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EDITORIAL : VAN DIE REDAKSIE

SOME RECENT ADVANCES IN CUSHING'S SYNDROME

All will agree that adrenocortical hyperfunction causes Cushing's syndrome, but its pathogenesis remains uncertain except in cases in which a hyperfunctioning benign or malignant neoplasm of the adrenal cortex is present. The causative role of these tumours is proved by the atrophy of the remaining adrenal cortical tissue and by the clinical cure of the patients after their removal.

Most patients with Cushing's syndrome have a diffuse or nodular hyperplasia of both adrenal cortices, without clinical evidence of pituitary tumour. It is probable, but incompletely established, that the levels of corticotrophin (ACTH) in the blood are abnormally high in this condition. Other patients show evidence of both pituitary tumour and adrenocortical hyperplasia. In many of these the clinical features which indicate a tumour of the pituitary are found only months or years after bilateral total or subtotal adrenalectomy has been performed.[1,2] This phenomenon has suggested that adrenalectomy may enhance the growth of pre-existing pituitary tumours in patients with Cushing's syndrome. Some of these patients develop extensive pigmentation of Addisonian type, which suggests that their tumours secrete excessive quantities of a melanocyte-stimulating hormone. Nelson and his co-workers[2] have found increased levels of plasma ACTH in 5 of 10 patients who had undergone adrenalectomy for Cushing's syndrome. This provides further support for the hypothesis that the pituitary may be responsible for the adrenocortical hyperplasia in Cushing's syndrome.

It is interesting that in most cases of Cushing's syndrome in which pituitary-tumour tissue has been microscopically examined, chromophobe cells have predominated. Extracranial metastases have occurred in a few patients, and in general the tumours have been more invasive than is usual in the ordinary case of chromophobe adenoma, which is unrelated to Cushing's syndrome.

In childhood, Cushing's syndrome is rare. The great majority of patients under 10 years of age have had adrenal carcinomas, and have presented with features of the adrenogenital syndrome (androgen excess) in addition to those of Cushing's syndrome (cortisol excess). Thus young girls grow rapidly, develop sex hair and facial hirsutes; the clitoris enlarges and the voice deepens, while their whole personality seems more 'grown-up' than is compatible with their chronological age. These phenomena occur together with obesity, facial rounding, skin atrophy, purple striae, acne and plethora. Biochemical investigations indicate overproduction of all four groups of adrenal steroids — androgens, oestrogens, cortisol and aldosterone.

A recent case of Cushing's syndrome in a boy, starting at the age of nine and not caused by tumour, has been described in Britain[3] — the fifth or sixth in the English-language literature. The patient stopped growing, developed obesity with 'moonface and buffalo hump' *(sic)*, hirsutes, acne, osteoporosis and hypertension. His urinary excretion of 17-hydroxycorticosteroids fell slightly from 60 to 50 mg. per 24 hours when triamcinilone was given. The 17-ketosteroid fall was more pronounced, from 53 to 26 mg. The 17-hydroxycorticoid level rose to 220 mg. after stimulation with intramuscular ACTH. These biochemical responses were considered to be indicative of bilateral hyperplasia of the adrenals rather than of tumour. At laparotomy hyperplasia was found to exist, and a bilateral adrenalectomy was performed. One year later he was quite well, while being maintained on cortisone, 12·5 mg. and a-fluoro-hydrocortisone, 0·1 mg., daily.

The association between intrathoracic neoplasia and adrenal cortical hyperplasia and hyperfunction has recently been recorded so frequently that there can be no doubt that the coexistence of these two disorders is more than fortuitous. Some patients with these conditions have presented with a typical picture of Cushing's syndrome, but more frequently the clinical state has been different.[4] Middle-aged males have predominated, the onset has been acute and the course fulminant, the usual features of Cushing's syndrome have been slight, and severe hypokalaemic alkalosis has been usual.

The alkalosis and potassium depletion naturally suggest that the production of aldosterone might be excessive, but low values of this steroid have been reported whenever it has been measured in the urine or the adrenal gland. On the other hand, the quantities of 17-ketosteroids and 17-hydroxycorticosteroids excreted in the urine, and the concentration of cortisol in the plasma, have been consistently raised, often to very high levels. From the small number of tests made in this syndrome, it would appear that dependence upon and responsiveness to corticotrophin may be absent or at least less prominent than in simple bilateral cortical hyperplasia.

The intrathoracic neoplasms associated with this syndrome have shown certain distinct features. The bronchial cancers have been of the small oat-cell variety, which is the least common of the four histological types. In other cases, in which bronchial adenoma or thymoma have been implicated, the cellular structure has been atypical, and reminiscent of oat-cell carcinoma. The adrenal glands in this syndrome have shown cortical hyperplasia, sometimes with a tendency to form adenomas. Metastatic deposits have been present in some instances, but not all. The glands have usually weighed more than those found in ordinary Cushing's syndrome, even allowing for any additional weight caused by metastatic deposits.

There can be little doubt that the adrenal cortex in this syndrome is overactive; it is unlikely that the neoplasm itself is secreting corticosteroid substances. It would appear probable that the neoplasm secretes a material which either acts as a corticotrophin or possibly as a stimulant to

pituitary corticotrophin production and release. Whatever the pathogenesis of this syndrome may be, its existence behoves the physician to be alert to the possibility of adrenal cortical overactivity (often clinically masked) in patients harbouring intrathoracic neoplasms; and to suspect such a neoplasm in any case of Cushing's syndrome with bilaterally hyperfunctioning adrenals which occurs in a mature male, which is abrupt in onset or rapidly becomes severe, or which is accompanied by hypokalaemic alkalosis or very high urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroids.

1. Salassa, R. M. *et al.* (1959): J. Clin. Endocr., **19,** 1523.
2. Nelson, D. H., Meakin, J. W. and Thorn, G. W. (1960): Ann. Intern. Med., **52,** 560.
3. Thursby-Pelham, D. C. and Crowe, G. G. (1961): Brit. Med. J., **2,** 1536.
4. Hills, A. G. and Woeber, K. A (1961): Ann. Intern. Med., **54,** 1295.

LIDMAATSKAPSGELDE EN DIE MEDIESE VERENIGING

Tydens sy jongste sitting wat op 5, 6, 7 en 8 September te Pretoria gehou is, het die Federale Raad van die Mediese Vereniging weer eens metodes bespreek om die lidmaatskap van die Vereniging te vergroot en om sy hegemonie in die algemeen te versterk. Die algemene gevoel van lede van die Raad skyn te wees dat die Mediese Vereniging van Suid-Afrika, wat die enigste, nasionale, professionele beroepsorganisasie van geneeshere in ons land is, 'n groot roeping en 'n taak het ten opsigte van leierskap in die professie op allerhande terreine — akademies sowel as prakties. Die gevoel is egter verder dat die Vereniging slegs daarin kan slaag om 'n bevredigende en waardige rol te speel in ons mediese, professionele beroepslewe as hy kan reken op die heelhartige ondersteuning van al die geneeshere in die land. Daarom is dit van die allergrootste belang om die Vereniging tot 'n liggaam uit te bou wat so sterk en heg as moontlik is.

Wanneer die kwessie van lidmaatskap van die Vereniging ter sprake kom, is daar altyd diegene wat in die eerste plek vra: wat kry ek daaruit? Die antwoord op hierdie vraag is betreklik eenvoudig: dit het naamlik dwarsoor die wêreld 'n gevestigde gebruik geword vir beroepslui om professionele organisasies te vorm waaraan hulle kan behoort en wat as middel kan dien om hulle materiële behoeftes te beskerm en ook om hulle kulturele en wetenskaplike ideale te verwesenlik.

In die meeste lande van die Westerse wêreld het geneeshere byvoorbeeld mediese verenigings gevorm wat op hulle beurt weer lede is van die Mediese Vereniging van die Wêreld. Die uitgesproke doelstelling van ons eie vereniging, die Mediese Vereniging van Suid-Afrika, is *om die mediese en verwante wetenskappe te bevorder en om die eer en die belange van die mediese professie te behartig.* In hierdie verband wil ons graag die aandag van alle geneeshere by vernuwing vestig op die uitstekende artikel: ‚The Medical Association of South Africa: its role in the past and its ideals for the future', wat in die uitgawe van die *Tydskrif* van 21 Mei 1960 gepubliseer is (**34,** 423). Hierdie artikel is geskryf deur dr. J. H. Struthers, afgetrede voorsitter van die Federale Raad, en dit handel oor die dienste wat die Vereniging lewer op die gebiede van die ekonomiese organisasie van die mediese praktyk, die publikasie van die *Tydskrif,* die rol van die Vereniging ten opsigte van die vooruitgang van mediese opvoeding in die wydste sin van die woord, internasionale affiliasie, en die Vereniging se hoop vir die toekoms.

Om alle en veral die jongere lede van die mediese professie aan te moedig om lede van die Mediese Vereniging te word en te bly, het die Federale Raad nou besluit om 'n wisselskaal van ledegelde in te stel wat van 1 Januarie 1963 af van krag sal wees. Die skaal is soos volg:

Tydperk na kwalifikasie en kategorie	*Ledegelde*
Eerste jaar na kwalifikasie (intern-jaar)	R5.00
Tweede „ „ „	R6.00
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Voltydse gesalarieerde lede wat minder as R4,600 verdien	R6.00

Hierdie skaal van ledegelde sluit nie die heffings van die aparte Takke in nie, maar dit is aansienlik genoeg om jonger algemene praktisyns en voltydse beamptes van allerlei aard, insluitende hospitaalpersoneel op die registrateursvlak, aan te moedig om lede van die Vereniging te word.

Bowe en behalwe hierdie geldelike toegewing wil ons dit egter ten sterkste aanbeveel dat elke Tak dwarsdeur die land 'n permanente, aktiewe werwingskomitee in die lewe roep wie se plig dit sal wees om gedurig op die uitkyk te wees na die moontlikheid om nuwe lede te werf. Die werwingskomitee in die universiteitstede moet elke nuwe graduandus persoonlik ontmoet en inlig oor die voordele van lidmaatskap. Verder moet die name van alle nuwe gegradueerdes, wat nog nie lede van die Vereniging is nie, deur die werwingskomitees van die universiteitstede na die werwingskomitees van die Takke waarin hulle hulle gaan vestig, gestuur word sodat verdere werwings- en opvolgwerk gedoen kan word. Ook moet die Vereniging deur middel van sy voltydse en ere-amptenare gedurig in aanraking bly met al die Takke.

Deur 'n doelgerigte en volgehoue poging om die lidmaatskap van die Vereniging te vergroot, kan die ideaal van 'n sterk, verenigde beroepsliggaam van geneeshere verwesenlik word. En hoe sterker dié liggaam is, met hoe 'n sterker stem sal hy namens elke indiwiduele geneesheer kan praat. In die moeilike tye wat voorlê, sal ons 'n groot behoefte hê aan so 'n verenigde front.