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EDITORIAL

ADRENOCORTICAL HYPERFUNCTION IN CHILDHOOD

Hyperactivity of the adrenal cortex with bilateral hyperplasia may occur during foetal life. In this condition an excess of androgenic hormone is secreted, which produces a masculinization of the developing female embryo. Mullerian duct derivatives persist, so that the uterus and vagina (and of course ovaries) remain, but the clitoris enlarges and only a single perineal opening develops, representing a common vaginal and urethral aditus. This is the usual form of female pseudo-hermaphroditism, the congenital adreno-genital syndrome. The basic lesion (described in a previous editorial[1]) is a failure in the pathway of formation of glucocorticoids in the adrenal cortex. Androgenic steroids accumulate and the cortex hypertrophies, probably under the influence of an increased production of pituitary corticotrophin. If the condition remains untreated, a premature, male type of puberty occurs, with beard growth, further phallic enlargement, deepened voice, and male muscular development and contours. The adult appearance resembles that of a short man with hypospadias and cryptorchidism. Distinguishing features are a female nuclear sex-chromatin pattern, high 17-ketosteroid output in the urine, and the possession of a uterus and ovaries. Suppressive therapy with cortisone has been remarkably successful.

Hyperplasia of the adrenal cortex with excessive androgen production may start after birth. In this case the intrauterine sexual development has been normal, so that there is no intersexuality. In females, however, masculinization occurs, with a sort of premature male puberty, as mentioned above. The affected patients first show a growth spurt, but eventually end up short because of premature fusion of the epiphyses. In these cases, then, we get a person of male general appearance, but of female genital development with a much enlarged clitoris. This variety of the adrenogenital syndrome may be caused also by a benign adenoma of the cortex; in this case operation is necessary, but cortisone (or analogue) is again a most satisfactory treatment for the hyperplasia.

Hyperplasia or adenoma of the cortex in little boys does not of course produce any heterosexual affliction, but causes

VAN DIE REDAKSIE

OORPRODUKSIE IN DIE BYNIERSKORS BY KINDERS

Oormatige werking van die bynierskors, met weersydige oormatige groei, kan reeds gedurende die baarmoederlike lewe van die vrug voorkom. By hierdie toestand word 'n oormaat van die androgeniese hormoon afgeskei, waardeur die ontwikkelende vroulike vrug vermanlik word. Reste van die oergeslagsgang bly voortbestaan, sodat die baarmoeder en skede (en natuurlik ook die eierstokke) gevorm word, maar die clitoris word vergroot en slegs één uitmonding ontwikkel in die perineum—'n gemeenskaplike skede- en uretra-uitgang. Hierdie afwyking is die gewone vorm van die vroulike skyn-dubbelslagtigheid—die aangebore bynier-geslagsindroom. Die grondoorsaak of letsel (wat reeds in hierdie rubriek beskryf is[1]) ontstaan wanneer die glukokortikoïede nie in die bynierskors gevorm word nie. Androgeniese steroïede hoop op en die skors verskrompel, waarskynlik onder die invloed van 'n vermeerderde produksie van pituitêre kortikotrofien. As die afwyking nie behandel word nie, ontstaan daar 'n vroegtydige, skynmanlike puberteit met baard-ontwikkeling, verdere vergroting van die penis, 'n diep stem, en manlike spiere en voorkoms. Die volwasse voorkoms is dié van 'n kort man met hipospadie en kriptorchidisme. Kenmerkend hiervan is die vroulike kernpatroon van die geslagschromatien; 'n groot uitskeiding van 17-ketosteroïede in die urine, en die aanwesigheid van baarmoeder en eierstokke. Kortisoon is reeds met besondere welslae as onderdrukkende behandeling gebruik.

Oorontwikkeling van die bynierskors met oormatige produksie van androgeen kan kort na die geboorte ontstaan. In hierdie geval was die baarmoederlike ontwikkeling van die vrug normaal, sodat daar geen dubbelslagtigheid is nie. By dogtertjies is daar egter, soos reeds beskrywe, 'n mate van vermanliking met 'n soort vroeë manlike puberteit. Die pasiënte toon eers 'n fase van vinnige groei, maar die volwassene is nog kort van postuur omdat die beenente vroegtydig sluit. In sulke gevalle sien ons dus 'n persoon met 'n algemeen manlike voorkoms, maar met 'n vroulike geslagstelsel en baie vergrote clitoris. Hierdie voorbeeld van die bynier-geslagsindroom kan ook deur 'n goedaardige gewas in die bynierskors veroorsaak word; by hierdie gevalle is snykundige ingreep nodig, maar kortisoon (of 'n ooreenkomstige middel) is ook hier 'n baie bevredigende behandeling vir die oormatige weefselgroei.

Oormatige weefselgroei of 'n gewas in die skors by seuntjies veroorsaak natuurlik nie 'n vervrouliking nie, maar

an isosexual precocious puberty. This pubertal development is in all ways like that at the normal age except that, since it is caused by adrenal androgen and not by pituitary gonadotrophin, the testes may remain small and fertility does not develop. There is no spermatogenesis. This distinguishes the condition from the precocious puberty of pineal tumour or the 'idiopathic' variety. Again, the affected people end up short because of early epiphyseal closure; this type of adrenogenital syndrome produces the 'pocket Hercules'.

Over-production of glucocorticoids, leading to Cushing's syndrome in childhood, is quite a different kettle of fish.[2] Until very recently there was apparently no report of Cushing's syndrome before the age of 10 which was not caused by an adrenal carcinoma. (One case of bilateral hyperplasia and one of adrenal adenoma have been described within the last few years.) Now, whereas an adenoma is biochemically active in the production of only a single hormone, so producing the pure picture of Cushing's syndrome (in adults) or the adreno-genital syndrome, a carcinoma really goes to town and produces greatly increased quantities of androgen, glucocorticoid and oestrogens (probably aldosterone also). Consequently a mixed clinical picture is produced, usually with one or other hormone predominating. The little girl may then become very fat, with a podgy, cushingoid, plethoric face, downy hairiness, muscular weakness, cessation of growth, and glycosuria. The purple striae characteristic of Cushing's syndrome in the adult are not so commonly seen, while the obesity is frequently distributed over the lower extremities and arms as well as the trunk. In addition, there may be features of virilism, with growth of the clitoris and increase of muscle mass instead of muscle atrophy, and with growth of darker hair of male type on the face and abdomen and sexual hair at axillae and pubis. Bone growth and bone age are static if the Cushing's syndrome prevails; on the contrary they are advanced if the adreno-genital side is foremost. The majority of cases are in girls (as in adults, most Cushing's syndrome occurs in females)—in little boys the tumour tends to produce a mixture of Cushing's syndrome and isosexual precocity. Very rarely the over-production of oestrogens prevails, and feminization develops (in boys) or isosexual precocity (in girls) with breast development and premature menstruation. No case has yet been reported in which the major hormone produced has mineralo-corticoid effects.

The prognosis of these children with Cushing's syndrome is poor, but not uniformly so—in several cases complete cure has followed operative removal. In others the progress of the disease and the secondary spread of the neoplasm are so rapid that some of the classical features of chronic Cushing's syndrome, such as osteoporosis, do not have time to occur.

1. Editorial (1955): S. Afr. Med. J., **29**, 512.
2. Bishop, P. M. F. (1954): *Recent Advances in Endocrinology*, 7th ed. London: Churchill.

dit veroorsaak wel voorbarige manlike puberteit. Hierdie (vroegtydige) puberteitsontwikkeling is presies soos dié wat op die normale ouderdom voorkom, behalwe dat die testes miskien klein bly en die seun onvrugbaar is omdat die puberteit hier deur die skors-androgeen veroorsaak word en nie deur die pituitêre gonadrotrofien nie. Saadvorming ontbreek. Dit is hierdie kenmerk wat hierdie bepaalde afwyking onderskei van die vroegtydige puberteit wat veroorsaak word deur 'n gewas in die corpus pineale, en van die ‚idiopatiese' soort. Ook by hierdie gevalle bly die seuns kort van postuur omdat die beenente vroeg sluit; hierdie soort bynier-geslagsindroom veroorsaak die soort postuur wat as ‚pocket Hercules' beskryf word.

Oorproduksie van die glukokortikoïede, met die Cushing-sindroom by kinders as gevolg, is heeltemal iets anders.[2] Tot onlangs was daar skynbaar geen verslae van die Cushing-sindroom by kinders onder tien jaar nie wat *nie* deur 'n bynierkarsinoom veroorsaak is nie. (Één geval van weersydige oormatige weefselgroei, en één geval van 'n bynier-gewas, is in die afgelope paar jaar beskryf.) Maar 'n kliergewas is biochemies aktief by die produksie van slegs 'n enkele hormoon en lei dus tot 'n ongekompliseerde Cushing-sindroom (by volwassenes) of tot die bynier-geslagsindroom, terwyl 'n karsinoom aan die ander kant hoogs vermeerderde hoeveelhede androgeen, glukokortikoïede, estrogene (en waarskynlik ook aldosteroon) voortbring. Die gevolg is 'n veelsydige kliniese siektebeeld waarby een van hierdie hormone gewoonlik die ander oorskadu. Die dogterjie kan dan baie vet word, met 'n poffige Cushing-agtige volbloedige gesig, donsige harigheid, 'n swak spierstelsel, beperkte groei, en glikosurie. Die pers strepe wat by volwassenes so kenmerkend van die Cushing-sindroom is, word minder dikwels by die kinders gesien, en die vetsug strek dikwels oor die arms en bene sowel as die lyf self. Daar kan ook trekke van mansagtigheid wees, met oorontwikkeling van die clitoris en sterker spierontwikkeling in plaas van spieruittering, en die groei van donker mansagtige hare op die gesig, buik, en skaamhare by oksel en pubis. Indien die Cushing-sindroom die beeld oorheers, bly die beengroei en -ouderdom beperk; hulle loop egter vooruit as die bynier-geslagsindroom die bo-toon voer. Die meeste gevalle kom by meisies voor (by volwassenes word die Cushing-sindroom ook oorheersend by vrouens aangetref); by seuntjies is die gewas geneig om 'n mengsel van die Cushing-beeld en 'n eie-geslagtelike vroegrypheid te veroorsaak. Dit is baie selde dat oorproduksie van die estrogene die siektebeeld oorheers, en dan kom daar vervrouliking by seuntjies voor; die meisies bereik baie vroeg 'n vroulike puberteit met ontwikkeling van die borste en maandstonde. Dusver is daar nog geen verslag van 'n geval waar die oorheersende hormoon mineraal-kortikoïede gevolge gehad het nie.

Die prognose vir hierdie kinders met die Cushing-siektebeeld is maar swak, maar daar is uitsonderings—by 'n hele paar gevalle het die pasiënte volkome herstel na snykundige verwydering. By ander vererger die siekte só gou, en versprei die gewas sekondêr só vinnig, dat sommige van die tipiese aspekte van die Cushing-sindroom, soos beenverweking, glad nie kans het om te ontwikkel nie.

1. Van die Redaksie (1955): S. Afr. T. Geneesk., **29**, 512.
2. Bishop, P. M. F. (1954): *Recent Advances in Endocrinology*, 7de uitg. Londen: Churchill.

THE TUBERCULIN REACTION

Many features of the mechanism of delayed hypersensitivity reactions, as exemplified by the tuberculin test, require investigation. It has been demonstrated in recent years that tuberculin is toxic to cells of hypersensitive animals (when applied to them in tissue culture), and that tuberculin hypersensitivity can be transferred by inocula of cells, especially the lymphoid cells, of the reticulo-endothelial system.

The influence of various specific and non-specific factors on the tuberculin reaction has recently been reviewed by Pepys,[1] who has made an attempt to demonstrate a pattern of the events leading to combination of antigen and antibody, and the development of the inflammatory response. He has shown that the character and intensity of the tuberculin reaction can be influenced experimentally by various modifications of technique. By the use of agents which modify the local cutaneous circulation and the permeability of capillaries and venules in the dermis the persistence of the tuberculin at the injection site in the skin can be considerably influenced. In order that a reaction should appear the antigen tuberculin must persist locally in adequate concentration and for a sufficient time. The local persistence of tuberculin is influenced by lymphatic absorption. By injecting histamine or adrenaline locally it was demonstrated that the reaction is modified. The effects were observed readily by using fluorescein as an indicator. Investigation also demonstrated that 'fixation' of tuberculin commences within a few minutes after injection. The rate and degree of 'fixation' has an important bearing on the mechanism of the test, and further work is needed to assess the nature and firmness of the 'fixation'. The relationship of immediate and delayed types of hypersensitivity may reveal the nature of the early 'fixation' of tuberculin.

Antibody as well as antigen is subject to modifications of a non-specific and specific nature. The specific reacting antibody has been studied, and much assistance has been gained from the demonstration of reticulo-endothelial tissue (the macrophages and especially the lymphoid cells) as a source of antibody. It has been shown that decreased or inhibited tuberculin reactions can be produced by reducing lymphoid tissue and cells, as by X-irradiation or specifically by the intravenous injection of tuberculoprotein. Studies with mononuclear cells have shown that their numbers and availability influence the extent of the reaction to tuberculin, and it would appear that the delayed nature of the tuberculin reaction may be due to the time required for a sufficient number of antibody-carrying cells to appear at the test site, where after reaction with the tuberculin an inflammatory response is excited. There appears to be an intimate relationship between the reacting antibody and the intact lymphoid cells. However, it still remains to be demonstrated whether preformed antibody can produce the tuberculin reaction without being taken up by specific lymphoid cells.

1. Pepys, J. (1955): Amer. Rev. Tuberc., **71**, 49.