This elevation in cerebral serotonin results in progressive euphoria, agitation and finally a schizoid type of psychosis. Many serotonin antimetabolities may result in mental disturbances. Reserpine causes depletion of brain serotonin from storage granules enabling MAO to destroy it and this probably explains the tranquilizing effects of reserpine.[1] Lysergic acid diethylamide, a serotonin antagonist with hallucinogenic properties, so interferes with 5-HT at the receptor sites as to cause a psychic reaction like in schizophrenia.[7] The MAO (monamine oxidase) inhibitors like iproniazid are psychic energizers which slow serotonin degradation in the brain by interfering with the enzyme monamine oxidase; hence, cerebral serotonin increases causing mood elevation and so they are useful in depressive reactions where they act as indirect CNS stimulants.[7]

Effects on Hemostasis

It is well known that platelets contain a large supply

of serotonin which they have derived from the intestinal mucosa where it was synthesized by the enterochromaffin cells. The mechanism by which platelets gain serotonin has been described by one authority Haverback[7] as follows: at the optimum temperature of 37°C, there appears to be a cation exchange whereby potassium ions leaves the platelets permitting serotonin to enter the cells. He says this is by active transport and so even when this exchange is inhibited by cyanides, iodoacetates or cardiac glycosides the platelets can still take up plasma serotonin just by increasing the concentration of the latter so as to increase the concentration gradient. Once the platelets take up the serotonin it must be bound for storage in a biologically active state, and ATP probably plays a role in the binding. The mechanism by which platelet serotonin is released is unknown.

Miscellaneous Effects

Other physiopharmacologic actions of serotonin in the human body are of lesser as well as somewhat more speculative importance. These include its actions on the genitourinary system. In the pregnant women there appears to be a progressive rise in urinary serotonin as term approaches and from dog experiments it has been shown to cause uterine contractions of increasing strength, each contraction followed by a period of inhibition of contraction lasting up to seven minutes.[9] In the kidneys serotonin acts as a renal diuretic first by decreas-

ing renal plasma flow and thereby decreasing the glomerular filtration rate and secondly by the facilitation of tubular reabsorption of water.[1] Serotonin also causes contraction of ureteric muscle, at least in dogs, slowing the passage of perfusion fluid through the ureters; this ureter spasm lasting longer than that seen transiently with the catecholamines.[9] Serotonin released by the mast cells plays an important part in connective tissue maturation. Finally it has been shown that large amounts of circulating serotonin are found following pulmonary emboli released by platelet disintegration and mast cell destruction both of which are rich in serotonin.[13]

Malignant Carcinoid Syndrome

The malignant carcinoid syndrome also known by the eponym Thorson-Biorck syndrome (two early recognizers of this syndrome)[4] is a complex of signs and symptoms resulting when a characteristically slow growing serotonin producting primary tumor, generally arising somewhere in the gastrointestinal tract, metastasizes to the liver or some other area where the venous drainage of serotonin from the secondary tumors may bypass the liver. These tumors produce large amounts of serotonin converting the majority of the dietary intake of the amino acid tryptophan to serotonin and in so doing leave little tryptophan for niacin and protein synthesis. Whereas normally one 1 per cent of the body's tryptophan stores give rise to

serotonin in this syndrome the carcinoid tumors may convert greater than 60 per cent of this amino acid to serotonin and in so doing cause hypoproteinemia and pellagra.[14]

The manifestations of each patient with the carcinoid syndrome vary somewhat, but many have the more typical signs and symptoms in common. The classical findings present at one time or another in these patients include: (1) peculiar episodic flushing especially of the face and neck from vasomotor changes in the skin with eventual telangiectasia and cyanosis; (2) chronic watery diarrhea with borborygmus and colicky abdominal pain from intestinal hyperperistalsis;[15] (3) an unusual type of "bronchial asthma with dyspnea" tachypnea, and hyperpnea due to bronchiospasm and bronchioconstriction;[16] and (4) pulmonary and tricuspid murmurs secondary to cardiac vascular disease with endocardial lesions of the right side of the heart.[9]

Other less common but nonetheless important findings in occasional patients with carcinoid syndrome are: (1) the patchy hyperpigmentation of the skin from nicotinic acid deficiency;[16] (2) increased capillary permeability with decreased glomerular filtration resulting in depressed renal function with oliguria which together with the hypoalbuminemia and possible portal hypertension causes edema, pleural effusion, ascites and anasarca;[16] (3) psychosis secondary to the poorly understood functions of serotonin on the central nervous

system,[3] and rarely arthropathy.[13]

As they develop, the clinical manifestations are initially mild and transitory, but they gradually increase in severity over a period of years with growth and metastases of the carcinoid tumor. These patients often present with palpitation, stiffness or swelling of the face and diarrhea consisting of up to twenty or thirty loose stools per day without any evidence of blood, leukocytes or other inflammatory products. With progression of the disease, episodes of weakness, tenseness and nausea may occur. Still later the patient may have flushing episodes of the skin especially over the face lasting minutes to days; respiratory distress from asthma-like attacks with dyspnea and wheezing; paresthesias with hot tingling sensations in the hands and feet; and gastrointestinal complaints of transitory dysphagia, abdominal cramps, borborygmi with the expulsion of flatus and watery stools. More terminally there is weight loss, shock-like attacks with weakness, severe abdominal pain, extreme cyanosis with cold wet skin, absence of recordable pulse and blood pressure and prolonged apnea possibly requiring artificial respiration. In the chronic patient with the carcinoid syndrome the superficial changes often make the diagnosis as in the patient with cutaneous telangiectasia, injected sclerae, extreme cyanosis during flushing episodes and finally a reddish hue with thickening of the skin.[10]

Incidence

The occurrence of carcinoid tumors is very uncommon; the general incidence being 0.08 per cent of all surgical and autopsy cases studied (138 out of 175,891 cases) according to one study referred to by Peskin et al.[2] Other similar combined studies of surgical and necropsy series by various investigators reviewing large numbers of cases have sited incidence ranging from 0.05 per cent to 0.20 per cent.[6] Since a large percentage of these carcinoid tumors are incidental non-serotonin producing asymptomatic tumors found in the appendix following appendectomies, perhaps 90 per cent of all carcinoid tumors, the incidence of malignant carcinoid syndrome is much smaller than the figures mentioned above. The incidence of carcinoids is between 0.1 per cent to 0.5 per cent of all tumors.[17]

There are no sex or race influences noted in studies done thus far, and no age group is exempt from having a carcinoid tumor. The literature is full of cases with these tumors ranging in age from ten days to eighty-nine years.[6] Appendiceal carcinoids are the commonest site in younger people especially between ten and thirty years of age and when found are usually benign appearing, non-serotonin producing tumors without any evidence of metastases or systemic symptoms discovered following either an obligatory or elective appendectomy.[6] Extra-appendiceal carcinoids, however, are

more often malignant in appearance with metastatic lesions and the manifestations of the malignant carcinoid syndrome. These are generally found after the age of fifty in the fifth and sixth decades of life.[2] Of interest also is the fact that multiple primary carcinoids have been reported in about one-third of the cases.[17]

Classification Based on Location

Various classifications of carcinoid tumors have been attempted, but the best and most recently accepted is that of Peart et al.[18] According to this classification the foregut derivatives include: (1) bronchus, (2) stomach and (3) pancreas; the midgut derivatives include: (1) midduodenum, (2) small intestine with caecum and (3) colon as far as mid-transverse colon; and the hindgut derivatives include: (1) descending colon and (2) rectum.[18]

Peart's classification is as follows:

The Classification of Carcinoid Tumors Derived from Different Embryonic Divisions of the Gut

| | Foregut | Midgut | Hindgut |
|---|---|---|---|
| Histological Structure | Tendency to be trabecular, may differ widely from classical pattern | Characteristic (nests of regular cells separated by connective tissue framework) | Tendency to be trabecular |

| | Foregut | Midgut | Hindgut |
|---|---|---|---|
| Argentaffin and Diazo Reactions | Usually negative | Positive | Often negative |
| Association with Carcinoid Syndrome | Frequent | Frequent | None |
| Tumor 5-HT (Serotonin) Content | Low | High | Not detected |
| Urinary 5-Hydroxyindoleacetic Acid | High | High | Normal |
| 5-HTP (Hydroxytryptophan) Secretion | Frequent | Rare | Not detected |
| Metastases to Bone and Skin | Common | Unusual | Common |

The location of the various carcinoid tumors plays an important part in the pathology, the tendency to cause the carcinoid syndrome and the relative malignancy of these tumors. They may arise anywhere in the body where argentaffin (Kultschitzky) cells are found including: any part of the gastrointestinal tract from the esophagogastric junction to the anus, and even the biliary tract and pancreatic ducts; the epithelium of the bronchial tree; and extremely rarely the ovaries in gonadal teratamas. Most, however, arise between the cardia and the anus from the argentaffin cells in the gastric glands or crypts of Lieberkuhn. The most common sites for carcinoids are: first-appendix, second-terminal ileum, and third-rectum with stomach, jejunum, duodenum, colon and Meckel's diverticulum following behind (in this approximate order).[16]

## Carcinoids of the Appendix

Various studies have shown that anywhere from 60 to 90 per cent of all carcinoids originate in the vermiform appendix.[16] Someone has generalized that about 90 per cent of all carcinoids are in the appendix and that 90 per cent of all tumors of the appendix are carcinoid.[19] There is no sex difference in the incidence, and the average age for appendiceal carcinoids is twenty to thirty-five years. These tumors are nearly always diagnosed post-operatively following appendectomy or laporatomy and occasionally at autopsy. They rarely became malignant and have a very low matastatic tendency possibly due in part to the fact that they most commonly occur in the distal tip of the appendix where early in their course they may cause obliteration of the appendix with appendicitis. Hence they are recognized early and at a young age while still a relatively benign tumor.

## Carcinoids of the Small Bowel

The small bowel carcinoids, although much less common than the appendiceal carcinoids, are the most common type of carcinoid to become clinically functioning tumors causing the malignant carcinoid syndrome. From 5 to 25 per cent of all small bowel carcinoid tumors cause this syndrome.[9] Of all the argentaffinomas, about 27 per cent occur in the ileum or je-

junum with the distal ileum being the most common side in the small intestine. In spite of the fact that the argentaffin cells are most numerous in the duodenum, carcinoids there are rare, and when present rarely become malignant. It is of interest that whereas most carcinoids of the small bowel are in the ileum, most carcinomas of the small bowel are in the jejunum. This same study by Diffenbaugh et al has shown that 23 per cent of all small bowel tumors are carcinoid.[20] Carcinoid tumors of the ileocecal valve, caecum, and colon can be included with this group as they act similarly to cause the carcinoid syndrome, although very few have been reported.[17] These carcinoids may extend widely about the bowel in the submucosa without causing ulceration or obstruction, and so often are not detected until after they have metastasized. The presenting manifestations then are usually due to the ulceration with bleeding, obstruction of the intestinal lumen or to the characteristic findings of the carcinoid syndrome.

In the ileum carcinoid tumors grow very slowly and metastasize late; hence unlike appendiceal carcinoids they have ample time to become malignant and spread before becoming symptomatic. These and other small intestinal carcinoids may manifest themselves as acute intestinal obstruction: (1) due to intussusception of a polypoid tumor, (2) by metastasizing to regional lymph nodes causing conglomerate masses which may cause kinking, volvulus or extrinsic compression of

the intestinal lumen, (3) by causing proliferation of connective tissue elements resulting in annular constriction of the lumen or (4) rarely by intrinsic growth with ulceration and secondary edema causing obstruction.[21] In a few cases the presenting manifestations were gastrointestinal bleeding, but only rarely has massive intestinal bleeding been noted. Rarely a case is reported where ascites, jaundice, and hepatomegaly secondary to a large metastatic portal system inplantations or obstruction of the ampulla of Valer has been the first evidence of carcinoid tumors. Most commonly, however, small bowel carcinoids present with one or several of the characteristic findings of the carcinoid syndrome namely cyanosis, flushing, asthma, diarrhea or valvular heart disease. Up to 25 per cent of these carcinoid tumors of the ileum may produce the carcinoid syndrome.[9] Multiple primary carcinoid are most common with small intestine carcinoids being recorded in 28 per cent of the cases in one study by Peskin et al,[6] multiple sites being common with extra-appendiceal carcinoids (16 to 34 per cent) but rare with the appendiceal tumors.

Of the numerous possible locations for carcinoid tumors those of the small bowel are probably most aptly located to metastasize and cause the malignant carcinoid syndrome. Since both the liver and the lungs have a rich supply of monamine oxidase which inactivates the serotonin passing through them, the primary carcinoid tumors or their metastases must be so

located that the blood flow from it bypasses the lung. A primary carcinoid so located as to have a venous drainage pattern bypassing the liver is unusual, so this syndrome is rarely caused by the serotonin secreted by a primary carcinoid tumor in the absence of metastases. The blood flow from these primary tumors invariably passes through the portal system and into the liver where the serotonin is inactivated. The exceptions to this being the rare carcinoids in ovarian teratomas or bronchial adenomas where their venous drainage bypasses the liver and so diagnostically high serotonin blood levels may be found without evidence of metastases.[16] The malignant carcinoid syndrome is almost always secondary, however, to the small bowel carcinoid which metastasizes to the liver where the serotonin they synthesize is dumped into the hepatic veins and inferior vena cava without coming into contact with the liver parenchyma, and its supply of monamine oxidase. This then explains why it is the intestinal carcinoid tumors, which can and do spread to the liver, that are the most frequent cause of the malignant carcinoid syndrome.

Carcinoids of the Rectum

The third most frequent site of the carcinoid tumor is the rectum where they are unique; they frequently may become malignant with metastases, but where they rarely have caused

a recorded case of the malignant carcinoid syndrome with its clinical manifestations. The rectal carcinoid tumors like those in the stomach have very few of the silver-staining granules present in the carcinoid tumors present in other gastrointestinal sites. These granules are called argentaffin granules because of their affinity for silver salts which react with a substance formed from the serotonin present in certain of these tumor cells. The infrequency with which rectal carcinoids take up silver stain indicates that they are unable to synthesize serotonin and may explain why there are no reported cases of functioning carcinoid syndrome due to rectal carcinoids or its metastases.[22] Rectal carcinoids occur equally in males and females; the average age being forty years in males and slightly younger in females.[23] These tumors are often found while still small, non-invasive and symptomatic on routine proctoscopic examination. When they do become symptomatic, the presenting manifestations are often hematochezia, melena, tenesmus, low back pain; constipation; diarrhea or obstructive symptoms as from an abdominal mass; but about one-third of all rectal carcinoids remain asymptomatic.[22]

The degree of malignancy of a rectal carcinoid, 8 to 40 per cent of which are said to become malignant, depends on the size of the tumor, evidence of local invasion, lymphatic involvement, or evidence of distal metastases.[22] The degree

of malignancy cannot be determined by the cellular elements on histological examination since even those which appear to be benign microscopically may cause distal metastase. Peskin and Orloff[2] after following a series of twenty-five cases of rectal carcinoid established the criteria now widely accepted as to the degree of malignancy and the choice of surgical resection for different rectal carcinoids. Of the twenty-five cases, ten had diameters measured by the pathologist of greater than 2.0 centimeters in their greatest diameter, of which nine of these cases were found to have metastases and/or widespread local extension. Of the remaining fifteen cases measuring less than 2.0 centimeters, only one showed any signs of malignancy. Furthermore, Haugh's[23] study and evaluation of the malignancy of rectal carcinoids, according to the size of the lesion, revealed the following:

| Size | Benign | Malignant | Total |
|---|---|---|---|
| less than 1 cm | 87-95% | 4-5% | 91 |
| 1-2 cm | 60-89% | 8-11% | 68 |
| more than 2 cm | 8-20% | 32-80% | 40 |

The size of rectal carcinoid tumors is an important feature as far as the choice of surgical procedure is concerned.[2] First, if distal metastases are present at the time of the operation, then only palliative treatment, as resection of the affected rectum with colostomy, is done. Secondly, if on biopsy the specimen appears to be confined to the submucosa of the bowel without evidence of local or distal extension and/or if

the tumor is less than 2.0 in greatest diameter, then only local excision is recommended for removal of these tumors. Third and finally, if histologic sections from the rectal biopsy reveal extension of the neoplasm into the muscle layer of the bowel and/or the tumor is greater than 2.0 centimeters in diameter, then an abdominoperineal resection should be done.

Carcinoids of the Stomach

Less commonly argentaffinomas occur in the stomach where they may comprise 2 or 3 per cent of all carcinoids. About 50 per cent are malignant with evidence of metastases, but because of their slow growth they often do not act malignant. Multiple primary lesions occur in the stomach in about 20 per cent of gastric carcinoids.[16] Like the rectal carcinoids they have very few artentaffin granules; but unlike the rectal carcinoids a few cases of the malignant carcinoid syndrome have been reported secondary to gastric carcinoid tumors. There distribution among the sexes is equal, and they generally occur after the age of forty years but have a good post-diagnostic survival time usually of eight to sixteen years.[3] They are reported as occurring with nearly equal frequency in the antrum, pyloric area, along either the greater or lesser curvatures or in the midgastric areas. The presenting manifestations may be epigastric pain, melena, hematemesis, weight loss, anemia, nausea or vomiting. On roentgenographic or gastroscopic examination a

small polyp-like filling defect is often noted. The treatment of choice is resection of the primary tumor plus removal of any metastatic lesions noted.[3]

Carcinoids of the Bronchial Passages

The gastrointestinal tract is not the only site where argentaffin cells are found, some are also dispersed throughout the bronchial epithelium and from these cells bronchial carcinoids have been known to occur. These are very uncommon as only about 5 to 10 per cent of all primary lung neoplasms are bronchial adenomas, the rest being bronchogenic cancer; but of these adenomas about 85 per cent are bronchial carcinoids[16] (the other 15 per cent are either cylindromas or mucous adenomas). Bronchial carcinoids are locally invasive, slow growing and only rarely metastasize. The cases reported with this type of lung neoplasm generally present with the same findings as other neoplasms in the lung: cough, hemoptysis or recurrent bouts of pneumonitis, and so biopsy is necessary to make the diagnosis, and radical surgery is the best treatment. A few cases of the carcinoid syndrome secondary to bronchial carcinoids have been reported, but the possibility always exists that these lung tumors may be secondary to a small unrecognized primary lesion occurring somewhere along the gastrointestinal tract. Histologically the bronchial adenomas causing the carcinoid syndrome differ from those carcinoid tumors

in the gut by having fewer argentaffin positive granules than intestinal carcinoids. They are similar, however, in having a high proportion of argyrophilic cells, a similar yellow color histologically, and being slow growing with long survivals even with metastases.[24]

Pathology - Gross Appearance

The pathology of the carcinoid tumors vary somewhat with their site of origin, but basically all extra-appendiceal carcinoids are classically alike. The primary tumors are small solitary, or occasionally multiple, nodules which are white, gray, tan, or yellow in color; the amount of yellow depending on the amount of cholesterol present.[1] They are usually well circumscribed, but not encapsulated, subepithelial nodules covered by intact mucosa with the neoplasm movable beneath the overlying epithelium. Intestinal carcinoids may be classified grossly on the basis of their appearance as: nodular, polypoid, sessile, plaquelike, ulcerating, annular or constricting. They arise from the glands of the crypts of Lieberkuhn, invading the submucosa but not the mucosa; and in about 25 per cent of the cases are found to be multiple, with all of the multiple primary lesions being very small, especially when compared to metastases in the liver or the regional lymph nodes.[16] The rectal carcinoid, due to the presence of solid fecal material, has more tendency to ulcerate than those elsewhere in the bowel.

Pathology - Microscopic Appearance

Under the microscope the carcinoid tumors consist of nests, columns or masses of small uniform, round or polygonal epithelial cells lying in a fibrous stroma. Frequently the cells are grouped about a space in such a manner as to resemble a gland or cause rosette formation with a central space containing an amorphous acidophilic material. Masson has described three types of cells in carcinoid tumors, the main difference between the three types being the distribution of the granules within them and their locations within the glands. Most of the cells are round or polygonal cells with a central, finely reticular nucleus surrounded by cytoplasm. Surrounding these cell clumps are a second type of cells lined up in columns called "palisade cells". Finally a third type of cells line the acini. All three types have fine eosinophilic granules in the cytoplasm basal to the nucleus and are capable of producing serotonin by reducing ammoniacal silver salts and of giving a bright yellow color with bichromate solutions; hence all three types are argentaffin positive. A few carcinoid tumors especially those of the bronchial epithelium and those occurring in the rectum are nonargentaffin positive as they lack the granules able to reduce ammoniacal silver salts. This latter group of argentaffin negative carcinoid tumors are rich in 5-hydroxytryptophan, but they are unable to synthesis 5-hydroxytryptamine

(serotonin) from it.[21]

The typical tumor cells are clumped and solidly packed without any evidence of degeneration, giant cells, anaplasia or mitoses. The nuclei are prominent, round and centrally located with a well defined nuclear membrane and much finely basophilic stippled chromatin. The cytoplasm is pale and acidophilic with many acidophilic granules and surrounded by a poorly visualized membrane. Yellowish-brown lipochromic pigmented granules may be present in the cytoplasm. These carcinoid cells are found in a fibrous or hyaline connective tissue stroma which may give a variety of architectures to these tumors. There is no true capsule to the tumor, but the condensation of smooth muscle fibers at the periphery of the tumor form a pseudocapsule.[9] Occasionally more pleomorphic tumors are seen with multinucleated cells having bizarre nuclei and frequent mitoses, but even these anaplastic forms do not necessarily metastasize.[9]

Pathology - Histochemistry

As mentioned above the argentaffin-staining characteristics of carcinoids does not always hold true as in the rectal and bronchial carcinoids. The argentaffin-staining characteristics of the carcinoid tumors is apparently due to the formation of a conjugated beto carboline derivative formed from the combination of formaldehyde and the serotonin present in car-

cinoid tumors.[25] This probably accounts for the reason that only carcinoid tumors located in certain areas are capable of synthesizing serotonin. It is only these tumors which are able to cause the carcinoid syndrome after they have metastasized.

The preparation of any biopsy or autopsy specimens suspected of being carcinoid tumors must be fixed immediately as autolysis destroys the tissues ability to reduce the silver salts. It is important that any specimen where a carcinoid tumor is suspected be divided in half with one half placed in formalin and the other half frozen.[21] The formalin fixed specimen is removed after four to six hours, and then ammoniacal silver salts are added to the specimens. If the silver salts are reduced by the tissues, it is suggestive of carcinoid tumors. The freezing is necessary as serotonin is destroyed by formalin and stable only in the frozen state.

Pathology - Pathogensis

There have been numerous theoretical explanations as to the pathogenesis of carcinoid tumors. In 1925, Torbus provided a list of the numerous theoretical explanations of carcinoid histogenesis up to that time, including origin: 1) from pancreatic rests, 2) from remnants of the omphalomesenteric duct, 3) from heterotopic embryonic material or 4) from Auerbach's plexus.[2] Later others compared the carcinoid tumors to

basal cell carcinoma of the skin, to nevi and to endothelial sarcoma.[6] Around the turn of the last century Lubarsch and Masson[2] recognized that carcinoids arise from the enterochrome chromaffin cells of the basi-granular layer of the crypts of Lieberkuhn. About this same time chromaffin cells of the crypts of Lieberkuhn were discovered by Kultschitzky. It is known that carcinoid tumors are never found in any area devoid of Kultschitzky cells.[2] As most Kultschitzky cells secrete serotonin into the blood, most, but not all, carcinoid tumors produce serotonin.

Likewise the embryonic origin of these chromaffin cells has been and still is debated. Bockus has summarized the three theories as: 1) differentiated from the epithelial cells of entodermal origin, 2) differentiated cells of mesenchymal origin or 3) migrated ectoderm from the neural crest which specializes as cells in the chromaffin system.[10] It is also unknown whether they arise from normal argentaffin cells or whether these normal cells pass through a neuromata stage before becoming carcinoid.[10] In any case once the cells have changed to carcinoid cells they gain a lot of lipoid material giving them a bright yellow color when cut whether benign or malignant, whether primary or secondary carcinoids. It is this similarity as well as many other histologic similarities which makes it impossible to distinguish between benign or malignant carcinoids or between the malignant primary or its

metastases.

Malignancy

Carcinoid tumors are an unusual type of cancer due to their benign nature and yet malignant tendencies. The earliest followers of these tumors believed them to be benign tumors, and yet they were named carcinoids meaning carcinoma-like. It is now known that many of these tumors are malignant, the relative malignancy depending on their location. Some clinicians as Pearson and Fitzgerald now believe that all carcinoids should be considered malignant; they have pointed out "that all carcinoids are malignant and their metastases are only a function of time".[23] In any case it is now realized that these tumors have a higher malignant potential to metastasize, regardless of the site, than was formerly realized. Differbaugh and Anderson after studying a series of 1496 cases reported their distribution and pathologic activity as follows:[20]

| Location | Total | Metastases | Percentage |
|---|---|---|---|
| Stomach | 29 | 4 | 13.7 |
| Gallbladder | 4 | 0 | 0 |
| Duodenum | 21 | 4 | 19. |
| Small Bowel | 438 | 150 | 34.2 |
| Appendix | 825 | 29 | 3.5 |
| Meckel's Diverticulum | 8 | 0 | 0 |
| Ileocecal Valve | 13 | 11 | 84.6 |
| Cecum | 21 | 16 | 76.1 |
| Colon | 7 | 3 | 42.8 |
| Rectum | 130 | 18 | 13.8 |

From this study we can see that whereas the percentage of ileocecal, cecal and colon carcinoids to metastasize is very high, it is the small bowel carcinoid tumors which occur so much more frequently and which actually cause the greatest number of cases of the malignant carcinoid syndrome. Likewise the appendiceal carcinoids, which are the most frequent tumors of this type, are the most benign and least likely to cause metastatic disease.

Before a carcinoid tumor metastasizes, it is impossible to distinguish benign from malignant tumors even on histological study unless there is definite submucosal invastion.[14] The only truly definitive way to determine malignancy is the finding of metastatic disease on laparotomy or autopsy. Even then, it may be difficult to determine if the multiple tumors present represent a primary carcinoid with its metastases or multiple primary carcinoid tumors developing in different areas of the gastrointestinal tract. It is reported that 25 per cent of the patients with small bowel carcinoids have multiple primary lesions and that about 10 per cent of all other extra-appendiceal cases with carcinoid will have multiple primary tumors.[2]

The spread of these metastatic carcinoid tumors is most commonly via the lymphatic system especially to the regional and retroperitoneal lymph nodes which are the site of most metastatic carcinoids.[14] Vascular spread, while less common, is more important as it permits wider and more distant metas-

tases to the liver, lungs, bones, spleen, kidneys, brain, adrenals, subcutaneous tissues, pancreas, testes, ovaries, bronchi, nasal cavity and cervix.[20] It is the spread via the portal system that is the most important factor in the resulting malignant carcinoid syndrome. It is here in the liver that large amounts of serotonin are produced using up to 60 per cent of the dietary tryptophan and so causing the bizarre symptom known as the malignant carcinoid syndrome.[16] Whereas metastases of appendiceal carcinoids is rare, and it is clinically considered a benign disease, all carcinoid tumors regardless of their location in the gastrointestinal tract must be considered potentially malignant.[20] Once metastases have occurred the prognosis is very poor, but five-year survivals relative to other types of cancer is fairly high.[1]

Pathophysiology of Flushes

The flushes are one of the earlier and more striking manifestations of the carcinoid syndrome. They are generally associated with a rise in urinary 5-hydroxyindoleacetic acid and a slight fall in blood pressure.[9] The flushing has been divided into three stages by Thorson.[6] The first stage is characterized by reddening and burning, usually beginning in the face and spreading over the trunk and extremities. The second stage begins with a fully developed flush and burning sensation indicating complete cutaneous vasodilation and is

accompanied by tachycardia and a rise in systolic blood pressure. The third stage begins as reddening and is succeeded by very pronounced cyanosis; it may be followed by a rise in diastolic blood pressure with the disappearance of the radial pulse. Subsequently all changes disappear including the cyanosis.

The typical flush is usually of short duration lasting five to ten minutes, but it may last as long as thirty minutes. There is a striking color change especially over the face where salmon red, bluish-white and normal colors may all be seen at once or in varying sequences. The face is the most severely involved and eventually may become permanently hyperemic with telangiectasia from dilation of the capillaries and venules.[1] The repeated flushing may result in a chronic permanent cyanosis of the face causing a plethoric facies resembling the patient with polysythemia. The fading which follows the flush starts in the center and extends peripherally giving a gypose and serpiginous pattern.[26] As the flush disappears hypotension may occur with possible syncope or even shock. This fall in blood pressure is an important differentiating factor between the flushing seen with pheochromocytoma which is accompanied by hypertension.[16]

The factors which precipitate these flushing episodes are not fully understood, but a few known factors which might result in flushing in the carcinoid patient are recognized.

These include the acts of eating and defecation, undue excitement or tension, ingestion of alcohol, certain foods such as bananas and cheese, massage of pelvic and extrarectal masses, and sudden temperature changes.[15] It is generally agreed that the serotonin release by the carcinoid tumors is capable of producing the characteristic flush, and this has been demonstrated by rapidly injecting serotonin intravenously in small doses (1.8 to 4.0 mgm.) into these patients.[13,21,26] Likewise the circulating serotonin and urinary 5-HIAA achieve their maximum elevation in patients with the malignant carcinoid syndrome at the time of the flushes.[26] Oates et al[27] have recently disagreed saying that intravenous serotonin does not cause the typical carcinoid flush, and that the level of plasma serotonin does not correlate well with the flushing episodes. They have reported finding cases where blood serotonin levels are normal in the presence of continuous severe flushes, and have tried to demonstrate a possible relationship between bradykinin and the carcinoid flushes. Others have performed similar experiments with histamine and the catecholamines: adrenaline and noradrenaline.[29] All these studies are inconclusive and still controversial with the serotonin induced flushing theory the most accepted explanation.

Pathophysiology of Heart Lesions

About fifty per cent of the patients with the carcinoid

syndrome are found to have heart lesions, most of which are confined to the endocardium of the right heart.[30] These lesions consist of subendothelial accumulations of a particular type of fibrous tissue which may lead to valvular stenosis or incompetence. With involvement of the right endocardium with its valve leaflets and chorda tendineae, three classical heart murmurs may occur: pulmonary stenosis, tricuspid stenosis and tricuspid insufficiency.[31] The mechanism by which these pathologic lesions are caused is probably related to the serotonin, synthesized by the carcinoid tumors, reaching the heart via the venous blood. As this is the accepted explanation for the right heart lesions why isn't the left heart also involved? Both the liver and lungs are abundantly supplied with monamine oxidase which is capable of inactivating serotonin. Hence any serotonin synthesized by the metastatic carcinoid tumors in the liver may be dumped directly into the hepatic veins and carried into the right atrium without ever coming into contact with the liver parenchyma or the lungs; hence very little of it is destroyed prior to entering the lungs. Therefore most of the synthesized serotonin formed in the liver reaches the right heart unchanged where it causes endocardial thickening and the above mentioned valvular lesions. After leaving the right ventricle the blood rich in serotonin enters the lungs. The lungs are rich in monamine oxidase and on passing through the lungs prior to reaching the left atrium

about two-thirds of the free serotonin is destroyed.[9] A few cases of malignant carcinoid with left-sided lesions and involvement of the mitral and aortic valve have been reported. In these cases either a right-to-left shunt, as with a patent foramen ovale, or else pulmonary metastases must be present to permit high enough blood serotonin levels to accumulate in the heart to cause significant involvement of the left endocardium.[30] The extent of left heart lesions in the carcinoid heart disease depends on 1) the quantity of serotonin and the related substances produced by the tumor, 2) the amount of inactivation of serotonin while passing through the lungs, and 3) the duration of the disease.[30]

Pathophysiology of Diarrhea and Ulcers

Aside from the flushing episodes, the diarrhea is probably the most outstanding manifestation of the patient with a carcinoid tumor. The severity of the diarrhea is variable, but it may result in as many as thirty watery yellow to green foul smelling stools per day.[6] The diarrhea is unusual in that it constantly may be present lasting throughout the night as well as during the day time hours. Yet only rarely is there melena. The possible theories regarding the effects of serotonin on the gastrointestinal tract are numerous. Some believe it may act upon the post-ganglionic cholinergic fibers of the intramural nervous system of the bowel. Others propose

that there may be an antagonist effect on acetylcholine and others feel that it may directly stimulate ganglion cells in the bowel producing spasm.[6]

It has also been noted that about 20 to 35 per cent of the patients with the carcinoid syndrome get peptic ulcers with an unusually high incidence of perforation. The physiology of ulcer formation in the carcinoid syndrome is probably related either directly or else indirectly to the high circulating blood levels of serotonin.[29] Serotonin may have a direct intrinsic ulcerogenic action on the gastric and intestinal mucosa, or it may be the result of the circulating 5-hydroxytryptophan which has a direct irritating effect on the gastric mucosa. The hyperserotonemia may stimulate the release of large amounts of histamine and so cause gastrointestinal ulceration by this mechanism. Serotonin stimulated gastric secretions are high in acid but of low volume, whereas histamine stimulates the gastric mucosa to produce a gastric juice high in acid and at the same time increases the volume of secretions.[6]

Pathophysiology of Asthma

The physiolopharmcologic action of serotonin on the bronchial musulature is that of bronchoconstriction. With narrowing of the bronchial tree by bronchial spasm, marked dyspnea may occur and so it is that the malignant carcinoid

produces asthmatic attacks. As the blood serotonin is elevated in the carcinoid patient, evidence of hyperpnea and tachypnea occur with subjective feelings of dyspnea and coughing. These manifestations of respiratory insufficiency have been observed during surgery to remove the carcinoid tumors, because as they manipulate the tumor large quantities of serotonin may be spilled into the blood.[21] Hence, the action of serotonin on the bronchial musculature is not unlike that seen with anaphylaxis, and a similar picture may be produced by the injection of small doses of histamine.[9]

Diagnostic Studies

The diagnosis of the carcinoid syndrome is not very difficult once the disease is suspected. The initial suspicion, however, must depend on the clinical findings such as episodes of flushing, recurrent diarrhea in the absence of any other etiologic entity, asthmatic-like attacks, right heart murmurs, or the other signs reported above. Once the presence of a carcinoid tumor is suspected the first laboratory test of importance is a 24-hour urine for 5-hydroxyindoleacetic acid (5-HIAA). This metabolite of serotonin degeneration is a normal constituent of urine, but the normal values are very low, ranging between 2 and 10 mg per twenty-four hour urine collection.[6] This substance may be measured qualitatively using the 1-nitroso-2-naphthal reagent. More

accurate measurements may be obtained using paper chromatography or spectrophotofluormetry.[6] A rise in urinary 5-HIAA is apparently an invariable feature of the malignant carcinoid syndrome, and so is very diagnostic in this disorder. It is most likely increased in any patient with a functioning carcinoid tumor, but no one is certain of the size a carcinoid tumor must be in order to cause a detectable rise in urinary 5-HIAA. Likewise the urinary 5-HIAA may be elevated in patients having no known liver metastases at death.

The advantages of determining urinary 5-HIAA are: 1) it is more reliable as a diagnostic procedure than blood serotonin determinations or liver biopsies;[32] 2) even when the tumors are so small as to be asymptomatic and resectable, this test may be positive giving the first index of suspicion;[32] and 3) no other clinical conditions cause a marked elevation of 5-HIAA excretion although mild rises have been noted in patients with schizophrenia, nontropical sprue and Whipple's intestinal lipodystrophy;[1] elevations are also seen in cancer of the liver, pancreas, bladder or larynx.[16] With a range of normal twenty-four hour urinary 5-HIAA between 2 and 10 milligrams any values between 15 and 30 mgms are suggestive of the carcinoid syndrome and values greater than 30 mgms (or black with 1-nitroso-2-naphthol reagent) are very diagnostic of the carcinoid syndrome if the patient has not eaten any cheese, bananas, or pineapples for forty-eight hours prior to the

test.[21] Also the medications the patient is on must be thoroughly investigated because the monamine oxidase inhibitors, rauwolfia alkaloids,[1] mephenesin or acetanilid[16] all may yield falsely high values; whereas the phenothiazines can cause a markedly decreased urinary 5-HIAA excretion.[21]

Less valuable diagnostic determinations are the measurement of plasma and urinary serotonin levels both of which are elevated in the carcinoid syndrome. Blood serotonin levels are especially important when elevations from the normals of 0.2 to 0.4 micrograms to the carcinoid levels of 2 to 4 micrograms occurs.[10] All circulating serotonin present in the blood, even in the patient with hyperserotoninemia, appears to be carried by platelets as only negligible amounts are ever found in the plasma free of platelets.[32] These measurements can also best be made spectrophotofluormetrically with values as small as 0.05 micrograms being measurable.[6]

The biopsy diagnosis remains the most frequently used, and the most valuable one especially in cases of asymptomatic carcinoid tumors. The presence of cytoplasmic granules which stain deeply with ammoniacal silver nitrate helps make the diagnosis of carcinoid tumors; but the absence of silver stained granules especially in rectal tumors does not rule out the carcinoid tumor, because they all do not readily pick up the silver stains. Failure of the granules to be stained black by the Masson or Gomori method does not mean that the

tumor is not carcinoid, nor is a positive result unequivocal evidence that a tumor is carcinoid, for other types of granules may yield a positive reaction.[2] Also it should be remembered that there are no histologic features of a carcinoid tumor which enable one to distinguish the benign from the malignant, or the primary lesion from its metastases.

Prognosis

The prognosis of the carcinoid tumors is good with or without regional metastases when compared with other types of cancer of the bowel.[10] Metastatic extension may be so slow as to permit twenty-five year survivals even if untreated. Clinically whether associated with the carcinoid syndrome or not, the carcinoid tumors do not behave like the typical malignancy, regardless of their location. The prognosis usually depends more on the pathologic and metabolic changes of hyperserotoninemia than on the location of the primary or metastatic sites.[3] Death usually comes from cardiac valvular damage, severe diarrhea or malnutrition, not from its metastatic nature; and so research aimed at the discovery of agents which would block serotonin metabolism would markedly improve survival rates and the prognosis. Of some interest is the fact that in small bowel carcinoids with metastases, resection of the primary tumor may greatly improve the prognosis and increase the length of life of the patient and even decrease the

malignancy of the syndrome, even though the metastases, not the primary, are the major serotonin producing tissues.[10]

Treatment - Surgical

The treatment of choice with carcinoid tumors whether they produce the malignant carcinoid syndrome or not is surgical therapy. The surgical removal of a carcinoid tumor and/or its metastases is more palliative and beneficial than it is in other malignancies.[16] Dramatic palliation with marked improvement may result from the surgical removal of the carcinoid tumors and its metastases. Occasionally, surgical excision of liver metastases may produce complete relief of the symptoms in the patient with the carcinoid syndrome. The surgical procedure recommended for small intestinal carcinoids is enterectomy of the involved bowel and its mesentery. With apical appendiceal carcinoids, appendectomy and resection of the mesoappendix is recommended; but with carcinoids in the base of the appendix, recurrence is much more common and right hemicolectomy should be considered.[17] As mentioned earlier there is a direct correlation between the size and the malignancy of rectal carcinoids, and so two criteria are used when they occur. If the tumor is less than two centimeters, local excision is the treatment of choice if there is no evidence of local invasion or extension to regional nodes. If the tumor is greater than two centimeters in diameter radical

abdominoperineal resection is recommended.[23] In any surgical procedure directed toward the removal of a carcinoid tumor, but especially those associated with the malignant carcinoid syndrome, caution must be taken during surgery to guard against the sudden release of serotonin into the blood due to induction of anesthesia or manipulation of the tumor. This could cause severe hypotension to occur. If this should occur, angiotensin is the recommended vasopressor. Aminophylline given intravenously would be the treatment of choice for bronchial spasm, not catecholamines which might increase the release of serotonin by the carcinoid tissues.[16] At the present time in all cases of carcinoid tumors, surgical excision is the treatment of choice. Resection should include as much of the metastases as possible because even partial removal may result in a prolonged, comfortable life for many years.

Treatment - Medical

Medical treatment has always been ineffective, partially because therapy has always been based on the assumption that the presenting clinical syndrome results from the release of 5-HT (serotonin) into the blood. This is an oversimplification since other substances in the tryptophan to serotonin to 5-hydroxyindoleacetic acid cycle besides 5-HT are probably formed in excess from the carcinoid tissue such as 5-HTP (5-hydroxytryptophan). These substances may be responsible

for causing some of the signs and symptoms present in the malignant carcinoid syndrome. This may explain why many of the proposed serotonin antagonists result in the improvement of some but not all of the manifestations present, such as the two most common and disturbing symptoms - the flushing and the diarrhea.[33] As of yet there are no specific tumoricidal carcinoid drugs and so therapy is directed at amelioration of the malignant carcinoid syndrome by the use of antagonistic agents.

The most successful but far from ideal serotonin antagonist known to date is chlorpromazine.[21] Although its mechanism is uncertain it apparently interferes with the action of serotonin on the tissues rather than to interfere with its synthesis. It provides its best antagonistic action by interfering with the cardiovascular actions of serotonin, and it also reduces the degree of serotonin induced peristalsis.[13] Chlorpromazine also offers some symptomatic value through its tranquilizing effects. Numerous other serotonin antagonists have been tried and found to offer only limited success.[13] Reserpine blocks the central action of serotonin causing the brain cells to release their serotonin stores, and thus exposes serotonin to the destruction by monamine oxidase. Lysergic acid blocks both the central and the peripheral actions of serotonin causing schizophrenic-like mental disturbances. Benadryl increases the pressor but not the

depressor response caused by serotonin, but at the same time it increases the intestinal affinity for serotonin causing increasing peristalsis. Regitine blocks only the slight pressor response. Yohimbin and ergotamine have some beneficial effects on the gastrointestinal tract and vascular components. Antiserotonin compound 45-50 causes marked changes such as a drop in blood pressure and an increase in pulse rate, but its antagonist effects rapidly subsides with continuous usage. Recently nicotinamide has been shown to be a serotonin antagonist, but the mechanism of its action and its effects in the carcinoid syndrome are unknown.[21] Deseril, which is 1-methyl-D-lysergic acid butanolamide tartrate, has been reported to be effective in markedly reducing the number of stools in the patient with the carcinoid syndrome. Along with a product called Ro5-1025, Deseril is effective in relieving flushing, but neither has been made available nor has been widely accepted for use in the malignant carcinoid syndrome.[33] It is thus clear that medical therapy is only palliative at best. There are no proven antagonists of serotonin.

Supportive and palliative medical therapy is often the best treatment the clinician can offer.[29] Paregoric or kaopectate, with or without hydrochloric acid, given before meals may decrease the amount of diarrhea. Fluid and electrolyte balance must be carefully watched with prolonged diarrhea. Adrenalin and intravenous aminophylline may be helpful in

attacks of acute bronchospasm. Niacin supplement will result in improvement of the pellagra-like skin lesions. Low tryptophan diets do not result in prolonged palliation, but it is possible that intravenous radioactivated iodotryptophan, which will be picked up by carcinoid cells, may offer some excellent results in the future treatment of the carcinoid syndrome.[16] Corticosteroid therapy may also offer some palliative relief of symptoms.[1]

Treatment - Chemotherapy and Radiotherapy

The use of chemotherapy and radiotherapy has offered very little measurable improvement in the treatment of either primary or metastatic carcinoid tumors or the syndrome they produce. The best tumoricidal doses for patients with the malignant carcinoid syndrome and known liver metastases is via hepatic-artery catheterization via the left brachial artery. This therapy may also be used for disseminated carcinoid tumors. Once the catheter is in place it can be left there as long as it is flushed once a week with heparin and the patient can lead a normal life, reporting to the hospital for weekly therapy with perfusion of 5-FU or alkylating agents.[34] Present results indicate that the best responses are with 5-FU although a few good short term responses have occurred following the use of nitrogen mustard, thio-tepa and cyclophosphamide.[34]

Radiotherapy and radioisotopes used to destroy metastatic tissue and decrease circulating serotonin have resulted

in only temporary palliation. Radioactive gold has given such inconclusive results that it does not appear to be the answer.[6] The best answer seems to be the approaching studies using intravenous radioactivated iodotryptophan which when picked up by the carcinoid tissues may result in their self destruction.[16] It also appears unlikely that carcinoids are radiosensitive neoplasms and no good results have been recorded using radiation therapy.[2]

## CONCLUSION

The malignant carcinoid syndrome is a group of pharmicophysiologic manifestations produced by the hyperserotoninemia resulting from these hypersecretory tumors rich in argentaffin tissue -- the carcinoid tumors. These tumors although malignant are not cancerous in the fashion that other tumors are malignant. They are not rapidly proliferative with an early history of widespread metastases, but rather they are slow growing tumors and late to metastasize. Their malignant nature is due to the severity of the symptoms produced by the excess of plasma serotonin synthesized from tryptophan by the carcinoid tumors. Normally only 1 per cent of the dietary tryptophan is utilized in the synthesis of serotonin, but this may increase up to 60 per cent in the more severe cases of the malignant carcinoid syndrome. Hence this is a disease of niacin deficiency as well as serotonin excess.

The symptom complex present in the carcinoid syndrome is basically the result of the action of serotonin on four target systems: 1) the vasculature with vasodilation causing flushing; 2) the gastrointestinal tract where hyperperistalsis results in diarrhea; 3) the respiratory system where bronchoconstriction produces asthmatic attacks; and 4) the heart where accelerated fibroblastic activity leads to valvular heart disease and right heart failure. This classical tetrad, although not always present in the patient with the carcinoid syndrome, should make the clinical diagnosis of a carcinoid tumor with metastatic disease an early suspect. Once it is considered it is an easy matter to confirm the suspicion as urinary studies will invariabily reveal a marked elevation in the twenty-four hours 5-HIAA, the end product of serotonin metabolism. It is important to remember that the site of the primary carcinoid tumor may be anywhere the reminants of the embryologic gut are found, but only those tumors or their hepatic metastases which are so located that they are able to deposit their serotonin load directly into the systemic venous channels and so bypass the liver and lungs, rich in monamine oxidase, are able to produce the malignant carcinoid syndrome.

A review of the pharmacology of serotonin, the pathology of these tumors, valuable diagnostic procedures, and the prognostic implications of this disease have been covered.

The therapeutic considerations to be investigated when confronted with the carcinoid tumor, with or without the associated malignant carcinoid syndrome are also discussed. Here it is important to remember that just as with all tumors, early surgical intervention is the best treatment and surest cure. As the disease progresses beyond the point where surgery can be considered, the clinician must face the problem of which of the, at best, poor palliative measures might offer some benefit: medical management with serotonin antagonists, chemotherapeutic agents or radiotherapy; or is the patient just destined to supportive of symptomatic therapy to make his life as comfortable as possible.

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