The Carcinoid Syndrome

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Preface

I came to the Carcinoid Syndrome first with the aim of unravelling some of the problems concerning the biosynthesis of serotonin, and stayed, fascinated by all the clinical and biological phenomena presented by the disease. The syndrome is bewildering, difficult and frustrating to manage but only by a knowledge of its pathology, biochemistry and pharmacology can the patients with the disease be helped. The secrets of the carcinoid syndrome are not yet all revealed but this monograph has been an exercise in trying to make a cohesive and meaningful up-to-date picture of the syndrome in terms of its clinical manifestations and the underlying abnormalities in the structure and function of the carcinoid tumour and its effects upon the patient. John Mayow said 'As a rule disease can scarcely keep pace with the itch to scribble about it'. One feels that the carcinoid syndrome will have no difficulty in keeping pace with the pen.

June 1972 David G. Grahame-Smith

Plate 1. This is a reproduction of the picture published by Cassidy in the Proceedings of the Royal Society of Medicine (1931) showing the flushed appearance of a man with a metastatic 'adenocarcinoma' who complained of flushing, diarrhoea and had cardiac valvular lesions. This was published in 1931 before the carcinoid syndrome had been described.

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CHAPTER 1

Introduction

It is necessary first to define terms and in doing so we are bound by the historical development of the subject. Oberndorfer (1907) introduced the term 'Karzenoide' ('Carcinoid') to describe a group of intestinal tumours which, although having some of the features of the more usual adenocarcinomas, were slowly growing and ran a more benign course. Gossett and Masson (1914) demonstrated that many of these tumours contained cells with granules within them which reacted with silver stains, and Masson (1928) identified the tumour cells with the Kultschitzky cells of the intestinal epithelium. Since these cells were argentaffin cells the tumours also came to be called argentaffinomas. In the period between 1952 and 1954 three groups recognized the association of certain clinical signs and symptoms in association with carcinoid tumours (Biörck, Axén and Thorson, 1952; Thorson, Biörck, Bjorkman and Waldenström, 1954; Isler and Hedinger, 1953 and Rosenbaum, Santer and Claudon, 1953) and this syndrome became variously called carcinoidosis, argentaffinosis and the carcinoid syndrome. Since then many cases of the syndrome have been described with tumours that are not argentaffin or even carcinoid in type, but the term 'Carcinoid Syndrome' has over the past few years come into general clinical usage and is here to stay as a descriptive term implying a distinctive clinical picture whatever the tumour type.

In retrospect though, it appears that isolated cases of the carcinoid syndrome had been described prior to 1952. Dr Maurice Cassidy presented a case at a meeting of the clinical section of the Royal Society of Medicine on 15 October, 1930. The patient was a 31-year-old man who had, 'Phenomenal flushing of the face, much exaggerated during emotion or during a meal. Numerous dilated venules of recent origin were present over the nose and cheeks.' Cassidy's illustration of this patient is shown in Plate 1 and his appearance is typical of one type of persistent carcinoid flushing. In addition, this patient had a mass of pelvic growth, hepatic metastases and at autopsy pulmonary stenosis. Without a doubt this was the carcinoid syndrome. Early cases of the

syndrome also include those reported by Millman in 1943 and Currens, Kinney and White in 1945.

However, it was with the reports already mentioned between 1952 and 1954 that the syndrome as a clinical entity gelled and in these early reports the distinctive flushing, diarrhoea, valvular lesions and bronchoconstriction were all mentioned. It seems strange that a dramatic clinical syndrome like this should have defied description until the 1950's. But what Charcot said is so true in relation to the carcinoid syndrome, 'Disease is very old and nothing about it has changed; it is we who change as we learn to recognize what was formerly imperceptible'.

In 1953 Lembeck, following up the lead afforded by Erspamer and his colleagues (see the review by Erspamer, 1954) on the presence of the pharmacologically active amine, 5-hydroxytryptamine or serotonin in the enterochromaffin cell system, isolated and characterized 5-hydroxytryptamine from a carcinoid tumour and showed that it contained a high concentration of this substance. It is ironic that this tumour was apparently not associated with the carcinoid syndrome.

The many studies of Udenfriend and his group on the mode of synthesis and metabolism of 5-hydroxytryptamine during the early 1950's quickly became of clinical relevance when forces were joined with Page and his group to show that patients with the carcinoid syndrome excreted large quantities of the 5-hydroxytryptamine metabolite, 5-hydroxyindole acetic acid, in their urine (Page, Corcoran, Udenfriend, Sjoerdsma and Weissbach, 1955). This increased excretion of 5-hydroxyindole acetic acid has remained a hallmark in the diagnosis of the syndrome even though the position of 5-hydroxytryptamine as the only active hormone secreted by the tumour has been more recently questioned, as will be discussed later. Let it suffice here to say that in addition to 5-hydroxytryptamine the roles of kallikrein, bradykinin, histamine and prostaglandins have now to be considered as agents involved in the production of the symptoms and signs of the carcinoid syndrome. In a similar expanding way and albeit that the main manifestations of the carcinoid syndrome remain those of flushing, diarrhoea, wheezing and cardiac valvular disease there is an important variability in the presentation of the syndrome which has led Sjoerdsma and Melmon (1964) to speak of the 'Carcinoid Spectrum'. This development is not just over specialization because there is no doubt that the differences in presentation of the syndrome from patient to patient reflect either a difference in the humoral products of the tumour or a variation in the individual patient's reaction to them. It is certain now that the early acceptance of 5-hydroxytryptamine as the substance solely responsible for all the manifestations of the syndrome was mistaken and that unfortunately the last line of the doggerel by Bean and Funk (1959) is probably not entirely or even partly true.

This man was addicted to moanin'.
Confusion oedema and groanin',
Intestinal rushes,
Great tricoloured blushes,
And died from too much serotonin.

To make matters more complicated, it appears that on occasions tumours producing the carcinoid syndome may also secrete ACTH, perhaps MSH and even insulin and the implications of this 'Ectopic' hormone production are most important.

Just as there has been a proliferation in the number of substances found to be produced in the syndrome, so the types of tumour found to produce the syndrome have increased. Though undoubtedly gastro-intestinal carcinoids, particularly those arising in the ileum, are most commonly associated with the syndrome tumours of the bronchus, biliary tract, pancreas, and teratomas, many of which have none of the classical microscopic features of carcinoid tumours, may also produce the syndrome. However different these tumours look, the fact remains that they produce the syndrome and are functionally similar, and recent investigations of their ultrastructure are in fact beginning to reveal certain structural similarities which may relate together all the different types of tumour which can cause the carcinoid syndrome.

From the outset, therefore, it will be apparent that we shall be dealing with a disease which is heterogenous in its pathology, biochemistry, pharmacology, and clinical manifestations. The correlation of structure and function and the understanding of the basis of this heterogeneity in the carcinoid syndrome are the main themes of this text.

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CHAPTER 2

The Cell of Origin

One of the fascinating problems highlighted by the carcinoid syndrome is the nature and function of the cell from which the tumour responsible for the syndrome arises. Here are tumour cells capable of producing several different hormones, arising often in differing anatomical sites, yet the very presentation of the carcinoid syndrome and the almost invariable association with increased 5-hydroxytryptamine synthesis shows that there is some relationship between these different types of tumour.

Let us concentrate first upon the isolated granular cells in the intestinal epithelium which were first described by Nicolas in 1891, which Kultschitzky redescribed in 1897, and which still bear his name. Schmidt (1905) found these cells to give a chromaffin reaction and two years later Ciacco (1907) called them enterochromaffin cells. Masson (1914) described the ability of these cells to take up and reduce silver salts in their granules, so called argentaffinity, and suggested that these cells were the origin of carcinoid tumours. He and Berger (Masson and Berger, 1923) in fact suggested that the enterochromaffin cells might secrete some humoral substance acting locally in the bowel wall, an example of inspired thinking. Cordier (1926) also propounded this idea and in addition showed that these enterochromaffin cells had a wide species distribution.

In 1932 Hamperl enlarged on the scope of the enterochromaffin cell system. In the argentaffin method used by Masson (1914) reliance was placed upon the ability of the intracellular granules to both fix and reduce the silver salt to produce brown or black staining. Hamperl, on the other hand, allowed tissues to fix the silver and then added an external reducing agent to reveal black granules where the silver had been fixed. This method demonstrated not only the previously described argentaffin cells but also a much wider system of cells, the 'argyrophil' cells. Since then there has been much controversy about the meaning and relationship of these two staining reactions which still continues.

Erspamer and his colleagues (see the review by Erspamer, 1954) have made an extensive study of the enterochromaffin cell system in nature

and have shown these cells to be present in the gastrointestinal mucosa, biliary tract and pancreas of all vertebrates studied, with the exception of certain fish. These cells are also present in invertebrate animals, witness the use of the posterior salivary glands of the octopus for the isolation and characterization of 5-hydroxytryptamine (Erspamer and Asero, 1953). The undoubted secretory properties of the cell and its presence in such a wide distribution of species suggests that its function must be a primitive but important one in the process of evolution. Erspamer (1939) came to the conclusion that argyrophil and argentaffin cells were related, the former in some cases maturing into the latter. My own interpretation of this situation is based upon the consideration of the basis of the histochemical reactions and their meaning. Some component of the granules within both these types of cells plainly fixes silver salts. Only in the argentaffin cells is the silver reduced by endogenous components of the cell and all the evidence points to 5-hydroxytryptamine. Barter and Pearse (1953) conclusively showed that 5-hydroxytryptamine fixed in gelatin gives positive histochemical reactions. More recently Pentilla and Lempinen (1968) have studied the distribution of argentaffin and argyrophil cells in the human intestine by applying a number of histochemical techniques including argyrophil and argentaffin stains, diazo-coupling, and formaldehyde-induced fluorescence. This latter technique depends upon the conversion of 5-hydroxytryptamine to 3,4-dihydronorharman derivatives which have a yellow fluorescence and which was used by Falck (1964) to map out the cellular localization of 5-hydroxytryptamine in brain. The technique is extremely sensitive and specific for the detection of this amine in tissues. Using these techniques, Pentilla and Lempinen (1968) correlated the histochemical characteristics of various parts of the intestine with the 5-hydroxytryptamine content of those parts. They found that the fluorescence method was the most suitable for demonstrating enterochromaffin cells and this correlated well with the argyrophil method. The argentaffin method was less sensitive than either the fluorescence or argyrophil methods but more sensitive than diazo-coupling. All cells which had positive fluorescence had a positive argyrophil test but not all had a positive argentaffin test. They found an extremely positive correlation between enterochromaffin cells in the intestinal mucosa and the concentration of 5-hydroxytryptamine (see Table 1).

It seems probable that although argyrophilia indicates fixation of silver by some intracellular structure it does not signify a specific functional characteristic, though it may indicate a general ability to store secretory products, for the cells of the adrenal medulla, of phaeochromocytomas of the organ of Zuckerkandle and the carotid body are also argyrophilic (Hamperl, 1952). Nevertheless, argyrophilia is

TABLE 1

The correlation between the number of enterochromaffin cells and the 5-hydroxytryptamine content of different areas of the gastrointestinal tract (Pentilla and Lempinen, 1968)

Site	*Number of enterochromaffin cells/mm³*	*5-hydroxytryptamine content (μg/G tissue)*
Duodenum (outlet of bile duct)	1875	6.2
Duodenum (pyloric ring)	1688	4.9
Jejunum	1166	3.3
Ileum	518	1.7
Meckel's diverticulum	700	1.8
Appendix	381	1.1

one characteristic of the enterochromaffin cell. It is of interest that if an animal is treated with reserpine which releases 5-hydroxytryptamine from its storage granules the argentaffinity of the gastrointestinal mucosa is markedly lessened while the argyrophilic properties are retained (Pletscher, 1958). All these lines of evidence lead one to agree with Bensch *et al.* (1968) that an argyrophilic enterochromaffin cell becomes argentaffin cell when it contains sufficient 5-hydroxytryptamine to reduce the silver salt. It is probably a matter of local 5-hydroxytryptamine concentration, and this will depend upon the balance between the rate of synthesis, storage and release of the amine. I would doubt whether an argyrophil cell is of necessity a precursor of an argentaffin cell. Although it may synthesize just as much 5-hydroxytryptamine it may release it so quickly that it never becomes argentaffin and if this is part of its functional capacity then argentaffinity may never become one of its properties. This does have bearing upon the histochemical techniques used in the examination of carcinoid tumours, since formaldehyde-induced yellow fluorescence, argyrophilia and argentaffinity would be expected to correlate with the 5-hydroxytryptamine content of the tumour and give an idea of at least one aspect of its function.

Williams and Sandler (1963) have partially taken this approach and have attempted to correlate the embryological derivation of the tumour, with its histochemical properties and functional activity (see Table 2). This approach has also been taken by Pariente *et al.* (1967).

Their classification takes as its reference point the ileal tumour derived from the mid-gut as being most typical because it is most common and

TABLE 2

The characteristics of carcinoid tumours derived from different embryonic divisions of the gut

	Fore-gut	*Mid-gut*	*Hind-gut*
Histological structure	Tendency to be trabecular; may differ widely from classical pattern	Characteristic	Tendency to be trabecular
Argentaffin and diazo reactions	Usually negative	Positive	Often negative
Association with the carcinoid syndrome	Frequent	Frequent	None
Tumour 5-HT content	Low	High	Not detected
Urinary 5-HIAA	High	High	Normal
5-HTP secretion	Frequent	Rare	Not detected
Metastases to bone (Usually osteoblastic) and skin	Common	Unusual	Common
Association with other endocrine secretion	Frequent	Not described	Not described

its behaviour fairly predictable. This type of tumour is frequently argentaffin, contains a high concentration of 5-hydroxytryptamine and is often associated with the syndrome. Carcinoid tumours arising in hind-gut derivatives, particularly the rectum, often do not show argentaffinity, are not associated with the syndrome and contain little or no 5-hydroxytryptamine. Carcinoids derived from the fore-gut often show negative argentaffinity, a low content of 5HT (though 5HIAA excretion may be high showing that 5-hydroxytryptamine is synthesized and either metabolized by or released from the tumour) and these tumours are often associated with the carcinoid syndrome, though the syndrome may be clinically atypical and associated with other endocrine abnormalities. Many of these features will be discussed in detail later, but this type of classification is useful in indicating several points. First, that overall carcinoid tumours are neither structurally or functionally homogeneous. Second, that by consideration of the embryonic derivation of the cell of origin the structure and function of these tumours can be partly systematised. Third, that perhaps the enterochromaffin cell system has a common parent cell type which during development differentiates structurally and functionally leading to the presence of cells in different anatomical sites which, while superficially similar, have different normal functions. Fourth, that the different histochemical reactions reflect real organised differences in

function rather than being haphazard differences in the cellular concentration of 5-hydroxytryptamine.

In terms of the incidence of the carcinoid syndrome and the function of its cell of origin there is one point which puzzles me very greatly, and which I shall document later. That is, that carcinoid tumours deriving from mid-gut structures are relatively common and very frequently give argentaffin reactions (Lille and Glenner, 1960) and yet overall are in fact infrequently associated with the carcinoid syndrome even in the presence of metastases. Unfortunately there is very little data upon which one can speculate as to the reason for this discrepancy. Certainly there is a case for careful and exacting clinical study of such cases to definitely exclude the carcinoid syndrome and for biochemical and histochemical studies of such tumours. Perhaps these tumours have lost the functional activity of their parent cell during the process of carcinogenesis as do tumours of other endocrine organs. It may be that the carcinoid tumour which does produce the syndrome and is therefore functionally active is the exception rather than the rule! Summarizing then, it appears that carcinoid tumours of the gastrointestinal producing the carcinoid syndrome arise from the enterochromaffin cells of the gastrointestinal mucosa (see Plate 2) and it is also probable that tumours producing the syndrome and arising in the bronchus, pancreas and biliary tract also arise from cells in these structures belonging embryologically to the enterochromaffin cell system, though it must be admitted that the superficial microscopic appearance and histochemical reactions of this latter group would seem often to belie their origin. This conclusion may be of some importance in regard to the 'Ectopic hormone' syndrome and is further discussed in Chapter 7.

The carcinoid syndrome in association with ovarian tumours also occurs (Waldenström, 1958) and recently this association has been reviewed by Chatterjee and Heather (1966). It appears that such tumours are usually teratomas containing argentaffin cell tissue. Although it is odd that, not infrequently, functioning argentaffin cell tissue is found in these teratomas, nevertheless the cell of origin of the functioning tumour mass is clear. Moertel *et al.* (1965) described a primary tumour of the thyroid associated with the carcinoid syndrome which was probably a type of medullary thyroid carcinoma. Williams (1968) has reviewed the role of the parafollicular cell system in the thyroid from which such tumours derive. There is no doubt that the parafollicular cell system contains 5-hydroxytryptamine (Falck *et al.*, 1964) and Williams (1968) has found as much as 10 μg/g of 5-hydroxytryptamine in a medullary thyroid carcinoma. More recently the case for these tumours secreting calcitonin (Tubiana *et al.*, 1968) and prostaglandins has been made (Sandler, Karim and Williams, 1968). Although the full blown carcinoid syndrome in association with medullary thyroid carcinomas is not

common it may occur and the cell of origin appears to be the parafollicular thyroid cell. Carcinoid tumours have also been described as arising from the cervix uteri (Driesdens *et al.*, 1964) and the testis (Brown, 1964; Dockerty and Scheifley, 1955; Simon *et al.*, 1954) has also been the site of the primary growth. It is indeed very difficult to unify in terms of structure and function the cells of origin of all these tumours in different sites but it is likely that such tumours spring from cells of the enterochromaffin cell system or cells closely related to them, present in many different tissues (see also Chapter 7 and Weichert, 1970).

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