Papers and Originals

Human Pituitary Disease*

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In 1889 Pierre Marie recognized the pituitary enlargement in acromegaly, but only over the last decade have the radioimmunoassays needed for testing human pituitary function become available, and also several new treatments for pituitary disease, whose place is now being assessed. Pituitary disorders possibly secondary to nervous disorders are also due for re-appraisal. While this gland was called "glandula pituitaria" by Galen and by Vesalius (1543), as they thought it elaborated mucus from the brain's excretions, we now know that its functions are controlled by releasing factors which reach it from the hypothalamus, whence the thyrotrophin-releasing hormone, a tripeptide, has been extracted, identified, synthesized, and shown to be active in man (Schally *et al.*, 1969).

This lecture reviews some aspects of the diagnosis and treatment of anterior pituitary disease, which are relatable to our unit's experience. As many colleagues in our unit have helped in studying the patients and in producing the data, I should like to thank particularly Drs. G. F. Joplin, M. Hartog, A. D. Wright, F. Doyle, J. C. Marshall, C. W. Burke, and D. C. Anderson.

Diagnostic Tools

Growth.—Major steps in defining the syndrome as well as the pathology of pituitary deficiency were made by Simmonds (1914) and Sheeham and Summers (1949); loss of sex function with dwarfing and weakness, or hints of the major signs seen in hypophysectomized animals, were notable features. To assess dwarfing in children an important aid is the new accurate growth charts which supplement bone age assessments (Tanner *et al.*, 1965). These enable us to separate probable dwarfs (under the third percentile) from small dwarfs ($2\frac{1}{2}$ - $3\frac{1}{2}$ S.D. below the mean) and from very small dwarfs (under $3\frac{1}{2}$ S.D. below the mean). In very small, otherwise unexplained dwarfs, whose bone age is retarded below two-thirds of the chronological age, the suspicion of growth hormone deficiency is very high; and high in similar small dwarfs. This, or rapid growth similarly assessed, gives the clue for growth hormone testing; and can lead to the recognition of pituitary tumours at an early age. In the adult, clinical appraisal of growth must be based on assessments of the rapidly replacing tissues such as skin and hair, and also of the skeletal tissue which is especially responsive to growth hormone supply. Here the radiologists can help in the assessment of skin thickness and heel-pad thickness (Kho *et al.*, 1970), as well as in picking up the changed bone shape seen with acromegaly in various bones; by which means can generally be indexed overproduction but not consistently underproduction of growth hormone.

Hormone measurements in clinically suspect cases provide the major aids to diagnosis, and assays of growth hormone and gonadotrophin have proved the most helpful. Indices of the mean 24-hour output are needed, but can be difficult to formulate when the serum levels fluctuate rapidly, as for

example with growth hormone and ACTH, or when the assay's sensitivity cannot easily measure normal basal levels. Stimulation and suppression tests must therefore be used with some hormones to reveal respectively defective or excessive secretion; but then it is difficult to set the standards for partial deficiency or mild overproduction, since minor variations in reserve may not modify the daily output.

Assessment of Growth Hormone Secretion

Half-hourly sampling from a normal subject has shown great variability as well as higher levels at night (Glick and Goldsmith, 1968) and also that the basic drive which maintains the 24-hour output is little influenced by short diet changes. Growth hormone secretion also rises briskly in the nervous patient.

Various stimulation tests for growth hormone reserve have been appraised. Amino-acid loads are usually good stimuli when given either orally or preferably intravenously, but men do not always respond unless they have been pretreated with oestrogen (Rabinowitz *et al.*, 1968). Oral Bovril seems to be a nearly equivalent test (Jackson *et al.*, 1968). The best available test of growth hormone reserve seems to be an intravenous insulin tolerance, though care must be taken to check that it induces adequate hypoglycaemia. In normals it then always induces a response, unless nervousness has started the test from equivalently high stimulated levels.

The insulin tolerance test was first introduced for recognizing hypopituitarism by the delayed blood glucose return (Fraser and Smith, 1941), but this was often normal in our milder hypopituitary patients found to have defective growth hormone responses. We have found the test gives repeatable growth hormone responses in the same subject. An intravenous dose of insulin is needed which causes a fall in blood glucose of over 50% and to below 50 mg./100 ml. (Fraser and Wright, 1968a). Thus with anticipated insulin resistance, as in obesity, Cushing's disease, or diabetes, thrice the standard dose must be used—that is, 0.3 unit/kg. The test can be used in diabetes provided the basal blood sugar has been brought under 200 mg./100 ml. before this augmented intravenous dose of insulin is given, so that the glucose fall can reach under 50 mg./100 ml. Among a group of diabetics so tested all the results fulfilling these criteria gave normal responses to over 30 ng./ml., whereas only about half of the subjects rejected with lesser hypoglycaemia did so. There is a reasonably defined normal response (Fraser and Wright, 1968a), though this response is slightly lower in children (Kaplan *et al.*, 1968). This growth hormone response fails in Cushing's disease, in which, therefore, there is a secondary disorder of growth hormone secretion, since this recovers with treating the primary disease (Hartog *et al.*, 1964). Recently a useful supplement has improved this test procedure considerably—by both minimizing the test's discomfort so that paediatricians need not fear this aspect, and also enhancing the growth hormone response seen in the test so that it is more consistently a maximal response (Parra *et al.*, 1970). The supplement is a beta-adrenergic blocking drug such as propranolol, administered before the test,

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with which we find the initial levels are more consistently basal and the peak response about doubled. The basis for this supplement was provided by Blackard and Heidingsfelder (1968), who found from studies with adrenergic blockers that adrenergic receptors, probably in the hypothalamus, modify and possibly mediate the growth hormone response to hypoglycaemia—alpha-receptors enhancing and beta-receptors reducing the growth hormone response to hypoglycaemia.

An insulin tolerance test is usually interpretable, when it shows either a normal or no growth hormone response; but what of intermediate test responses? Studies such as ours of the effect of varying degrees of pituitary ablation on diabetic retinopathy give a clue to interpreting intermediate responses. The best retinal responses were attained when the growth hormone response was eliminated; while a nearly equivalent effect was seen when the insulin tolerance test response did not exceed 5 ng./ml. suggesting, with other similar evidence, that responses below this level imply partial growth hormone deficiency (Wright *et al.*, 1969a).

For suspect acromegaly a good suppression test is provided by samples taken from a quiescent patient after oral glucose—that is, from one to two-and-a-half hours of an oral glucose tolerance test (Fraser and Wright, 1968a). Among our acromegalic patients given this test it has emerged that in this disease the hyperglycaemia tends even to raise rather than lower their serum growth hormone (Wright *et al.*, 1969b)—an abnormal response also observed in the newborn and in uraemics. In our acromegalic subjects with small tumours the growth hormone tends to rise during an insulin tolerance test as in normal subjects, and, as noted, during the glucose tolerance test also it tends to rise. But those with larger tumours have a relatively fixed growth hormone level largely unstimulated or un-suppressed by changes in blood sugar level, presumably because the pituitary enlargement has impaired the portal blood flow from the hypothalamus. In most but not all acromegalics it is also possible to index the 24-hour growth hormone output from urinary measurements (Wright and Fraser, 1968, unpublished data on urinary human growth hormone), but no normals show measurable growth hormone levels in unconcentrated urine.

Assessment of Gonadotrophin Secretion

Assessment of gonadotrophin secretion is the next most important direct pituitary assay for clinical diagnosis, for this hormone often fails early, and gonad secretions are not so readily measurable as are those of the other pituitary-dependent glands, and, anyhow, the pituitary dependence of gonad failure always needs assessment.

The two gonadotrophins, follicle-stimulating hormone and luteinizing hormone, have structural similarities, so that our most specific antibodies and the dependent radioimmunoassays usually show some crossover—that is, our radioimmunoassay of luteinizing hormone measures only predominantly luteinizing hormone. Our results, however, show that for indexing pituitary gonadotrophin output this handicap is not serious. Further, in contrast to growth hormone, good indices of raised or lowered mean secretion are readily obtainable, for luteinizing hormone does not fluctuate rapidly through the day and is readily measurable in serum and urine.

The radioimmunoassay of serum luteinizing hormone provides a useful basal measurement which can distinguish hypopituitary from normal subjects, and also reveal the increased gonadotrophin output of gonad failure as in the menopause. Such basal measurements can be supplemented by tests of gonadotrophin responsiveness (Marshall, *et al.*, 1970), both (a) to assess testicular responsiveness by measuring serum testosterone-like substances in response to an injection of human chorionic gonadotrophin (Anderson, 1970); and (b) to test the hypothalamo-pituitary responsiveness by measuring the serum luteinizing hormone response to clomiphene, which can reveal a defect in the feedback control of gonadotrophin

output. A suppression test can similarly assess the suppressibility of serum luteinizing hormone.

Since many years (Forbes *et al.*, 1941) isolated gonadotrophin failure has been recognized as a fairly frequent basis for apparently “simple” hypogonadism, or one unassociated with any other deficiencies. The above tests of gonadotrophin responsiveness can identify any hypogonadism's dependence on pituitary-gonadotrophin failure and clearly distinguish isolated gonadotrophin failure from Klinefelter's syndrome, the clinical presentation of which it simulates.

Radioimmunoassays for ACTH and thyroid-stimulating hormone are less widely available but less needed. For their basal pituitary outputs the serum or urine levels of the dependent gland's hormone can provide alternative measurements. Further, good stimulation and suppression tests are available for the adrenal cortex—an insulin test, metyrapone, corticotrophin, and dexamethasone, so that the pituitary dependence of a patient's adrenal failure or overactivity can be appraised either from ACTH or cortisol measurements. Recently it has been recognized how closely psychiatric syndromes with severe mood disorders can simulate the normal pattern of Cushing's syndrome (Butler and Besser, 1968a, 1968b). While the severity of such a psychiatric syndrome usually makes its primacy obvious, suitable differential diagnostic procedures probably need sharpening for this problem. Changes in thyroid-stimulating hormone are probably similarly reflected in serum thyroxine levels, though more sluggishly. But while the triiodothyronine suppression test is well established, we also need a practical stimulation test for pituitary thyroid-stimulating hormone. The recently synthesized thyrotrophin-releasing hormone tripeptide may well provide the basis for this, for Hall *et al.* (1970) have confirmed Schally's findings that injection of thyrotrophin-releasing hormone into normal humans can induce a sharp rise in serum thyroid-stimulating hormone.

At present we sadly lack a test of pituitary prolactin production. Such a test could be helpful in assessing breast carcinoma subjects and subjects with Chiari-Frommel and allied syndromes of galactorrhoea with amenorrhoea, and also because prolactin and melanophore-stimulating hormone are the two pituitary hormones controlled from the hypothalamus predominantly by inhibitory factors.

Which Pituitary Hormones Fail Most Easily?

Many case studies have already clearly established that several of the pituitary hormones may suffer isolated failure—most clearly growth hormone (Rimoin *et al.*, 1968) and gonadotrophin (Forbes *et al.*, 1941; Biben and Gordon, 1965; Odell *et al.*, 1966), but also thyroid-stimulating hormone (Lohrenz *et al.*, 1964) and ACTH (Odell *et al.*, 1960). The basis of these failures may sometimes be genetic, but sometimes may arise in hypothalamic disease. But when the pitu-

FIG. 1.—Correlation between the lowering of the growth hormone response and of the adrenocortical secretion status at three months after ^{90}Y pituitary implant (after varying dosage for diabetic retinopathy). Note the more ready lowering of growth hormone than of ACTH secretion. (From Wright *et al.*, 1969a.) *Peak serum level during an insulin tolerance test.

pituitary suffers any generalized disease, which failure is most likely to be evident first? Histological studies of the human pituitary have so far shown a diffuse distribution of the different cells throughout the anterior pituitary (Bain and Ezrin, 1970), which fits with the general experience that, except in the early stages, anterior hypopituitarism is usually panpituitary. Our experience in studying the effects of varying ^{90}Y doses implanted for diabetic retinopathy suggests that lesser lesions cause failure in growth hormone and gonadotrophin first, while thyroid-stimulating hormone failure tends to be the last, with adrenal failure lying intermediate. The correlation observed between the degree of growth hormone failure and adrenal failure (Fig. 1) suggests that growth hormone failure is more readily induced (Wright *et al.*, 1969a); similar correlation studies suggest that thyroid-stimulating hormone tends to be the last to fail.

Presentation of Pituitary Disease

It needs no emphasis today that the minor anaemia-like syndrome of subtotal panhypopituitarism failure has few identifying clinical features and can be easily overlooked. As is familiar, apparently isolated amenorrhoea or very occasionally obesity can also lead to the discovery of a pituitary tumour. Amenorrhoea with galactorrhoea, or the Chiari-Frommel syndrome, immediately suggests pituitary stalk interruption. Interestingly, this syndrome is sometimes merely a manifestation of myxoedema (Ross and Nusynowitz, 1968), and so can be reversible with thyroxine treatment; presumably, as the stalk's myxoedema is corrected, so also is the pituitary portal blood flow. Sometimes but not always this Chiari-Frommel syndrome is the first manifestation of a pituitary tumour (Forbes *et al.*, 1954), possibly a prolactin-producing tumour (Fig. 2). Minor distortions or double floors on

FIG. 2.—x-ray film of sella turcica in patient who presented with Chiari-Frommel syndrome. Note double floor indicating asymmetric pituitary tumour, confirmed by tomography.

plain x-ray films as illustrated here may be easily overlooked in such patients, but tomography can clarify doubtful pictures.

It is also well to remember that, like the growth hormone failure in Cushing's disease, secondary changes in pituitary function may occur with nutritional disorders and with mood disorders as well as with other endocrine diseases. Growth hormone levels are high in severe malnutrition (Pimstone *et al.*, 1968). Careful clinicians are unlikely to misdiagnose anorexia nervosa as pituitary disease, but its amenorrhoea often lasts months or even years after the weight loss is corrected, at which stage is also seen a low gonadotrophin level which is unresponsive to clomiphene stimulation, but this gradually recovers with further improvements in the mental state.

Treatments of Hypopituitarism

Replacement of the adrenocortical thyroid deficiencies relieves the major disabilities, and this is well illustrated by the healthy survival to a mature age of those with isolated growth hormone failure (Rimoin *et al.*, 1968). While only marginal improvements occur with growth hormone treatment in such adult cases, treatment in childhood of the dwarfing certainly can be very helpful. Several centres have now reported the "catch-up" growth that can be induced in growth-hormone-deficient dwarfs, whether the failure is part of a pan-anterior deficiency or an isolated growth hormone failure (Tanner and Whitehouse, 1967; Henneman, 1968; Prader *et al.*, 1968; Soyka *et al.*, 1970).

Obviously not all apparently similar very short dwarfs are growth hormone deficient. The case with an isolated growth hormone deficiency closely resembles a constitutional dwarf. Gifford's constitutional or ateliotic dwarfs are like the pygmies in showing normal growth hormone reserve during an insulin tolerance test and yet no metabolic or growth response to injected growth hormone. Particularly when dwarfing is not severe or an insulin tolerance test suggests a partial growth hormone deficiency—that is, neither clearly a normal response nor no response on an insulin tolerance test—it is important to carry out such an acute growth hormone metabolic test before either discarding or embarking on growth hormone treatment (Melvin *et al.*, 1967). Such tests will also pick up some patients, reported by Laron *et al.* (1966), who presumably circulate an abnormal growth hormone in high normal levels, since with human growth hormone injections they have a pronounced acute metabolic response and can be made to grow.

Some growth disorders probably arise from intrauterine hypothalamic malfunction, and some of these might involve an early growth hormone deficiency. For example, the Russell-Silver dwarfs (Russell, 1954; Silver, 1964) superficially resemble growth hormone deficiency but usually show the associated sign of asymmetrical growth—a combination somewhat reminiscent of another hypothalamic syndrome—that is, polyostotic fibrous dysplasia with precocious puberty or Albright's syndrome. The Russell-Silver dwarf's intrauterine defective growth may not be recoverable, but there are hints of a partial response to subsequent growth hormone treatment (Tanner and Ham, 1969). The apparent converse of hypothalamic dwarfing is also recognized—that is, cerebral gigantism—which shows only moderate levels of basal growth hormone but little response thereof during an insulin tolerance test (Stephenson *et al.*, 1968; Abraham and Snodgrass, 1969). No other clues are yet available, suggesting that this excessive growth is mediated by growth hormone.

Some Hyperpituitary States

Under this heading I would like to consider three conditions which we have found treatable with ^{90}Y pituitary implants: (a) acromegaly, (b) Cushing's disease, and (c) functionless pituitary tumours, disabling from the pressure effects of the tumour. It is odd that pituitary hyperactivity seems only to have been discovered affecting either growth hormone or ACTH, while ectopic tumours have been reported producing many pituitary hormones.

Pituitary radiology offers important aids to the diagnosis of suspected pituitary disease, though normal radiology cannot exclude a pituitary tumour. For example, a young patient's slight dwarfing and amenorrhoea suggested pituitary stalk interruption, which was confirmed both by hormone tests and by finding calcification from old tuberculous meningitis in the region of the pituitary stalk. As already noted, a suspicious appearance on plain x-ray films can usually be clarified by pituitary tomography. Further, the extent of a tumorous lesion can be defined by an air encephalogram before treatment is determined (Fig. 3). Sometimes the diaphragma may

FIG. 3.—Tomograms from the air encephalogram (lateral and anteroposterior) of pituitary tumour subject, showing no expansion of the sella floor upwards but an asymmetrical downward expansion (from MacLachlan *et al.*, 1970).

be found sunken, perhaps from previous treatment, infarction, or cyst formation, and assessing the extent of the upward extension can be helpful in determining the appropriate treatment. Often an enlarged sella is recognizably pressed down from above, but this source of sella enlargement sometimes needs careful excluding; here finding papilloedema may help, for this is very rarely if ever a feature of pituitary tumours. For example, a patient was referred for pituitary tumour because of her 18-month history of headaches with increasing visual impairment, and apparently typical lateral skull x-ray picture (Fig. 4). But her papilloedema led to carotid angiography, which revealed hydrocephalus with enlargement of the third ventricle; this was confirmed by ventriculography. Appropriate neurosurgical treatment has arrested the progress of the visual impairment and the pituitary function remains normal. Other cerebral lesions have also presented in this way.

Acromegaly

Over 90% of these patients show on x-ray examination an enlarged sella turcica and other evidence indicating that the basic problem is usually a functional pituitary tumour; but

operative treatment need not now be withheld until this tumour produces local pressure symptoms. Hamberger *et al.* (1960) reinitiated a transnasal operation (Hirsch, 1959) for excising these tumours, now without mortality and with minimal morbidity; and Ray *et al.* (1968) reported similarly for a transfrontal route. But after these operations replacement therapy is almost always needed. At the other extreme external deep x-ray therapy can only curb the tumour's progress, and therewith give one to two years' relief of the severer symptoms such as headaches, paraesthesiae, and field defects; but only very rarely does it lower serum growth hormone (Roth *et al.*, 1968). Thus to avoid the need for replacement therapy, expected after operative treatment, a more effective procedure than deep x-ray therapy is required, which can at least severely curb the tumour while preserving an adequate rim of normal pituitary tissue. Such a compromise is more likely to succeed when treatment is given early, before the tumour enlargement has progressed too far. Several procedures have recently been tested for this purpose— ^{90}Y implanting, cauterization by cryostat, and proton-beam therapy—as well as other less tested procedures. These three procedures may eventually prove to be nearly equivalent, but most experience has been obtained with ^{90}Y , the results of which we shall consider.

Does relatively symptom-free acromegaly need treatment? To appraise the long-held view that acromegaly reduces life expectancy some of my associates made a follow-up of 194 patients admitted to certain London hospitals from 30 years ago in order to ascertain their mortality (Wright *et al.*, 1970a). This was compared with the mortality expected in a normal group of similar sex and age composition, followed over the same time, as derived from tables. This sampling of

FIG. 4.—A, lateral skull x-ray film showing expanded sella turcica; B, associated papilloedema found due to internal hydrocephalus from aqueductal stenosis.

acromegals suffered an enhanced mortality after the third decade and especially in the fourth and fifth decades. The main causes were found to be cardiovascular, cerebrovascular, and respiratory deaths; and on analysis this mortality was partly accounted for by an associated hypertension or by diabetes mellitus. Among this group 35% had diastolic blood pressures over 100 mm. Another factor in the vascular disease may be the frequently found hypercalcaemia (Nadarajah *et al.*, 1968). Thus, apparently symptomless acromegaly warrants treating before headaches or visual disturbances begin, and while a benign form of treatment can still be most effective. As is familiar, some of these acromegalic patients develop both a kyphus and an osteoarthritis-like joint disease (Kellgren *et al.*, 1952), probably dependent on the lax ligaments which they develop. Correcting the acromegaly should prevent the advancement of this process.

Medical treatment would, of course, be optimal, but is not yet available in adequate potency. It is interesting to note that the old oestrogen treatment does alleviate several of the indices of acromegaly, including the serum growth hormone level (Fig. 5), so it can at least help with patients unsuitable for more radical treatment.

Analysis of our first 80 acromegalic patients implanted with ⁹⁰Y during the past 10 years, usually with the objective of partial pituitary ablation, showed that a dose of 50,000 rads or our present dose-plan usually gives a satisfactory clinical remission (Wright *et al.*, 1970b). The raising of the dosage from 20,000 to 50,000 rads has not altered the proportion (circa 25%) needing replacement therapy. The effect observed on serum human growth hormone with this 50,000 rad dose-plan is shown in Fig. 6. We have segregated the 60% showing a satisfactory fall in serum human growth hormone—that is, to under 50% and under 50 ng./ml.—or curbing to at most mild acromegaly; replacement therapy is needed in only 25%. Looking at the unsatisfactory responses we see that most of these started from initial levels of serum human growth hormone over 100 ng./ml. With such more florid cases, which often also have large tumours, we now use either a larger radiation dose or a more radical treatment. Our

FIG. 5.—Some effects observed after oestrogen treatment in two cases (top, a woman aged 60; below, a woman aged 35) of acromegaly; note restoration towards upper normal range in the several values shown.

precision has also improved from the current routine usage of air encephalograms and tomography. The case of a patient illustrates this. Her extension into the sphenoidal sinus was overlooked initially and her acromegaly was little affected by pituitary implantation; but later eradication of this extension by a transnasal operation has ameliorated the acromegaly. The morbidity of the ⁹⁰Y procedure is now minimal, practically the only hazard being a treatable rhinorrhoea in 5–10% with considerably fewer suffering permanent diabetes insipidus. An important related recent advance is that more than half of such postoperative permanent diabetes insipidus patients can have this satisfactorily controlled by oral chlorpropamide (Wales, 1970; Webster and Bain, 1970).

FIG. 6.—Changes in serum growth hormone of 46 acromegalic subjects treated by 50,000 rad pituitary implants of ⁹⁰Y. Note satisfactory response—that is, fall to under 50 ng./ml. and 50% of pretreatment value—in 61% of all cases and in 78% of 26 with serum growth hormone initially under 100 ng./ml.

Cushing's Disease

Cushing's disease should also be amenable to treatment directed similarly at the pituitary. By Cushing's disease we mean here pituitary dependent Cushing's syndrome or cortisol overproduction, which can be diagnosed only after demonstrating this dependence biochemically—both by metyrapone stimulation and by some dexamethasone suppressibility. Ectopic-ACTH producing tumours will not show this dependence—unless the ectopic tumour is in the sella turcica, as we have recently found with a ganglioma. Finding on x-ray examination an expanded sella turcica can re-enforce this diagnosis, but others report this in only 10–20% of Cushing's disease (Salassa *et al.*, 1959), or at most in 40% in our recent analysis of 31 such patients (Fraser and Wright, 1968b), perhaps reflecting in part some selective referrals as well as the practised gaze of our radiologists. The biochemical pituitary dependence of Cushing's disease with an obvious pituitary tumour is not distinguishable from that seen in the commoner Cushing's disease without an obvious pituitary tumour; in which situation, however, a small pituitary tumour may often be present. The dramatic response of one patient (Fig. 7) to pituitary ablation suggested this—within a few months a rapid remission to cortisol-dependence along with preservation of normal responses in all other pituitary hormones. In other cases similar treatment has produced an equivalently satisfactory remission to apparently normal basal adrenal cortical function, along with, however, a continuing resistance to dexamethasone suppression (Hartog *et al.*, 1967), implying possibly a primary hypothalamic disease, as other studies by Landon and his colleagues (James *et al.*, 1968) have suggested.

The final proof of the pituitary dependence of Cushing's disease is, of course, its treatability via the pituitary. This has already been reported for about one-third of such patients treated by deep x-ray therapy (Dohan *et al.*, 1957), and for several treated by surgery or ^{90}Y implantation (Molinatti *et al.*, 1967). Recent analysis (Fraser and Wright, 1968b) of our first 31 Cushing's disease patients followed for one year or more after ^{90}Y implant, given in various doses as we discovered the optimal plan, has shown the practical importance of segregating those with obvious pituitary tumours, as they are much more prone to recur. While their initial response is often dramatic, local recurrence has proved frequent; after one year 7 out of 13 patients had only partial or poorer remission. With these patients now, total pituitary ablation is our initial objective, supplemented shortly afterwards by total adrenalectomy if the remission is not complete. In the commoner Cushing's disease without an obvious pituitary tumour a satisfactory clinical remission was observed in 50% and a

partial remission in all but one of the other 18 patients. We are now ascertaining the adequacy of a higher dose plan of ^{90}Y .

Apparently Functionless Pituitary Tumours

Following our initial experience with active pituitary tumours we have now treated several patients who had apparently functionless pituitary tumours presenting with headaches, hypopituitarism, or field defects. An analysis of the field defects and their response following implant is shown in Fig. 8. Understandably, long-standing field defects

FIG. 8.—Initial losses in visual fields seen in ten subjects with pituitary tumours before treatment by ^{90}Y implant; and the remission seen six months later.

have responded only partially, but improvement has been the rule and is usually considerable. Headaches can be relieved almost always, and often hypopituitarism, as exemplified by one patient originally suffering headaches and hypopituitarism but now still fully relieved four years later.

Conclusion

It is evident that pituitary disease can now be assessed reasonably precisely with a combination of hormone assays and radiology, and that several effective treatments are available.

We may now anticipate being able to distinguish between primary hypothalamic and primary pituitary disease, and also to have available both stimulators and suppressors of pituitary function.

REFERENCES

- Abraham, J. M., and Snodgrass, G. J. A. I. (1969). *Archives of Disease in Childhood*, 44, 203.
- Anderson, D. C. (1970). *Clinica Chimica Acta*, 29. In press.
- Bain, J., and Ezrin, C. (1970). *Journal of Clinical Endocrinology and Metabolism*, 30, 181.
- Biben, R. L., and Gordon, G. S. (1955). *Journal of Clinical Endocrinology and Metabolism*, 15, 931.
- Blackard, W. G., and Heidingsfelder, S. A. (1968). *Journal of Clinical Investigation*, 47, 1407.
- Butler, P. W. P., and Besser, G. M. (1968a). *Lancet*, 1, 1234.
- Butler, P. W. P., and Besser, G. M. (1968b). *Lancet*, 2, 51.
- Dohan, F. C., Raventos, A., Boucot, N., and Rose, E. (1957). *Journal of Clinical Endocrinology and Metabolism*, 17, 8.
- Forbes, A. P., Fraser, R., Miller, R. B., and Reifstein, E. C. (1941). *Transactions of the Association of American Physicians*, 56, 43.

FIG. 7.—Patient before and eight months after pituitary implant of ^{90}Y for Cushing's disease. (December 1968 and August 1969.)

- Forbes, A. P., Henneman, P. H., Griswold, G. C., and Albright, F. (1954). *Journal of Clinical Endocrinology and Metabolism*, **14**, 265.
- Fraser, R., and Smith, P. H. (1941). *Quarterly Journal of Medicine*, **10**, 297.
- Fraser, R., and Wright, A. D. (1968a). *Postgraduate Medical Journal*, **44**, 53.
- Fraser, T. R., and Wright, A. D. (1968b). In *Clinical Endocrinology II*, ed. E. B. Astwood and C. E. Cassidy, p. 78. New York, Grune and Stratton.
- Glick, S. M., and Goldsmith, S. (1968). In *Growth Hormone*, ed. A. Pecile and E. E. Müller, p. 84. Amsterdam, Excerpta Medica.
- Hall, R., Amos, J., Garry, R., and Buxton, R. L. (1970). *British Medical Journal*, **2**, 274.
- Hamberger, C.-A., Hammer, G., Norlén, G., and Sjögren, B. (1960). *Acta Otolaryngologica*, Suppl. No. 158, p. 168.
- Hartog, M., Gaafar, M. A., and Fraser, R. (1964). *Lancet*, **2**, 376.
- Hartog, M., Joplin, G. F., Fotherby, K., Mattingly, D., and Fraser, T. R. (1967). *Memoirs of the Society for Endocrinology*, **17**, 271.
- Henneman, P. H. (1968). *Journal of the American Medical Association*, **205**, 828.
- Hirsch, O. (1959). *Acta Ophthalmologica*, Suppl. No. 56.
- Jackson, D., Grant, D. B., and Clayton, B. E. (1968). *Lancet*, **2**, 373.
- James, V. H. T., Landon, J., Wynn, V., and Greenwood, F. C. (1968). *Journal of Endocrinology*, **40**, 15.
- Kaplan, S. L., Abrams, C. A. L., Bell, J. J., Conte, F. A., and Grumbach, M. M. (1968). *Pediatric Research*, **2**, 43.
- Kellgren, J. H., Ball, J., and Tutton, G. K. (1952). *Quarterly Journal of Medicine*, **21**, 405.
- Kho, K. M., Wright, A. D., and Doyle, F. H. (1970). *British Journal of Radiology*, **43**, 119.
- Laron, Z., Mannheimer, S., and Guttmann, S. (1966). *Israel Journal of Medical Science*, **2**, 152.
- Lohrenz, F. N., Fernandez, R., and Doe, R. P. (1964). *Annals of Internal Medicine*, **60**, 990.
- MacLachlan, M. S. F., Edwards, C., Lavender, J. P., and Fraser, T. R. (1970). *Clinical Radiology*. In press.
- Marie, P. (1889). *Brain*, **12**, 59.
- Marshall, J. C., Anderson, D. C., and Fraser, R. (1970). Publication pending.
- Melvin, K. E. W., et al. (1967). *British Medical Journal*, **3**, 196.
- Molinatti, G. M., Camanni, F., Massara, F., and Messina, M. (1967). *Journal of Clinical Endocrinology and Metabolism*, **27**, 861.
- Nadarajah, A., et al. (1968). *British Medical Journal*, **4**, 797.
- Odell, W. D., Green, G. M., and Williams, R. H. (1960). *Journal of Clinical Endocrinology and Metabolism*, **20**, 1017.
- Odell, W. D., Ross, G. T., and Rayford, P. L. (1966). *Metabolism*, **15**, 287.
- Parra, A., Schultz, R. B., Foley, T. P., and Blizzard, R. M. (1970). *Journal of Clinical Endocrinology and Metabolism*, **30**, 134.
- Pimstone, B. L., Barbezat, G., Hansen, J. D. L., and Murray, P. (1968). *American Journal of Clinical Nutrition*, **21**, 482.
- Prader, A., Zachmann, M., Poley, J. R., Illig, R., and Székely, J. (1968). In *Growth Hormone*, ed. A. Pecile and E. E. Müller, p. 388. Amsterdam, Excerpta Medica.
- Rabinowitz, D., Merimee, T. J., Nelson, J. K., Schultz, R. B., and Burgess, J. A. (1968). In *Growth Hormone*, ed. A. Pecile and E. E. Müller, p. 105. Amsterdam, Excerpta Medica.
- Ray, R. S., Horwith, M., and Mautalen, C. (1968). In *Clinical Endocrinology II*, ed. E. B. Astwood and C. E. Cassidy, p. 93. New York, Grune and Stratton.
- Rimoin, D. L., Merimee, T. J., Rabinowitz, D., Cavalli-Sforza, L. L., and McKusick, V. A. (1968). In *Growth Hormone*, ed. A. Pecile and E. E. Müller, p. 418. Amsterdam, Excerpta Medica.
- Ross, F., and Nusynowitz, M. L. (1968). *Journal of Clinical Endocrinology and Metabolism*, **28**, 591.
- Roth, J., Gorden, P., and Bates, R. W. (1968). In *Growth Hormone*, ed. A. Pecile and E. E. Müller, p. 124. Amsterdam, Excerpta Medica.
- Russell, A. (1954). *Proceedings of the Royal Society of Medicine*, **47**, 1040.
- Salassa, R. M., Kearns, T. P., Kernohan, J. W., Sprague, R. G., and MacCarty, C. S. (1959). *Journal of Clinical Endocrinology and Metabolism*, **19**, 1523.
- Schally, A. V., Redding, T. W., Bowes, C. Y., and Barrett, J. F. (1969). *Journal of Biological Chemistry*, **244**, 4077.
- Sheeham, H. L., and Summers, V. K. (1949). *Quarterly Journal of Medicine*, **18**, 319.
- Silver, H. K. (1964). *American Journal of Diseases in Childhood*, **107**, 495.
- Simmonds, M. (1914). *Deutsche medizinische Wochenschrift*, **40**, 322.
- Soyka, L. F., Bode, H. H., Crawford, J. D., and Flynn, F. J. (1970). *Journal of Clinical Endocrinology and Metabolism*, **30**, 1.
- Stephenson, J. N., Mellinger, R. C., and Manson, G. (1968). *Pediatrics*, **41**, 130.
- Tanner, J. M., and Ham, T. J. (1969). *Archives of Disease in Childhood*, **44**, 231.
- Tanner, J. M., and Whitehouse, R. H. (1967). *British Medical Journal*, **2**, 69.
- Tanner, J. M., Whitehouse, R. H., and Takaiski, M. (1965). *Archives of Disease in Childhood*, **41**, 454.
- Vesalius, A. (1543). *De humani corporis fabrica*. Basileae, J. Oporini.
- Wales, J. (1970). In preparation.
- Webster, B., and Bain, J. (1970). *Journal of Clinical Endocrinology and Metabolism*, **30**, 215.
- Wright, A. D., et al. (1969a). *British Medical Journal*, **2**, 346.
- Wright, A. D., McLachlan, M. S. F., Doyle, F. H., and Fraser, T. R. (1969b). *British Medical Journal*, **4**, 582.
- Wright, A. D., Hill, D. M., Lowy, C., and Fraser, T. R. (1970a). *Quarterly Journal of Medicine*, **39**, 1.
- Wright, A. D., et al. (1970b). *Proceedings of the Royal Society of Medicine*, **63**, 221.

Flucloxacillin, a New Isoxazolyl Penicillin, Compared with Oxacillin, Cloxacillin, and Dicloxacillin

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Summary: Flucloxacillin, a new isoxazole penicillin, is active against penicillinase-producing strains of *Staphylococcus aureus* and is well absorbed in man after oral and intramuscular administration. Compared with isoxazole penicillins in current clinical use—namely, oxacillin, cloxacillin, and dicloxacillin—flucloxacillin has proved as active against Gram-positive cocci, including penicillin-resistant staphylococci. The extent of binding of flucloxacillin to the protein of human serum was similar to that of oxacillin and cloxacillin and less than that of dicloxacillin. In man flucloxacillin given orally produced total and free serum levels higher than those obtained with oxacillin and cloxacillin; total serum levels similar to those of dicloxacillin, and free levels greater than those of dicloxacillin. Similarly, after intramuscular injection the free serum levels of flucloxacillin were higher than those of oxacillin, cloxacillin, and dicloxacillin.

Introduction

The isoxazolyl series of semisynthetic penicillins, first synthesized and evaluated in these laboratories (Doyle *et al.*, 1961;

Hanson *et al.*, 1965), combines resistance to penicillinase with acid stability and activity against Gram-positive bacteria. The isoxazole penicillins in current clinical use—namely, oxacillin, cloxacillin, and dicloxacillin—are absorbed when given by mouth or by injection and show significant activity against penicillin-resistant staphylococci and other Gram-positive cocci. The therapeutic efficacy of the isoxazole penicillins in the treatment of staphylococcal and streptococcal infections is now well established.

Oxacillin, cloxacillin, and dicloxacillin have closely related chemical structures (Fig. 1), and the antibacterial activities of these compounds are also similar, though oxacillin is somewhat less active than cloxacillin and dicloxacillin against penicillin-resistant staphylococci, and cloxacillin is rather less active than oxacillin and dicloxacillin against pneumococci (Knudsen *et al.*, 1962; Bennett *et al.*, 1965; Knott *et al.*, 1965). The main differences among the isoxazole penicillins lie in the serum concentrations obtained after administration of the compounds and in the extent to which they are bound to serum protein.

Oxacillin, the first member of the series, gives rise to serum concentrations which are substantially lower than those obtained with cloxacillin both by mouth and by injection (Knudsen *et al.*, 1962; Bunn and Milicich, 1964; Gravenkemper *et al.*, 1964), while dicloxacillin results in serum levels higher than those of cloxacillin when given by mouth (Bennett *et al.*, 1965; Knott *et al.*, 1965). Dicloxacillin,

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