THEORETICAL AND CLINICAL CONSIDERATIONS IN ANAESTHESIA FOR SECRETING CARCINOID TUMORS*

RAYNALD DÉRY, M.D., F.R.C.P.(C)†

A DECADE HAS now passed since Stone and Donnelly reported on the anaesthetic significance of serotonin secreting carcinoid tumors.[1] During this time, important progress has occurred, which has significantly changed our understanding of the physiopathology of this syndrome. More specifically, it was discovered that serotonin was not the only endocrine factor involved in the genesis of the carcinoid attacks. It is now recognized that the kallikrein-bradykinin system plays an important part in the production of many signs and symptoms previously attributed to serotonin.[2–4]

In the light of the recent advances in this field, it is timely to refocus the attention of the anaesthetists on the complex mechanisms underlying the physiopathology of this disease. This may lead to modifications in anaesthetic techniques, as well as to the introduction of more specific chalones, which can both result in a better management of anaesthesia, and the saving of more human lives.

This report deals first with a review of the biochemistry and the pharmacology of the carcinoid syndrome. Such knowledge proves of prime importance in establishing a sound fundamental background to clinical practice. Then we shall describe our clinical experience in the management of 16 carcinoid tumors, 7 of which were functional and secreting.

BIOCHEMISTRY AND PHARMACODYNAMICS OF THE CARCINOID SYNDROME

In the first place, a fundamental distinction must be drawn between carcinoids of the appendix and extra-appendicular carcinoids. Carcinoids of the appendix usually give rise to appendicular obstruction and are consequently removed on the surgical diagnosis of an acute appendicitis. Although usually confined to the mucosa and the sub-mucosa, the tumor cells may penetrate the muscularis and reach the serosa. In very rare cases, there is a spread to the regional lymph nodes, but never distant metastases. Thus, they are generally considered as non-secreting tumors.[5]

Extra-appendicular carcinoids, from the anaesthetist's point of view, are more interesting because of the systemic disturbances which they may produce. The primary lesion is usually located in the ileum, but may be found in various organs, such as the duodenum, the stomach, the rectum, and the pancreas. The

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†Associate professor, Department of Anaesthesia and Resuscitation, L'Hôtel-Dieu de Québec and Laval University School of Medicine.

demonstration by Pierre Masson, by means of silver impregnation, that the tumors arose from the argentaffin Kultschitsky cells of the gastrointestinal tract, was of major importance.[6] These tumors differ from appendicular carcinoids in two main particulars. First, they are usually malignant growths, and spread not only to adjacent and distant lymphoid tissue in the abdomen, but may give birth to metastases in the liver, the lungs, and any other organ. Secondly, a certain proportion (perhaps 25 per cent) of the malignant carcinoids of the gastrointestinal tract produce local hormones, especially serotonin and bradykinin. Clinically, these tumors remain silent, except for intestinal obstruction, until liver metastasis has occurred. This permits the entrance of the forementioned hormones into the suprahepatic venous flow, without having been exposed to the destructive action of liver enzymes. They may then exert their pharmacological activity in the whole body economy.

In order to trace the biochemistry and the pharmacology of the carcinoid syndrome to its actual source, let us now concentrate our attention on the carcinoid cell. We shall be mainly concerned with two components of its ultrastructure, the enterochromaffin granule and the lysosome. Figure 1 gives a view of the carcinoid cell, as seen with the electron microscope.

The enterochromaffin granule is easily recognized by the pathologist either by fluorescent techniques or by impregnation with specific chrome and silver salts. This granule is the site for the biosynthesis, storage, and release of serotonin, and will be thereafter referred to as the serotoninergic granule. The metabolic sequences for both the synthesis and the catabolism of serotonin are outlined in Figure 2. Attention should be drawn to the fact that these sequences include enzyme mechanisms which are common to serotonin and catecholamines. The same enzyme, L-amino acid decarboxylase, catalyses the decarboxylation of 5-hydroxytryptophan and DOPA. Similarly, the oxidative deamination leading to the formation of 5-hydroxyindoleacetic acid is catalysed by MAO.[7] This striking interplay between the enzyme systems responsible for the pharmacodynamics of both serotonin and catecholamines will be referred to later on when dealing with clinical situations.

The uptake of tryptophan by the serotoninergic granules of the argentaffin cells, normally accounts for 5–10 per cent of the whole ingested tryptophan. As we know, large amounts of tryptophan come from the consumption of some foods, such as bananas, tomatoes, avocados, red plums, walnuts, and eggplants. In the presence of a secreting carcinoid tumor, at least 60 per cent of the ingested tryptophan is captured by the tumor cells, thus leading to malnutrition and hypoproteinemia.[8] This uptake, of course, can be reduced to a very low level by the prescription of a tryptophan-poor diet. Modifications of the normal pattern of plasma proteins can be induced in three ways: (1) by extensive uptake from the carcinoid tumors; (2) by loss of hepatic tissue through metastatic involvement, and (3) by dietary tryptophan deprivation. This should be assessed in the preoperative period and coped with by the anaesthetist.

The biosynthesis of 5-hydroxytryptophan into 5-hydroxytryptamin involves the enzymatic activity of dopa-decarboxylase. This step, as can be predicted, will be powerfully inhibited by alpha-methyl-dopa, alpha-methyl-p-tyrosine, and alpha-methyltryptophan.[9,10]

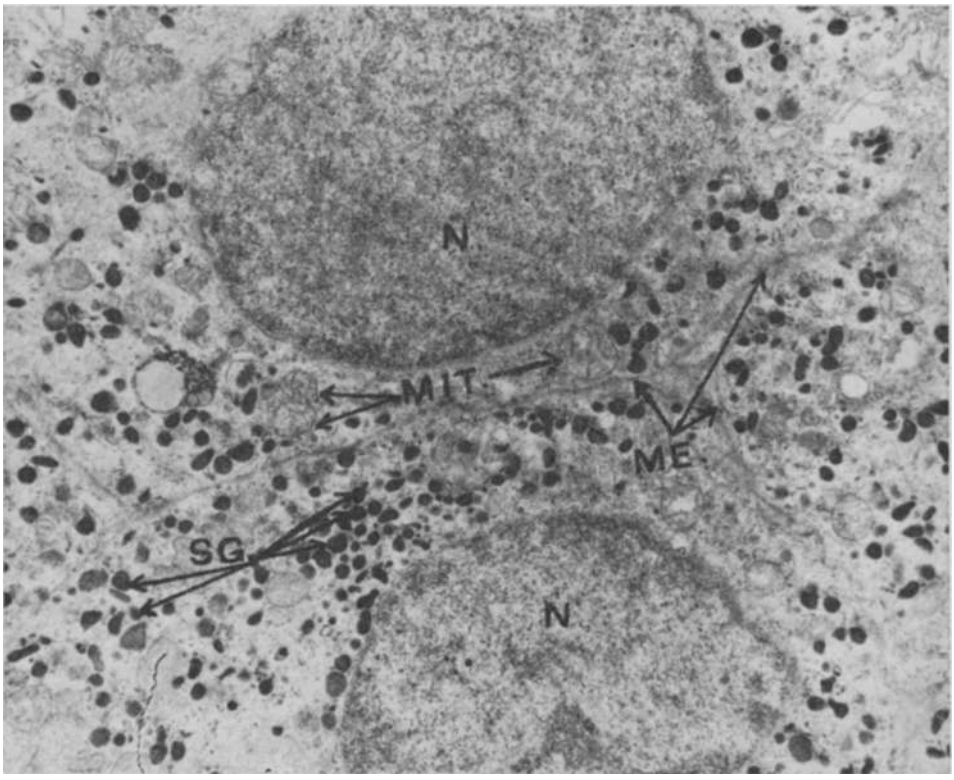

FIGURE 1. Electron micrograph of a field of carcinoid cells, as they appear when stained with uranyl acetate and lead citrate. Note the cell membranes (ME), the large mitochondria (MIT), the nuclei (N) and the serotoninergic granules (SG) which are shown as deep black inclusions. Their different impregnation with the tinctorial agent seems related with their serotonin content. (Preparation and Photograph: Doctor Jeannine Morin, Pathologist and Electron Microscopist, L'Hôtel-Dieu de Québec, 1969.) × 5000.

Little is known about the factors which can promote the storage of serotonin in the granule. Lahti and Platz found that alpha-methyl-5-hydroxytryptophan can protect serotonin storage against the depleting action of reserpine.[11] Two other chemicals, ninhydrin and dinitrophenol, can effectively achieve the same result. Evidence is also available that phenothiazines and antihistaminics exert their serotoninolytic activity by decreasing the permeability of the storage granule. These latter drugs can also directly block peripheral serotoninergic receptors, as do some other pharmacological agents, namely methylsergide and LSD-like compounds.[12,13]

Release of serotonin by the storage granule is enhanced by a large number of drugs that can be divided into three groups: (1) those which block the storage of serotonin inside the granule (reserpine, tetrabenasine, prenylamine); (2) those which both block the storage and alter the activity of the membrane pumps which hold serotonin inside the granule (tyramine, guanethidine, monoamine inhibitors); and finally, those which include a variety of unrelated substances (dextrans, propamidine, toluidine blue, morphine, Polymyxin B).[14]

The catabolism of serotonin, initiated by monoamine oxidase, occurs principally

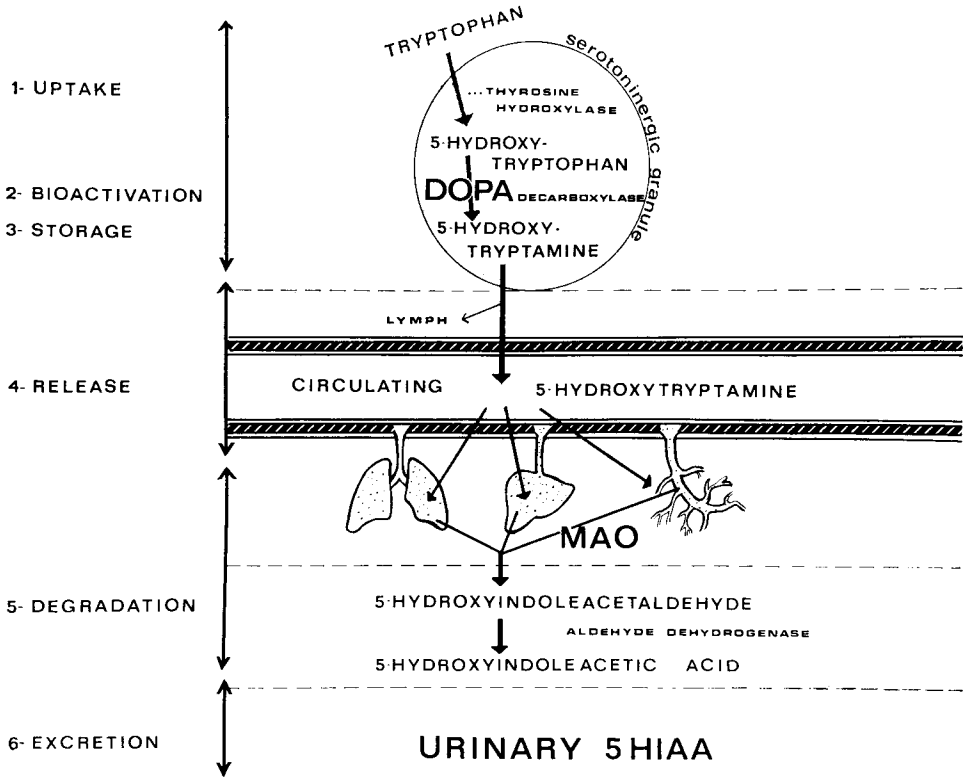

FIGURE 2. The pharmacodynamic sequence of the 5 HT-5 HIAA system.

in the blood stream, in the liver and in the lungs. This enzymatic degradation results in the formation of 5-hydroxyindoleacetic acid (5 HIAA). This substance is the principal urinary metabolite of serotonin, and the urinary output of 5 HIAA is used as an index of the rate of serotonin metabolism in the body. The normal amount excreted in 24 hours ranges from 1.5 to 10 mg. This is of prime importance in detecting carcinoid secreting tumors. It has, however, some degree of unreliability when serotonin-containing foods are consumed by the patient. Moreover, exceptional patients have presented the full-blown carcinoid syndrome, with generalized metastases, although they never have shown increased urinary 5-hydroxyindoleacetic acid. But as a rule, a tumor of the enterochromaffin cells is to be suspected if the excretion of 5 HIAA exceeds 25 mg in 24 hours.

Observing once again the microcosmos of a carcinoid cell, we notice, beside the serotoninergic granule, another infrastructure that must receive special attention, the lysosomes. These are small vesicles covered with very thin membranes and filled with a dangerous array of confined enzymes of two kinds. First, the hydrolases, among which have been isolated acid phosphatase, glucuronidase, acid ribonuclease, and acid desoxyribonuclease. Second, the proteinases; among these can be recognized pepsinases, tryptases, and kallikrein. Once liberated, each can react with cell or plasma proteins to break the peptidic bonds of large molecules, or to withdraw some amino acids from the long protein chains. The

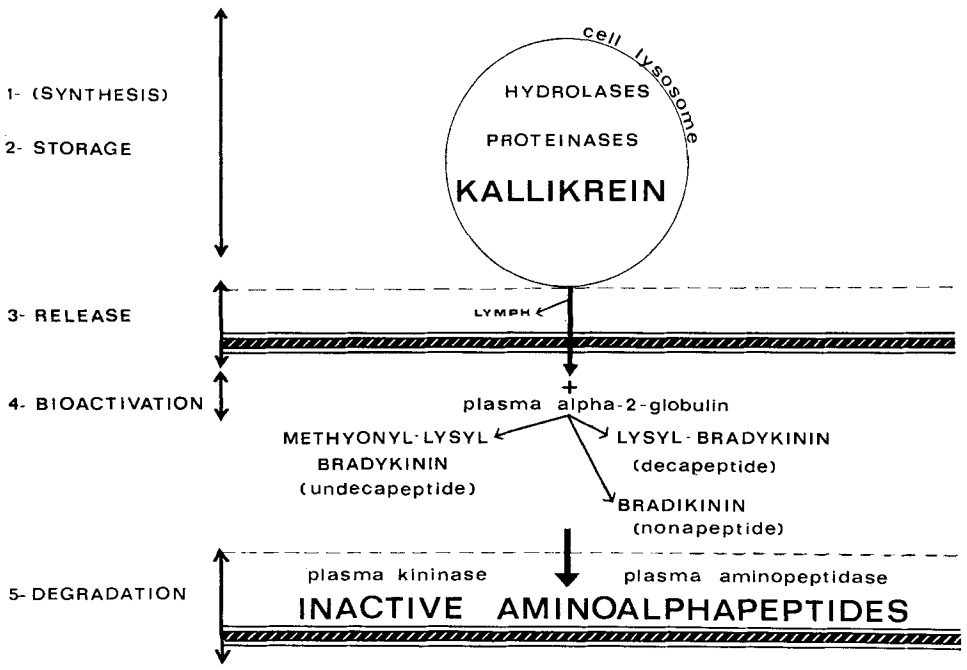

FIGURE 3. The pharmacodynamic sequence of the Kallikrein-Bradykinin system.

pharmacodynamics of these proteinases, kallikrein in particular, have not been completely elucidated. However, major advances in this field have been made in the recent years.[15–18] Figure 3 summarizes the metabolism of the whole kallikrein-bradykinin system. The factors which enhance the liberation of the lysosomal content are protean and poorly defined. Damage to the lysosomal membrane, with subsequent leakage of its kallikrein stores, has been imputed to mechanical trauma, pH variations, anoxia, alcoholic intoxication, and, remarkably, catecholamines.[19]

Once liberated into the extracellular fluid and blood, kallikrein reacts with an alpha-2-globulin to yield the following active peptides: (1) the undecapeptide arginyl-lysyl-bradykinin; (2) the decapeptides lysyl-bradykinin and arginyl-bradykinin; (3) the nonapeptide bradykinin.

Normally, the presence of bradykinin and associated kinins in the blood is rapidly coped with by kininases and plasma aminopeptidases. These divide the active undeca, deca, and nona peptides into inactive amino-acids alpha peptides. The active peptides, however, may have a longer half-life in the blood stream. It may be assumed that, as long as the stimulus for their production continues, or, as long as the protective kininase mechanisms are overridden, large amounts of highly active kinins may produce their systemic pharmacological effects. Much evidence exists that these conditions can occur in the carcinoid syndrome.

Fortunately, an increasing number of specific antagonists of the kallikrein-bradykinin system, have recently been available to block the various steps of this threatening sequence. Among these, some are still at their experimental

stage and shall not be mentioned here. Three drugs, currently available, shall retain our attention. (1) Trasylol, which has been isolated by Kunitz and Northrop, has proved a potent inhibitor of both the kallikrein-kinin and the trypsin systems.[20] It specifically blocks the activity of the proteinase kallikrein, thus preventing its further proteolytic action on alpha-2-globulin. The initial dosage may vary according to the clinical situation between 25,000 and 125,000 KIU. Doses, as high as 2,500,000 units, have been infused intravenously over 24-hour periods. (2) Epsilon-aminocaproic acid (EACA), also named Amicar, was introduced by Okamoto.[21] It performed as a potent antagonist of the proteinases and has been extensively used as a fibrinolytic inhibitor. The initial dose for EACA is 5 gm in 5 per cent dextrose in water; maintenance doses of 1 gm per hour can be added if necessary. (3) Iniprol (CY 66), an antipeptidase, has been used to block the kallikrein, the fibrinolysin, and the trypsin systems. The dosage administered is 1,000,000 units, intravenously. Larger doses can be injected, according to the urgency of the clinical situation.

Physiopathology of the Carcinoid Syndrome

Since the pattern of the carcinoid syndrome can now be traced to two specific hormones, it becomes more satisfying to relate a particular symptom or sign to its physiopathologic cause. It is implicitly accepted that histamine plays no part in this syndrome. Since M. Rocha e Silva demonstrated the absence of any detectable histamine in shock states caused by kallikrein, there should remain no doubt on this proposition.[19]

The comparative effects of serotonin and bradykinin are displayed in Table I.

At first sight, many statements which appear in the comparative outline just proposed, may catch the eye as oversimplifications of a more complex and confusing picture. Therefore, we have tried to integrate a synthesis from experimental facts gathered from copious literature on the subject. In our view, this could open clearer avenues to be followed by the anaesthetist. The reader who may want to add more pertinent data to the schematic abstracts just proposed may consult our references. Furthermore, additional pharmacological details are included in the discussion of our clinical study.

Clinical Study

Vivid descriptions of the carcinoid syndrome are well known from many excellent papers on the subject.[22–27] It would be superfluous to reproduce this now classical knowledge. We wish rather to expose our own clinical experience in the management of anaesthesia of the patient affected with this disease.

Patients included in this study were selected among the 90,000 who received anaesthesia in our department during the last ten years. From 1960 to 1970, 16 extra-appendicular carcinoids were diagnosed. Table II outlines the clinical and biochemical features of these cases, along with short comments on the course of their anaesthestic and surgical experiences. These patients can be readily

TABLE I

THE COMPARATIVE CLINICAL COMPONENTS OF THE CARCINOID SYNDROME AS RELATED TO THEIR SEROTONINERGIC OR BRADYKININERGIC ETIOLOGY

	Serotonin	Bradykinin and associated peptides
Psychic manifestations	slow awakening following anaesthesia	
Heart	positive inotropic activity tachycardia pathological changes in the endocardium	tachycardia
Blood vessels	vasoconstriction erratic effects	vasomotor paralysis
Blood flow	hyperkinetic effect	hypokinetic effect tendency to sludging and DIC
Respiration	hyperpnea	bronchoconstriction
Digestive tract	nausea, vomiting, abdominal cramps and diarrhea	
Metabolism	hyperglycaemia hypoproteinaemia	bradykinin shock with acidosis, hypotonicity and hypovolaemia
Kidney	oliguria, pre-glomerular vasoconstriction	
Skin		flushing
Interstitial tissues	oedema, slight	more conspicuous oedema

classified in four categories. The first group (patients Nos. 1 to 10) included those patients who, either preoperatively or at post-mortem examination, demonstrated small, non-functional carcinoid tumors. These local growths had remained strictly silent on clinical and biochemical grounds, as well as from the standpoint of anaesthesia. Of the 16 carcinoid tumors observed, 9 conformed with these features. Therefore, these will be given no further consideration in our discussion. The second category was set for our patient No. 10, owing to particular incidents encountered during the management of his anaesthesia; accordingly, this case will be described in detail. The third group was composed of patients Nos. 11, 12, and 13, who disclosed in the preoperative period the classical picture of the carcinoid syndrome. In these, the diagnosis was corroborated by elevated urinary excretion of 5 HIAA. They received a conventional anaesthesia without any incident and made an uneventful recovery. The last group, composed of patients Nos. 14, 15, and 16, elicited fundamentally the same pre-anaesthetic features as those mentioned for our third group. They were undoubtedly recognized as bearing functional carcinoid tumors, with known active metastases. In these, the administration of anaesthesia was accompanied by characteristic incidents. We want to document the management of this group, because it offers the background for the elaboration of more specific and physiopathological approach.

TABLE II

CLINICAL AND BIOCHEMICAL DATA IN 16 PATIENTS WITH CARCINOID TUMOR

Patient and record number	Age and sex	Preoperative diagnosis	Urinary 5 HIAA mg/24 hrs	Anaesthetic management	Comments
1. (A-37357)	69,F	Acute intestinal occlusion		Uneventful	Coexistence of a caecal adenocarcinoma with a benign carcinoid tumor of the ileum.
2. (A-26792)	78,F	Subarachnoid haematoma		Uneventful	Post-mortem finding of a benign carcinoid tumor of the ileum.
3. (992,81)	84,M	Primary carcinoma of the lung		Uneventful	Post-mortem discovery of a benign carcinoid tumor of the ileum.
4. (836,33)	55,M	Carcinoid syndrome (skin rash, asthma, and diarrhea)	15 negative results	Severe per and post anaesthetic bronchospasm	Adenocarcinoma of the sigmoid colon. Allergic background.
5. (466,17)	83,M	Cancer of the head of the pancreas		Uneventful	Post-mortem discovery of a benign carcinoid tumor of the duodenum.
6. (231,08)	55,M	Haemorrhoids	3 post-operative negative results	Uneventful	Resection, through the rectoscope, of a malignant carcinoid tumor.
7. (1231,08)	53,F	Acute intestinal obstruction	3 post-operative negative results	Uneventful	Coexistence of an adenocarcinoma of the recto-sigmoid with a malignant carcinoid tumor of the caecum. Liver scanning: normal.
8. (401,68)	65,F	Hiatal hernia, peptic ulcer, cholelithiasis	3 post-operative negative results	Uneventful	Preoperative finding of a benign carcinoid tumor of the ileum.
9. (227,48)	33,F	Nonspecific colitis, chronic anxiety	3 post-operative negative results	Uneventful	Resection, through the rectoscope, of a benign carcinoid tumor.
10. (957,13)	56,M	Cholelithiasis	10 post-operative negative results	Serotonin r-gic crisis	During the resection of a Meckel's diverticulum which nested a carcinoid tumor
11. (69,73)	69,M	Acute intestinal obstruction in a patient previously treated for Hodgkin's disease	3-post-operative negative results	Uneventful	Carcinoidosis with peritoneal and liver metastases

TABLE II (concluded)

CLINICAL AND BIOCHEMICAL DATA IN 16 PATIENTS WITH CARCINOID TUMOR

Patient and record number	Age and sex	Preoperative diagnosis	Urinary 5 HIAA mg/24 hrs	Anaesthetic management	Comments
12. (X-1672)	46,M	Carcinoid syndrome	480 445 31	Uneventful	First operation: malignant carcinoid tumor of the ileum, with liver metastases.
12. (X-1672)	48	Exploratory	375	Uneventful	Carcinoidosis, inoperable.
13. (E-259,65)	75,M	Anuria with retro-peritoneal tumors		3 Uneventful anaesthetic experiences	Carcinoid tumor of the retro-peritoneal space with generalized metastases.
14. (64,5350)	59,M	Carcinoid syndrome, hepatomegaly	67.3 71.6 375.0	Serotoninergic crisis	Carcinoidosis, inoperable; liver biopsy.
15. (64,6019)	52,M	Acute intestinal obstruction: History of abdominal cramps and diarrhea after drinking of alcohol	38.8	Serotoninergic crisis	Malignant carcinoid of the ileum; cirrhosis of the liver.
16. (76,551)	52,F	Carcinoid syndrome	148 103 100	Bradydininergic crisis and Serotoninergic crisis	Malignant carcinoid of the ileum; peritoneal and liver metastases.

Patient 10: This 56-year-old patient was admitted to the hospital for a lithiasis of the gallbladder. Physical examination and laboratory findings were within normal limits. His blood pressure remained stable at 130 mm Hg systolic, and 80 diastolic during the whole preoperative period. The electrocardiogram showed only minor and nonspecific alterations of the T-waves over the lateral precordial area. After the intramuscular injection of meperidine 75 mg and atropine 0.4 mg as a premedication, the induction was carried out with the intravenous injection of thiopentone 450 mg, soon followed by succinylcholine 60 mg and endotracheal intubation. Removal of the gallbladder was easily achieved under stable anaesthetic condition maintained with 50 per cent oxygen, 50 per cent nitrous oxide, halothane-ether azeotrope, and gallamine. Blood pressure was 120 systolic, 80 diastolic, with a pulse rate at 92 per minute. A complementary appendectomy followed, under unchanged conditions. Then the surgeon discovered a Meckel's diverticulum, the lumen of which was partially filled with a small hard tumor. Manipulation of the tumor, which was biopsied and soon identified as a carcinoid tumor, induced a tremendous hyperkinetic state of the cardiovascular system. The arterial blood pressure suddenly rose to 180/120, and the pulse rate reached 140. Resistance to ventilation and skin colour underwent no significant change. The hyperkinetic state continued for 20 minutes and soon improved following the intravenous administration of Nozinam® 2.5 mg. Removal of the tumor was then uneventfully completed. Postoperatively, 10 urinary 5 HIAA determinations disclosed normal results.

Patient 14: This 59-year-old patient, previously in good health, had presented, for the last two months before his admission, the characteristic carcinoid syndrome. He complained of abdominal cramps, frequent diarrhea, along with a peculiar flushing of the

skin which occurred after each stool. This skin flushing disappeared spontaneously within 5 minutes. The physical examination disclosed a hepatomegaly and multiple abdominal tumors. On rectal examination, an infiltrating lump could be felt through the anterior rectal wall. Careful compression of this new growth elicited a severe carcinoid attack, with flushing, bronchospasm, and arterial hypotension. The arterial blood pressure, which read 120 systolic over 80 diastolic under normal conditions, fell to 100/60 during the short-lived attack. After a premedication including meperidine 75 mg, atropine 0.4 mg, along with chlorpromazine 25 mg, the patient was given general anaesthesia with usual drugs: thiopentone 500 mg, nitrous oxide 50 per cent, methoxyflurane, and gallamine. The surgical procedure was reduced to an exploration of the peritoneal cavity, which showed inoperable carcinoidosis. The surgeon also removed, for pathological examination, a small liver metastasis. Meanwhile, anaesthesia remained quiet, with a stable blood pressure at 120/80 and a heart rate of 88 per minute. In the recovery room, however, observation of the patient disclosed an extreme sinus tachycardia, with a heart rate over 160 per minute. The patient had no complaint of dyspnea, and his blood pressure remained stable. This paroxysmal tachycardia proved resistant to ocular, as well as carotid sinus compression. A full digitalization with Cedilanid 1.2 mg also had no effect. The tachycardia progressively abated during the next 12 hours with three doses of chlorpromazine 25 mg. In the late postoperative period, the patient received Cobalt therapy and was discharged with prescriptions for chlorpromazine and 5 Fu.

Patient 15: This 52-year-old chronic alcoholic was treated for acute intestinal obstruction. Three days previous to his emergency operation, he had suffered acute abdominal pains, constipation, and had vomited faecaloid matter. Corrective measures, devoted to the treatment of hypovolaemic and septic shock, proved effective. Anaesthesia was then induced by inhalation of halothane-ether and endotracheal intubation was performed without the use of myorelaxants. Maintenance was conducted with the same anaesthetic agent, along with nitrous oxide and gallamine. The central venous pressure read 2.5 cm of water, while the arterial blood pressure remained quite stable at 130/90. The pulse rate was 100 per minute. Palpation of the carcinoid tumors, found in the ileum and in the adjacent mesentery, repeatedly triggered hypertensive-tachycardic episodes, which lasted 5 minutes. Palpation of the cirrhotic liver disclosed the same hyperkinetic crisis, with blood pressure readings over 200 mm Hg, systolic, and heart rates over 140. Meanwhile, the CVP moved slightly, and no changes were detected either in pulmonary dynamics or in skin colour. The postoperative course was uneventful, and the high 5 HIAA levels subsided to a certain degree, following the administration of methylsergide.

Patient 16: This 54-year-old female, who previously had a vagotomy and a pyloroplasty, was admitted complaining of diarrhea, abdominal cramps, vomiting, and asthenia of two-weeks duration. She also described flushing episodes, with accompanying dyspnea, 5 hours after each meal. These episodes were short-lived, and usually followed by oedema of the fingers. Previous to surgery, examinations were performed including a biopsy of the liver, the uptake of C^{14} tryptophan, and a low tryptophan diet. Also preoperatively, we traced various antiserotonin treatments: methylsergide, promethazine, and cyproheptadine.

As a premedication, she received diazepam 10 mg, meperidine 50 mg, diphenhydramine 25 mg and atropine 0.4 mg. Narcosis was then induced with oxygen, nitrous oxide, and methoxyflurane by inhalation. Meanwhile, regional anaesthesia of the larynx was achieved by superior laryngeal nerve block with 1 per cent lidocaine. Intubation was further eased with the administration of gallamine 60 mg. The blood pressure was initially stable at 140 systolic, 80 diastolic, with a pulse rate of 100 per minute. During the opening of the abdominal wall, the patient suddenly went into a hypertensive crisis, arterial pressure rising to 180, with a pulse rate of 136. This hyper-

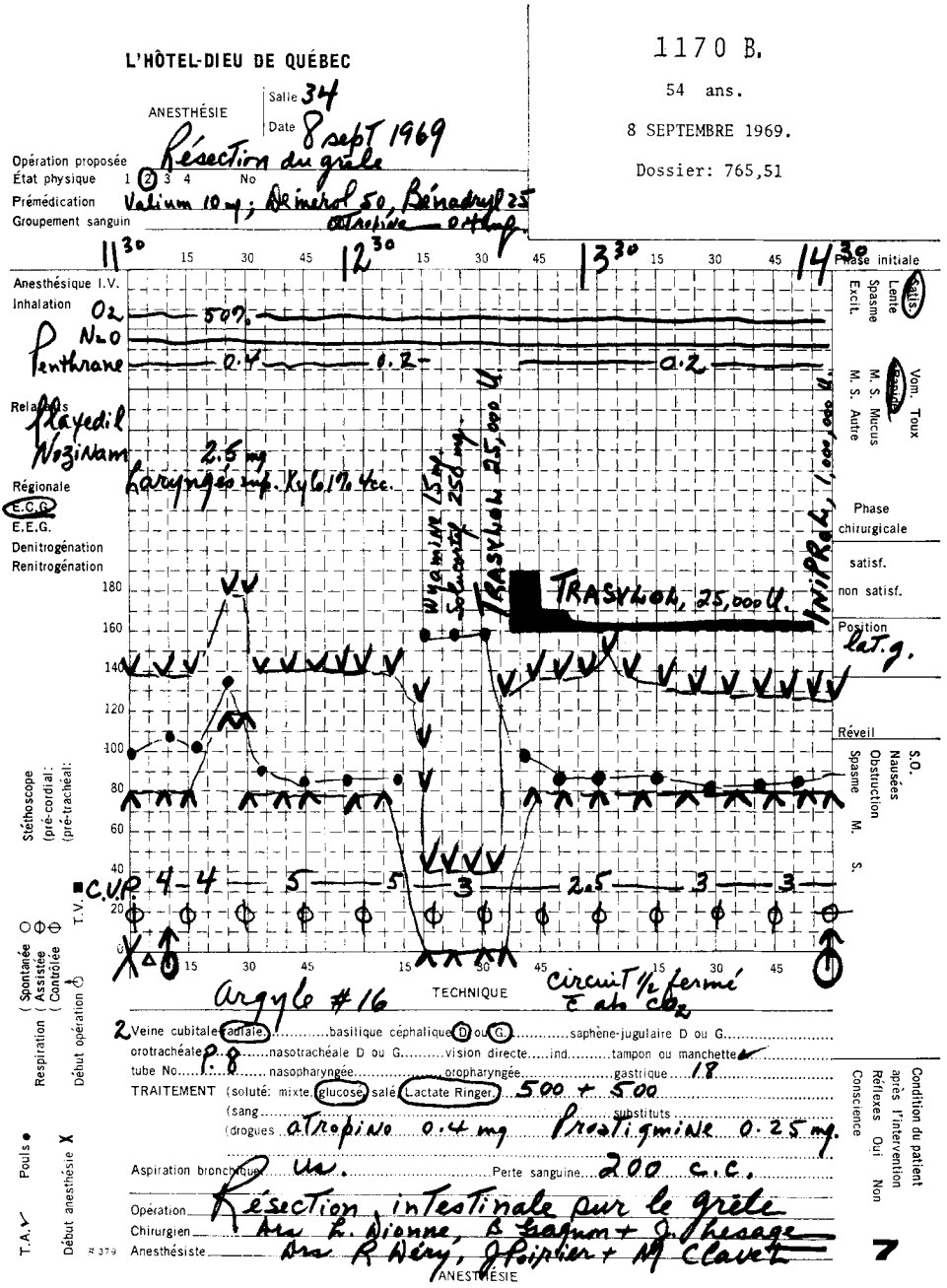

FIGURE 4. Record of the management of anaesthesia in a patient with secreting carcinoid tumor (case 16, Table II).

kinetic state, imputed to hyperserotoninemia, was easily overcome with the intravenous administration of Nozinam® 2.5 mg. In the course of abdominal exploration, a completely different picture suddenly occurred, displaying a fiery red flushing of the skin, severe bronchospastic attack, a blood pressure fall to 40 mm Hg, along with a heart rate at 160 per minute. Every measure devoted to correct this alarming situation, including the administration of fluids, vasopressors, and cortisone, desperately failed. Even the interruption of surgical manipulations proved nonbenevolent. After 20 minutes, the situation was still deteriorating, as evidenced by the appearance of hypoxic EKG changes and fixed dilated pupils. This stormy episode was suddenly and completely cured by the intravenous injection of Trasylol 25,000 units. Thereafter, the operation, a resection of the ileum and the adjacent metastases, proceeded in a normotensive, eupneic, and normorythmic patient. Her skin was rather pale, as often seen during methoxyflurane anaesthesia. An intravenous drip of Trasylol, 25,000 units in 500 cc dextrose in water was slowly administered until the end of the procedure.

The patient's awakening was very slow. Although her blood pressure read 140/100, with a pulse rate at 100 per minute, she displayed the characteristic features of shock. The electrocardiogram soon indicated the appearance of bigeminy. The central venous pressure had fallen, from its previous level of 5 cm of water, to 2 cm of water. A biochemical analysis of the arterial blood was carried out at this time. It disclosed tremendous electrolyte and tonicity changes, as demonstrated by the following figures:

pH	7.28	
Pao_2	248	mm Hg
$Paco_2$	40	mm Hg
HCO_3	16	mEq/l
K	2.9	mEq/l
Na	97	mEq/l
Cl	74	mEq/l

These disturbances were related to plasma leaking during bradykinin shock, and were successfully corrected with the administration of hypertonic sodium chloride. Meanwhile a drip of 1,000.000 units of Iniprol in 500 cc of dextrose in water, was given intravenously. Bigeminy, probably induced by myocardial dysionic changes, proved resistant to both intravenous lidocaine and dilantin. It spontaneously disappeared when the ionogram improved. After two hours of intense postoperative care, the clinical condition of the patient no longer gave cause for apprehension. The anaesthetic record of this patient is presented in Figure 4.

Discussion

In retrospect, the integration of our clinical experience with new pharmacological knowledge can lead us to formulate an up-to-date sketch in the management of anaesthesia for the patient with a secreting carcinoid tumor. First, a new classification of the stormy incidents, likely to arise during both the anaesthesia and recovery periods, may prove useful. Then we may come to utilize more specific therapeutic means to prevent or reduce both the incidence and severity of the carcinoid attacks.

In outlining a practical classification for the complex features which have currently been included as a whole under "carcinoid syndrome," we can now suggest a bi-directional division, namely a serotoninergic and bradykininergic approach.

The serotoninergic dysfunctions

(1) *Slow awakening from anaesthesia*: There is a definite participation of serotonin in the metabolism of the brain.[28] Although serotonin does not directly cross the blood-brain barrier, the large amounts of 5-hydroxytryptophan that

can be released during surgery may well display a central depressant effect, once they have crossed the barrier. This concept is in agreement with the recent work of Jouvet, who demonstrated that the serotonin-containing cells in the nuclei of the raphe induce sleep.[29,30] Consequently, this mechanism appeared to be a logical explanation for the long lasting sleep exhibited by some of our carcinoid patients.

(2) *Hyperkinetic cardiovascular attacks, with tachycardia and/or arterial hypertension*: In the unanaesthetized patient, the cardiovascular effects of serotonin have been described by Page and McCubbon as "amphibaric." They used this word to define conflicting responses of the vasculature, depending upon the previous state of the vessels.[31] During anaesthesia, however, we found that serotonin seemed to display a pressor activity and a vasoconstriction of the circulatory bed. Of major importance is the fact that this pressor activity, as stressed by Page, is greatly augmented by ganglion blockade.[32] With this in mind, we can question the association of halothane or its ether azeotrope, with hyperserotoninaemia.

During haemodynamic studies in animals, Buccino, Covell, Sonnenblick, and Braunwald described a positive inotropic action on the myocardium, as well as a clear-cut tendency to tachycardia.[33] Parks also noticed an important increase in the heart rate following intravenous infusion of serotonin. This response is a direct effect of serotonin on the pacemaker, although it can also be related, in part, to an indirect stimulation of the adrenal medulla by serotonin.[34]

On this ground, it seems likely that both tachycardic and hypertensive paroxysmal episodes, which occur during surgery for carcinoid tumor, can be related with these pharmacological effects of serotonin.

(3) *Hyperglycaemia*: Hyperglycaemia, although of modest importance, was a constant feature of the carcinoid syndromes we have described. Preoperative glycaemia averaged 154 mg per cent in 4 patients. Higher peaks (225 mg per cent in Patient No. 16), may occur during surgery and in the recovery period. These changes in glucose metabolism have been attributed by Mansour, to a glycogenolytic and a glycolytic activity of serotonin, along with stimulation of phosphorylase and increased formation of $3', 5' - AMP$.[35] It is then of interest to monitor the evolutive changes in glucose metabolism by means of serial Dextrostix determinations.

(4) *Hypoproteinaemia*: This is also a metabolic consequence of the high tryptophan-serotonin turnover. Indeed, when the patient becomes the host of massive liver metastases and generalized new growths, his electrophoretic pattern may become grossly disturbed. These deviations from the normal pattern of protein metabolism should be assessed and kept in mind during the management of such patients.

(5) *Hyperpnea*: Serotonin has been demonstrated to increase the impulse traffic in the carotid chemoreceptor nerves.[34] Of course, this phenomenon has little practical significance, owing to the predominant depressive effects of the anaesthetic agents upon the respiratory system. However, an increased activity in the chemoreceptors may result through a central interplay in the activation of the nearby adrenergic centers. This should contribute to the pressor response elicited by serotonin.

The Bradykininergic Dysfunctions

They have occurred in our carcinoid patients with various degrees of intensity. They especially affect the cardiovascular and the respiratory systems, as exhibited by the following features:

(1) *Flushing*: Recent works by a pleiad of authors indicate that flushing of the skin may be, in fact, due to the release of large amounts of bradykinin and associated vasodilating peptides from the carcinoid tumor tissue. Robertson, Peart, and Andrews were unable to correlate flush with the serotonin content of the blood.[35] On the other hand, Oates, Melmon, Sjoerdsma, Gillespie, and Mason found that infusion of bradykinin intravenously caused skin flushing identical with that of the carcinoid syndrome.[37,38] Both bradykininolytic and serotoninolytic agents have been used with unequal success to reduce flushing attacks in the conscious patient. However, our impressive result with Trasylol in patient No. 16 suggests that further clinical trial should be advocated during life-threatening attacks in the anaesthetized patient. In this situation, maximal blood levels of circulating kinins offer the best situation for an optimal dose/response relationship.

(2) *Vasodepressive attacks*: They share the same physiopathology as flushing of the skin, and usually occur simultaneously. The parallelism between the vasomotor paralysis in the skin and severity of the drop in arterial blood pressure seems to indicate that they are bound to the same mechanism. The intensity, coupled with the duration of the attacks, conduce to the last step in the haemodynamic failure, bradykinin shock.

(3) *Bradykinin shock*: Bradykinin is more than a potent vasodepressor of the microcirculation. High concentrations of the active kinins can not only induce a severe peripheral vasodilation, but also modify the permeability of the capillary walls.[39] Capillary pores open widely, and moreover, biochemical distortions may create new fenestrations in the molecular layers of the endothelium. Then, a dramatic hypovolaemia can occur in minutes, with the leaking of plasma and electrolytes. This peculiar vasoparetic-hypovolaemic shock is particularly well illustrated in our patient No. 16. It is interesting to note that the pattern of this shock is strikingly similar to anaphylactic shock. Usually both are heralded by sudden erythrodermia, collapse of the arterial blood pressure and soon followed by oedema of the tissues.

(4) *Bronchospastic attacks*: Previously related to the effects of serotonin on the bronchomotor tone and pulmonary arterial tension, the asthma-like attacks of the carcinoid syndrome are more recently traced to the kallikrein-bradykinin system. The partial failure of both antihistamine and antiserotonin agents in the treatment of these attacks, favourably militates the bradykininergic thesis. In 1964, Oates and his collaborators measured serotonin and bradykinin in the supra-hepatic venous blood and in hepatic metastases. Their work suggests that bradykinin is likely the cause of bronchoconstriction, which proved difficult to ascribe to serotonin.[37] The disappearance of a severe bronchospastic crisis with Trasylol in patient No. 16 also prompted us to adopt this view.

Now, to propose a practical approach for the management of anaesthesia in a patient with a secreting carcinoid tumor, we must avoid therapeutic absolu-

tism. The forementioned classification and principles point out clear-cut landmarks, trace safe pathways and propose fixed attitudes. However, the scarcity of recent literature in this field,[40] should warn us against hasty and dogmatic conclusions. We know that patients submitted to standard anaesthesia often deviate from our safeguards and choose to make the trip through narrow, foggy and blind roads not indicated on the maps of our textbooks. So, it is with understandable hesitation that we shall set forth the following practical statements:

(1) The patient known to have a carcinoid syndrome should preferably be given therapeutic trials in the preoperative period with both bradykininolytic and serotoninolytic agents.

(2) The premedication should include a serotoninolytic drug; many antihistaminic and psycholytic drugs with well known anti-serotonin effects are suitable. Morphine should be excluded from the premedication, for reasons previously mentioned. In the operating room, before the induction of anaesthesia, a bradykininolytic agent should be administered intravenously, or at least, be readily available.

(3) The induction of narcosis should be smooth; adrenergic overactivity may trigger both serotoninergic and bradykininergic systems. Muscular agitation should be avoided, and positioning should be gentle. The fasciculations, resulting from the use of succinylcholine, may be dangerous as they increase intra-abdominal pressure.

(4) The endotracheal intubation should not stimulate the laryngo-tracheal mucosa. Failure to quiet this reflexogenic area may induce, through adrenergic mechanisms, a carcinoid attack.

(5) Curare may be a rather poor choice as a myorelaxant. First, it may induce a bronchoconstriction of its own. Moreover, owing to its ganglion-block action, it will precipitate any serotoninergic attack.[32]

(6) The occurrence of serotoninergic attack can be easily abated with the intravenous injection of small doses of Nozinam, or another serotoninolytic agent.

(7) The occurrence of a bradykininergic episode demands the administration of an anti-proteinase agent. Prevention of further activation of kinins can be obtained with a continuous infusion of smaller dosages of a bradykininolytic agent.

(8) A prolonged bradykininergic attack prompts the anaesthetist to check the effective blood volume, and inquire about the electrolyte disturbances which may have been induced by plasma leaking through the microcirculation.

(9) Cardiac arrythmias should first be related to their usual causes. Whenever attempted corrective measures fail, the arrythmia should be integrated into the serotonin-bradykinin physiopathology and treated accordingly.

(10) Blood glucose demands special corrections infrequently; however, its changes during anaesthesia should be monitored.

(11) Regional anaesthesia affords no protection against the carcinoid syndrome. The action of the liberated amines is located directly on the peripheral receptors and thus, is not influenced by denervation. Quite the contrary, ganglion blockade, induced by spinal or peridural anaesthesia, will precipitate a carcinoid attack.

Summary

The recent discovery that both serotonin and bradykinin were involved in the clinical manifestations of the carcinoid syndrome, has important implications in the management of anaesthesia.

In this report we reviewed the fundamental aspects underlying the biochemistry, the physiology, and the pharmacology of the secreting carcinoid tumor. Bradykinin and associated peptides were traced from their origin in the lysomal granules to their inactivation in the blood, the liver and the lungs. The pharmacological opportunity to block this proteolytic system with anti-peptidases (Trasylol, Iniprol, EACA), was stressed. Serotonin metabolism was also described. The pharmacodynamic pattern, involved in serotonin synthesis, uptake, storage, release, and degradation, was followed from the serotoninergic granule to the urinary excretion of 5 HIAA. The choice of drugs available to interfere with the steps of this sequence was emphasized.

We also reported our clinical experience with the management of anaesthesia in 16 cases of carcinoid tumors, 7 of which were functional and secreting. The carcinoid attacks which occurred during anaesthesia were classified in two categories, namely the bradykininergic and the serotoninergic dysfunctions. Accordingly, preventive and corrective measures described were related to a more specific approach to these incidents with either bradykininolytic or serotoninolytic agents.

This integration of new pharmacological knowledge with a clearer understanding of the clinical profile of the carcinoid attacks can result in a better management of the emergencies likely to arise during anaesthesia.

Résumé

In s'est présentement écoulé une décennie depuis que Stone et Donnelly ont mis à jours l'anesthésie du patient porteur d'une tumeur carcinoïde fonctionelle. Depuis ce temps, des modifications importantes sont survenues dans la physiopathologie de ce syndrôme, de sorte qu'il nous a semblé opportun de reviser certains aspects de ce sujet.

A côté de la sérotonine, le schéma biochimique du syndrôme carcinoïde s'est enrichi du système kallikréine-bradykinine, auquel on accorde aujourd'hui une très large place dans la genèse de certaines composantes du tableau clinique bien connu. De telles notions ne vont pas sans comporter des implications majeures dans la conduite de l'anesthésie pour ces patients.

Sur le plan biochimique, la cellule argentaffine de Kultschitsky renferme deux inclusions susceptibles de retenir notre attention. Tout d'abord, le granule sérotoninergique, où s'élaborent les diverses étapes de capture, de biosynthèse, d'emmagasinage et de libération de la 5-hydroxytryptamine. Fait important à noter, la DOPA-décarboxylase, que nous retrouvons par ailleurs dans le biosynthèse des catécholamines, joue un rôle clef dans la transformation du tryptophane en sérotonine. Cette constatation ouvre des avenues thérapeutiques logiques et efficaces en vue d'un blocage de la formation de sérotonine à partir des cellules carcinoïdes tumorales.

La sérotonine, une fois libérée dans le torrent circulatoire, en cours de crise ou pendant la chirurgie, est rapidement soumise à l'action oxydante de la monoamine oxydase, enzyme que nous sommes habitués de rattacher au schéma catabolique des catécholamines. Cette parenté qui se perpétue entre la sérotonine et les catécholamines, à un autre niveau toutefois, invite l'anesthésiste a faire emploi, en cours d'attaque sérotoninergique, d'agents adrénolytiques et sérotoninolytiques secondaires, notamment les phénothiazines et les antihistaminiques. Certes, en cours de chirurgie d'un carcinoïde malin et fonctionnel, les quantités de sérotonine libérées dépassent largement les possibilités cataboliques de la monoamine oxydase, et il faudra y suppléer par des blocages pharmacologiques dont le point d'impact sera généralement enzymatique. Au demeurant, certains produits, apparentés au LSD et aux dérivés de l'ergot, possèdent un effet sérotoninolytique très périphérique, situé directement au niveau du récepteur.

Les attaques sérotoninergiques, à la lumière d'études pharmacologiques multiples, semblent se solder sur le plan hémodynamique par un état hyperkinétique, fait de tachycardie et d'hypertension artérielle. L'action inotrope positive de la sérotonine ne fait plus de doute. L'effet vasopresseur périphérique qu'on lui reconnaît semble relever soit d'une activation directe du muscle lisse, soit d'une stimulation adrénergique déclanchée par la 5 HT.

Le lysosome, ce sac à suicide des cellules, renferme des hydrolases et des protéinases dont l'énumération est devenue touffue. Parmi ces dernières, la kallikréine, qui abonde dans les vésicules lysosomales de la cellule carcinoïde, est susceptible d'être libérée dans la circulation en cours de manipulations chirurgicales de la tumeur. La kallikréine réagit aussitôt avec l'alpha-2-globuline plasmatique pour engendrer des polypeptides actifs : l'undécapeptide arginyl-lysyl-bradykinine, les décapeptides arginyl-bradykinine et lysyl-bradykinine, et enfin, le nonapeptide bradykinine. Habituellement, la demi-vie de ces peptides est fort brève; leur dégradation est assurée par des kininases et des amino-peptidases sanguines qui inactivent les peptides en les décomposant.

En cours de chirurgie pour carcinoïde symptomatique, les doses massives de peptides actifs dépassent largement les possibilités lytiques des systèmes enzymatiques de dégradation, et il s'ensuit la persistance dans le flot circulatoire de polypeptides actifs dont l'effet s'avère extrèmement délétère sur la physiologie. Le point d'impact de ces peptides est surtout cardio-vasculaire et respiratoire. Au premier chapitre, on leur attribue maintenant le "flushing," les poussées hypotensives et le choc bradykininique. Au niveau respiratoire, il semble bien confirmé que les crises bronchospastiques relèvent davantage d'une origine bradykininergique plutôt que sérotoninergique.

Ces données biochimiques et pharmacologiques nous permettent déjà d'élaborer certaines règles de conduite, notamment l'addition d'agents à tropisme bradykininolytique (type Trasylol, Amicar, et Iniprol), à notre arsenal thérapeutique.

Nous avons voulu objectiver ces principes en les reliant à une étude clinique effectuée dans notre département au cours des dix dernières années. En faisant le relevé de nos dossiers chirurgicaux, il nous a été possible d'extraire 16 cas de carcinoïdes extra-appendiculaires, dont 7 se sont avérés fonctionnels et secré-

tants. A une exception près, ces derniers patients étaient porteurs de métastases hépatiques et pulmonaires.

L'anesthésie, sans incident dans deux cas, a donné lieu tantôt à des crises sérotoninergiques, tantôt à des épisodes bradykininergiques. Les poussées hypertensives et tachycardiques rattachées à la première variété ont cédé remarquablement bien à l'administration d'agents sérotoninolytiques, en particulier au Nozinam. Par ailleurs, les épisodes bradykininergiques, plus rares et plus menaçants, ont également pu être inversés d'une façon spectaculaire avec l'administration intraveineuse d'anti-peptidases, en l' occurence le Trasylol et l'Iniprol.

Basés sur cette expérience clinique, et à la lumière des données expérimentales dont nous avons fait la revue, nous croyons que, dorénavant, il nous faille aborder le problème des syndrômes carcinoïdes sous son double aspect bradykininergique et sérotoninergique. Conséquence logique, nous croyons également qu'une approche pré, per et post-anaesthésique de ces syndrômes doive comporter, selon les circonstances, un volet bradykininolytique et un volet sérotoninolytique.

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