CURRENT ENDOCRINE CONCEPTS

Edited by

E. D. WILLIAMS

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Preface

In the 'classical' era of endocrinology, we learnt to recognize endocrine syndromes and the hormones that mediated them. A complex of symptoms and signs was attributed to the overproduction of a single hormone, that hormone was identified chemically, and its cell and tumour of origin identified pathologically.

One of the fascinating aspects of endocrinology is that at a time when many thought the classical era of endocrinology was past, new syndromes, new hormones and their cells of origin and associated tumours are still being identified, and advances in these fields are progressing side by side with, for example, receptor studies, one of the new fields of investigation that enable us to understand not only some of the mechanisms of hormone action and endocrine control but also some of the mechanisms of the causation of disease.

The results of these studies illustrate the complex network of checks and balances that maintain the constancy of the internal environment. For example, the original simple negative feedback loop that linked thyroxine (T_4) production to thyroid-stimulating hormone (TSH) release is now complicated by our understanding of the production of triiodothyronine (T_3) as well as T_4 by the thyroid, peripheral deiodination of T_4 to both reverse T_3 and T_3, and the importance of T_3 rather than T_4 in the control of TSH production. Hypothalamic sensitivity to thyroid hormones, thyrotrophin releasing hormone production, autoregulation of the thyroid cell in its responsiveness to TSH, and autoregulation of the target cell in its response to thyroid hormones are some of the additional features which, if all are put down in one diagram, lead to the type of complex flow chart that delights some minds and infuriates others. The multiplicity of controls which modulate the simple push–pull system leads to a very stable yet responsive mechanism, but also to a network of interdigitatory effects that allows one to draw effective parallels between endocrine and neural control systems.

Endocrinology is a rapidly expanding subject in more ways than in its understanding of hormone actions. Organs which used to be thought of only as 'endorgans' as far as the endocrinologist is concerned are now being recognized as containing a multiplicity of endocrine cells—indeed the gut could be regarded as an elongated hollow endocrine gland with a secondary absorptive function! Studies of these gut endocrine cells again strengthen comparison with the nervous system; the same regulatory peptides that occur as neurotransmitters are secreted as 'local hormones' by cells of the diffuse endocrine system.

The papers presented at the Royal College of Pathologists' 1981 Symposium on Endocrinology therefore not only illustrate some of the current thinking and work on the complex endocrine mechanisms and the way in which they are altered in disease states but also our expanded knowledge of both classical and recently recognized endocrine cells. This volume presents a selection of reviews and recent advances in endocrinology that illustrate the many facets of this all-pervasive subject.

E. D. WILLIAMS

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PART ONE

Royal College of Pathologists Roy Cameron Lecture

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Hyperplasia and Neoplasia in Endocrine Glands

E.D. WILLIAMS

The concept of malignancy is usually discussed in absolute terms: either a tumour is malignant or it is not. The application of this belief to the identification of malignancy in human tumours is usually relatively simple: in tumours of the lung, for example, the major morphological types of squamous carcinoma, adenocarcinoma and oat-cell carcinoma generally show both the microscopic and clinical features of malignancy, and there is rarely any difficulty in establishing the diagnosis either by cytology, biopsy or resection. The one tumour of the lung where problems face both pathologist and clinician in assessing the presence or absence of malignancy is the endocrine tumour of the lung, the bronchial carcinoid. Even though invasion may be difficult to establish, and metastasis occurs in only about 10 per cent of cases, this tumour is generally regarded as of low-grade malignancy, and was previously regarded as a bronchial adenoma. Indeed, if tumours showing atypical features are excluded, the proportion with metastasis is very small indeed (Arrigoni, Woolner and Bernatz, 1972).

The bronchial carcinoid is a typical endocrine tumour, and the difficulty it poses in establishing malignancy is shared by many endocrine tumours, as the existence of such terms as 'malignant adenoma' of the thyroid testifies. Even Rupert Willis, who tended to be dogmatic in his approach to tumour classification, commented that no sharp separation of epithelial hyperplasia, benign tumours and malignant tumours is possible in the thyroid (Willis, 1948). He went on to make another very illuminating comment, saying 'Of course it is convenient and necessary to assign thyroid overgrowths to one or another group, and in most cases the behaviour of the lesion corresponds with the experienced pathologist's opinion'.

It is important in all pathology—but especially in endocrine pathology—to distinguish the theoretical separation of benign and malignant tumours from their separation in practice. In theory, we may define a malignant tumour as one which is capable of invasion and metastasis, and a benign tumour as one which is capable of neither. In the practical application of this theory, we rely in large part on past experience of the behaviour of tumours showing various characteristics. This is particularly true in the thyroid, where not only are many of the carcinomas very slowly growing, but also our knowledge of their behaviour is largely based on studies of resected specimens. The usual convention followed by the pathologist in the case of a

suspicious follicular tumour is to take seven to ten capsular blocks, to make a diagnosis of carcinoma if capsular and/or vascular invasion is present, and to make a diagnosis of adenoma if they are absent. The degree of nuclear pleomorphism and frequency of mitotic activity are considered of little or no importance—provided they fall short of the characteristic changes of anaplastic carcinoma. The term 'atypical adenoma' is used to describe tumours lacking capsular or vascular invasion, but showing pleomorphism and mitotic activity (Hazard and Kenyon, 1954; Lang et al, 1980).

It must be recognized that this is a pragmatic approach—the studies quoted have shown that tumours showing the histological features of atypical adenoma on resection do not later develop metastasis. These studies have not shown that they are benign, but merely that, in the absence of capsular or vascular invasion, metastasis has not yet occurred. It could be argued that these lesions are at the most slowly-growing end of the spectrum of follicular malignancy; studies from the Mayo Clinic have shown that in follicular carcinoma the likelihood of metastasis is correlated with the extent of vascular invasion found (Woolner et al, 1961), and it is obvious that a tumour with a very limited capacity for invasion is more likely to be resected before invasion occurs than is a more aggressive lesion.

Even with this approach, the distinction between follicular adenoma and carcinoma is not consistently applied, as can be seen from a recent comparative study of diagnosis of thyroid tumours by different pathologists where the agreement on the diagnosis of follicular carcinomas was very much worse than with other types of thyroid malignancy (Saxen et al, 1978).

If the distinction between follicular adenoma and carcinoma is difficult, the distinction between nodule and adenoma is even less certain. The definition of a nodule causes problems. Both modern medical dictionaries and old English language dictionaries equate the word to a tumour: for example, Richardson's dictionary defines a node or nodule as 'a bump, protuberance or swelling' (Richardson, 1863). Incidentally, the same dictionary explains the word tumour as 'a disease in which the parts of the body recede from their natural state by an undue encrease of their bigness'!

In endocrine pathology, the term nodule has acquired the specific meaning of an area of focal hyperplasia which is not regarded as a true tumour. Nodules are commonly multiple, and the background gland is often hyperplastic, while true adenomas are usually single, with the background gland normal or at times suppressed. This distinction between a solitary tumour (adenoma) and multiple lesions (nodules) is of course not absolute, although it is common enough to justify a comparison with the old Scottish proverb 'Ane rook's a craw, twa craws is rooks', which points out that the crow and the rook—two generally similar birds—can be told apart by their solitary or gregarious lifestyles (Williams et al, 1980). Individually, nodules and adenomas may be very difficult to separate, and here again the problem is common to most endocrine glands. Nodules are common in the pathology of the thyroid, parathyroid, pancreatic islets and adrenal cortex, and are occasional in adrenal medulla and pituitary. Nodular hyperplasia is the characteristic finding in endocrine glands affected by the multiple endocrine neoplasia syndrome.

With this background in human pathology of a practical problem, common to the various endocrine glands, of making a clear distinction between nodule, adenoma and carcinoma, I would now like to discuss experimental endocrine carcinogenesis. Over the past few years, we have been looking at several factors influencing the development of tumours in thyroid follicular cells, thyroid C cells and parathyroid cells. The thyroid follicular cell studies are based on the early work by Purves and Griesbach (Griesbach, Kennedy and Purves, 1945), who showed that long-term administration of goitrogen alone will eventually lead to the development of thyroid tumours in the rat, and on the work of Doniach (Doniach, 1958), who demonstrated the importance of radiation in experimental thyroid neoplasia. The observation that rat thyroid tumours could be separated into those derived from follicular cells and those derived from C cells (Williams, 1966) enabled the earlier work to be reappraised, and it was recognized that the common spontaneous thyroid tumour of the experimental rat was a C cell tumour.

The role of radiation in the genesis of rat follicular and C cell tumours has been assessed in our laboratory over the past few years. Animals were given radiation in the form of iodine-131 within 48 hours of birth in a dose of 0, 5, or 10 μCi, and were killed at intervals over a two-year period. Follicular tumours were almost exclusively confined to the radiated groups in each of two large experiments, with only four follicular tumours occurring in 228 non-irradiated animals, while 210 out of 435 irradiated rats showed tumours. These figures include rats of a very wide age range. If the figures are restricted to animals between one and two years of age, the comparison is even more striking: two follicular tumours were found in 97 non-irradiated animals, while 138 were found in 199 irradiated rats (Triggs and Williams, 1977a; Thurston and Williams, 1982b).

These figures show that radiation from ^{131}I is a potent carcinogen for the rat thyroid. However, it is clear that the carcinogenic effect of ^{131}I is also dependent on other factors, as it has been shown that the administration of thyroid hormones after radiation abolished carcinogenesis (Nichols et al, 1965; Doniach, 1974) and that a combination of a low iodide diet and radiation was ineffective in thyroid carcinogenesis in hypophysectomized rats (Nadler, Mandavia and Goldberg, 1970). We have shown that the administration of ^{131}I to newborn rats leads to a considerable elevation of thyroid-stimulating hormone (TSH) and, compared with the non-irradiated control animals, a reduction in thyroid mass, despite the high TSH (Thurston and Williams, 1982b).

Interestingly, the T/S ratio—a measure of the thyroid's response to TSH based on the iodide pump—showed a slow rise following radiation, with a peak that occurred later than the TSH peak. In the normal rat treated with goitrogen, the T/S ratio closely follows the level of TSH. These results suggest that there is an impaired functional response to TSH in the irradiated gland, as well as an impaired growth response comparable to the impaired response to goitrogen seen after small doses of radiation. The sequence of events following the administration of moderate doses of ^{131}I can therefore be interpreted as follows: radiation impairs function, and the resulting drop in output of thyroid hormone leads to a rise in TSH. The damage to function

and to the growth response prevents an adequate output of thyroid hormone, so that the rise in TSH continues with an inappropriately low T/S ratio. After about eight months, the improvement in the ability of the gland to produce thyroid hormone, dependent on improving function and steadily increasing thyroid weight, leads to a drop in TSH, but the T/S ratio continues to rise, as functional impairment diminishes. By about 15 months, the T/S ratio is beginning to drop, and by 18 months, both TSH and T/S ratio are virtually back to normal—but many of the animals have tumours. Whether the steady improvement in function is due to improvement in the function of individual cells or to an increase in the proportion of daughter cells with less radiation-induced impairment of function is not known. The time course would suggest that the latter explanation is more likely, with the progeny of the least damaged cells having a selective advantage. The growth response to TSH, therefore, is an essential part of the carcinogenic effect of radiation on the thyroid follicular cell.

The scattered distribution of C cells in the rat thyroid meant that in these experiments they were exposed to very similar radiation doses, as the mean path length of β radiation from ^{131}I is long relative to follicular diameter. We have shown that radiation is carcinogenic for C cells (Triggs and Williams, 1977a), and more recently have analysed the C cell response to radiation using morphometry. The dose of radiation used in these experiments led to the disappearance of the great majority of C cells, with an increase in numbers occurring only about one year later. This reappearance occurred in small islands of cells, interpreted as clones, each derived from one surviving C cell (Thurston and Williams, 1982a).

In a study examining the influence of dietary vitamin D levels on the incidence of thyroid tumours, no effect on follicular tumours was found. However, there was a significant increase in C cell tumours in animals given a high vitamin D diet (Thurston and Williams, 1982b), most marked in radiated animals. It seems that after radiation at the doses given, therefore, the large initial cell death rate is followed by re-growth of the survivors, leading first to nodular hyperplasia, and later neoplasia, and that this process is helped by a high vitamin D diet and hindered by a low vitamin D diet.

In the rat, the parathyroid glands are usually embedded in the thyroid lobes and, as a result, irradiation to the thyroid from ^{131}I gives approximately the same dose to the parathyroid as to the peripheral thyroid follicles. In the experiments quoted above, the parathyroids were also studied. Initially, the glands were reduced in size, and the serum calcium was slightly lowered in the radiated groups. With time, the glands increased in size, and eventually single or multiple tumours occurred. These lesions were confined to the irradiated animals, and were more common in those given a low vitamin D diet and less common in those given a high vitamin D diet.

These experiments therefore demonstrate for thyroid follicular cells, thyroid C cells and parathyroid cells that the combination of radiation and hyperplasia is a potent carcinogen—as was demonstrated for pituitary cells some years ago by Furth (Furth, 1953). However, they also demonstrate that one of the effects of radiation is, by both reduction in cell mass and efficiency of function, to lead to an increase in growth stimulus. This, however, cannot

explain all the effects of radiation carcinogenesis in endocrines, as although radiation is very poorly carcinogenic if hyperplasia is removed, radiation and a massive hyperplastic stimulus are more carcinogenic than the hyperplastic stimulus alone.

In these experiments on endocrine carcinogenesis, the same problems in separation of nodule, adenoma and carcinoma are found as in human pathology, but in the absence of the necessity to predict the behaviour of individual tumours they cause far fewer difficulties. They are generally solved by regarding any abnormal demarcated mass of cells as a tumour, and using the term carcinoma only when invasion or metastasis can be identified. However, the ability to study the development of tumours at different time intervals following the combination of radiation and a hyperplastic stimulus shows that these stimuli together lead to hyperplasia, nodules, adenomas and carcinomas. They do not show whether they arise sequentially out of each other; there certainly seems no reason why the cells forming nodules should be spared from the possibility of progression to adenoma or carcinoma, and it may well be that they are more likely to do so than normal cells. It is not known whether these tumours arise from single cells or groups of cells, although here work in man may provide a useful comparison.

The clonality of human tumours has been studied by Fialkow, using the high frequency of abnormalities of the x-linked enzyme glucose-6-phosphate dehydrogenase in negro women (Fialkow, 1979). Most of the tumours he studied were considered to be monoclonal, including all the malignant tumours. Obviously in the rat model under discussion, the cells of diffuse hyperplasia are polyclonal, but from the human work cited it would seem likely that the carcinomas are monoclonal. It may well be that the clearest distinction between a nodule and an adenoma is that the former is polyclonal and the latter monoclonal. While this distinction may not always agree with the present usages of the terms, it does at least provide a theoretical basis for their distinction, and one which can be tested by experiment. Work currently in progress is investigating the clonality of liver tumours produced in mice with a deficiency of the histochemically demonstrable x-linked enzyme ornithine carbamyl transferase. It would also accord with the progressive changes seen with time after radiation and with the application of natural selection to carcinogenesis. A hyperplastic stimulus initially leads to growth in all cells. Variable damage from radiation or variation in the behaviour of a group of cells, perhaps supplied by one vessel, results in a lack of uniformity of the hyperplastic response, with the development of one or more nodules. A true neoplasm is monoclonal and results from a heritable change which confers its selective growth advantage on the original cell and its progeny. If this change allows invasion to take place, then the tumour is malignant; if not, it is benign.

However, as in the genetic instability theory of ageing (Hayflick, 1979), increasing numbers of mitoses are associated with an increasing risk of error, so that the chance of a malignant tumour developing is likely to be greater in an adenoma than in normal tissue. The principles of natural selection obviously ensure that clones with a greater growth rate will

dominate, providing they can organize their blood supply, maintain their growth rate, and avoid triggering any destructive mechanism.

Observations by Baylin and his group in a very comparable situation in man to one of the experiments described here lend support to this concept. They studied a female black patient with a genetically determined medullary carcinoma and also two forms of glucose-6-phosphate dehydrogenase (G6PD), providing an x-linked marker for the clonality of any tumour. In the thyroidectomy specimen, C cell hyperplasia was found with multiple tumours of medullary carcinoma. The G6PD content of two tumours showed that each was monoclonal, but with different forms of G6PD, proving that they must have arisen from different cells (Baylin et al, 1978).

The importance of a continued hyperplastic stimulus in the genesis of nodules and tumours in endocrine glands is unquestioned. The mechanism by which the cell makes the switch from controlled to poorly or uncontrolled growth is not known. In an attempt to throw light on this we have been studying the control of thyroid follicular growth in hyperplasia before tumours appear. A continued stimulus, achieved by continuous goitrogen treatment, has long been known to lead to an initial rapid growth phase, followed by limitation of growth and an eventual plateau phase, out of which tumours arise. In a series of investigations, we have shown that this takes place despite continued high TSH levels, and that there is an uncoupling of the functional and growth responses of the follicular cell, with T/S ratio continuing to respond to the high TSH, while the metaphase index, initially high, drops after a few weeks to a low level (Wynford-Thomas, Stringer and Williams, 1982, unpublished data). This implies the existence of a mechanism, which we believe to be intrathyroidal, which can limit the growth response of the thyroid follicular cells to TSH. This may well be an example of a general mechanism of growth control. The initial stage that leads to tumour formation may then be a heritable failure in one cell of the growth limitation mechanism, rather than a true neoplastic transformation. The progeny of the cell concerned will then continue to respond to TSH in the same way as the normal follicular cell at the start of goitrogenesis, leading to the development of a circumscribed mass of growing cells. The continued mitotic activity leads to an increased chance of further error, and the development of a tumour that is no longer dependent on TSH for its continued growth.

It is proposed, therefore, that a hyperplastic stimulus to an endocrine gland leads to the development of tumours through a number of successive stages. An initial phase of hyperplasia is controlled by a growth-limiting mechanism, although irregular hormonal response on a regional basis may lead to the development of nodules which are polyclonal. Escape by an individual cell from this mechanism leads to the development of a tumour, which is monoclonal, but still trophic hormone dependent. A further heritable change within the lesion leads to the development of a tumour which is no longer dependent for growth on the presence of the trophic hormone, although it may still retain some responsiveness; yet further change is likely to be required to cause true malignancy to develop.

This stepwise progression from simple hyperplasia to malignancy is

dependent on errors in DNA synthesis or repair, which are more likely to occur in growing cells. They are also of course likely to occur more frequently in the presence of carcinogenic agents such as radiation or chemical carcinogens. The progression to endocrine neoplasia dependent on hyperplasia on the one hand and classical carcinogenic agents on the other is difficult to discuss in terms of initiator and promotor, as either mechanism can cause neoplasia, and the classic carcinogens may be effective in part because they induce a trophic stimulus. The two mechanisms act very effectively together, and while naturally occurring tumours may be due to a dominant trophic response, or to the dominant effect of a carcinogen, all grades of interaction can happen, giving rise to a variety of patterns of response.

This concept can help in the understanding of many of the problems in endocrine pathology in man. Perhaps the best example to choose is hyperparathyroidism, where there is great variation in the frequency of diagnosis of hyperplasia in different series (Williams, 1974). Hyperplasia of the parathyroid can occur in a number of different clinical situations, both those where the mechanism leading to the hyperplasia is understood—as in renal failure, or vitamin D deficiency—and where the mechanism is not understood—as in primary nodular hyperplasia and primary water clear cell hyperplasia. The only tumorigenic factor known other than hyperplasia is radiation which has been shown to be related to parathyroid adenoma formation in man and in experimental animals (Rosen, Strawbridge and Bain, 1975; Tisell et al, 1976; Triggs and Williams, 1977b: Thurston, Wynford-Thomas and Williams, 1982, unpublished data).

In patients with a prolonged severe hyperplastic stimulus as in chronic renal failure, single or multiple nodules of the parathyroid may arise from the hyperplastic glands. The pathology is often very similar to that of primary nodular hyperplasia, which can be assumed to be a consequence of a prolonged unknown hyperplastic stimulus. A carcinogenic agent may lead to the development of a single pathological tumour in the absence of hyperplasia. Lesser degrees of hyperplasia will obviously enhance minor 'doses' of the carcinogenic factor and the frequency with which hyperplasia is diagnosed in the presence of one or more nodules or adenomas clearly depends on the criteria used for making the diagnosis. While the recognition of minor degrees of hyperplasia is of considerable theoretical interest, it should not obscure the pragmatic approach to treatment—based on past experience. The chance of recurrence is high if only one of four enlarged glands is removed; it is very low if one enlarged gland is removed and three normal sized glands remain, even if biopsy of these glands shows minor degrees of hyperplasia.

In conclusion, then, I have attempted to review some of the problems of hyperplasia and neoplasia in endocrine glands, and to separate the theory of carcinogenesis from the pragmatic approach to diagnosis and treatment in individual cases. I would propose that nodules are polyclonal, while adenomas and carcinomas are monoclonal. Both hyperplastic stimuli and carcinogenic factors are important in the genesis of endocrine tumours, and their interplay can explain many of the variable and often confusing features of endocrine pathology in man.