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EDITORIAL

HORMOONBEHEER VAN BORSKANKER

HORMONAL CONTROL OF MAMMARY CANCER

Die begrip van 'n hormoon-afhanklike gewas is nie nuut nie. Meer as 60 jaar gelede is die eierstokke van 2 pasiënte met gevorderde kanker van die bors verwyder met heilsame gevolge,¹ en vir baie jaar daarna is terapeutiese kastrasie sporadies uitgevoer. Lacassagne se eksperimentele bewys dat neoplastiese veranderinge in die borsweefsels van muise, wat op groot hoeveelhede estrogeen gevoer is, teweeggebring kan word, is gedurende die afgelope jare gesteun deur die ontwikkeling van borskanker by manlike pasiënte wat met estrogene vir kanker van die prostaat behandel is.² Indien die kanker deur die estrogeen bevorder is, is dit 'n logiese afleiding dat die kanker sal afneem, of ten minste gestuit sal word, as hormoonproduksie ingekort word. Dit kan nie deur ooferektomie alleen gedoen word nie, nie eers deur ooferektomie gevolg deur adrenalectomie nie, want dit is gevind dat estrogeenuitskeiding—alhoewel dit onbestendig en spasmodies is—uiteindelik amper altyd weer hervat.³ Dit lyk of hipofisektomie self nie eers estrogeen uit die urien verwyder nie.⁴ 'n Rede hiervoor mag wel wees dat die chirurgiese neutralisasie van die besondere kliere onvolledig is, maar dit skyn verkeerd te wees om dit te aanvaar, en die moontlikheid dat ander bronne van estrogeen mag bestaan, moet ondersoek word. Miskien produseer die gewas self hormone, alhoewel dit bekend is dat terugwyking in die aanwesigheid van aanhoudende estrogeenproduksie kan geskied.

Wat ookal die teoretiese en eksperimentele beskouings mag wees, is die hormoonbeheer van borskanker 'n agtenswaardige en algemeen-aangenome behandelingsmetode. By Guy's Hospitaal, Londen, het ooferektomie met algehele adrenalectomie teen die einde van 1953 die standaard-behandeling geword vir pasiënte met onopereerbare kanker wat nie geskik was vir radioterapie en chirurgie nie, en wat nie op hormone gereageer het nie. Tot op daardie tydstip is 18 gevalle op hierdie wyse behandel met wisselende sukses. Dit is gevind dat gekombineerde adrenalectomie beter resultate gelewer het as net ooferektomie. Intussen het hipofisektomie op die voorgrond getree as die alternatiewe operasie. Luft en sy Sweedse span het 41 gevalle van borskanker, op wie hierdie operasie uitgevoer is, aangemeld. Twee-en-twintig van hulle (54%) het objektiewe afname, wat ongeveer 18 maande geduur het, getoon—slegs een vir langer as 2 jaar.⁵ (Luft bepaal 'objektiewe afname' as krimping van sigbare, voelbare of radiologiese metastases, of toenemende beëindigtheid sonder toename van die ou metastases, of voorkoms van nuwes.) Terwyl ander navorsers naasteby 'n ooreenstemmende graad van terugwyking aangemeld het (Pearson *et al.* 51% van 41 gevalle;⁶ Kennedy 64% van 28 gevalle⁷), het hulle nie dieselfde mate van sukses gehad as die Swede met die duur van die afnameperiode nie.

The concept of a hormone-dependent neoplasm is not new. More than 60 years ago the ovaries of 2 patients with advanced cancer of the breast were removed with beneficial results,¹ and for many years thereafter therapeutic castration was practised in a sporadic manner. Lacassagne's experimental evidence of producing neoplastic changes in the mammary tissue of mice fed on large amounts of oestrogen has been supported in recent years by the development of breast carcinoma in male patients on oestrogens for carcinoma of the prostate.² If the cancer is promoted by the oestrogen, a logical deduction is that the cancer will regress, or at least be halted, if hormone production is curtailed. This cannot be done by oophorectomy alone, nor even by oophorectomy followed by adrenalectomy, for it has been found that oestrogen excretion—though variable and spasmodic—is nearly always eventually re-established.³ Even hypophysectomy itself does not appear to eliminate oestrogen from the urine.⁴ A reason for this may well be that the surgical neutralization of the particular glands is incomplete, but it seems wrong to assume this, and the likelihood that other sources of oestrogen may exist must be examined. Perhaps the tumour itself produces hormones, although it is known that regression can occur in the presence of continuing oestrogen production.

Whatever the theoretical and experimental considerations, the hormonal control of mammary carcinoma is a reputable and widely-accepted line of treatment. At Guy's Hospital, London, oophorectomy with total adrenalectomy had become by the end of 1953 the standard practice in patients with inoperable cancer who were unsuitable for radiotherapy and surgery, and who had not responded to hormones. By that date 18 cases had been treated in this manner with variable success. It was found that combined adrenalectomy gave better results than oophorectomy alone. Meanwhile hypophysectomy had come to the fore as the alternative operation. Luft and his Swedish team reported 41 cases of breast cancer upon which it had been carried out, 22 of which (54%) showed objective remissions which lasted about 18 months—only one longer than 2 years.⁵ (By 'objective remission' Luft denotes shrinkage of visible, palpable or radiological metastases, or increased bone density without progression of the old metastases, or appearance of new ones.) Whilst other workers reported a roughly

By nie een van die reekse het die gemiddelde terugwyking langer as 7½ maande geduur nie. Nietemin reken die span van Guy's Hospitaal dat hulle gehipofisektomeerde pasiënte oor die algemeen 4 maande langer as die geadrenalektomiseerde pasiënte gelewe het. Inderdaad is Atkins en sy kollegas, waar hulle die resultate van die twee metodes sorgvuldig vergelyk, skynbaar ten gunste van hipofisektomie, alhoewel hulle beklemtoon dat die operasie statisties nie die oorhand oor adrenalectomie het nie.

Watter geval behoort aan operasie onderwerp te word? En aan ooferektomie met adrenalectomie, of aan hipofisektomie? Soos die *Lancet* skryf, is 'daar nog geen bevredigende wyse om te voorspel watter pasiënte met borskanker op adrenalectomie of op hipofisektomie sal reageer nie'.⁸ Luft *et al.* doen aan die hand dat ouer pasiënte, veral vrouens by wie die maandstonde opgehou het, waarskynlik minder bevredigend sal reageer. Eweneens word dit verklaar dat metastases in die lewer of brein met 'n betreklik langdurende bestaan, prognosties van slegte betekenis is. Die mening is dat terapeutiese kastrasie 'n goeie aanduiding van die moontlike uitwerking van hipofisektomie gee; as die pasiënt op ooferektomie reageer, is dit moontlik dat sy ook op hipofisektomie sal reageer. Maar hierdie is slegs kliniese aanwysers en spesifieke aanduidings vir operasie was baie moeilik om vas te stel. Tot onlangs kon die patoloog baie min nuttige inligting verskaf. Daar is geen wederkerige betrekking tussen tellings van mitotiese selle en reaksie op behandeling nie. Uitskeiding van estrogen en gonadotrofin in die urien word nie beïnvloed nie. Kalsiumvlakke in die urien is nuttig slegs as osteologiese metastases aanwesig is—'n daling van die vlak na 'n inspuiting van estrogen en 'n styging na kortisoon, doen aan die hand dat die gewas hormoon-afhanklik is en dat adrenalectomie van nut sal wees. Vroeër vanjaar het die kliniese patoloog by Guy's Hospitaal die aandag gevestig op 'n betekenisvolle verskynsel wat wel mag bewys dat dit 'n oplossing mag bied vir watter gevalle vir operasie gekies moet word. Merivale *et al.* het die breuke van algehele neutrale 17-ketosteroïede in die urien van 15 gevalle van borskanker, voor en na operasie (of hipofisektomie of adrenalectomie met ooferektomie) bestudeer. By hierdie gevalle is die verhouding van 11-deoksi-17-ketosteroïede tot 11-suurstofhoudende (of -gehidroksileerde) -17-ketosteroïede geskat. By die 11 gevalle wat klinies deur die operasie gebaat is, is dit gevind dat hierdie verhouding groter as 1 is, en dat die uitscheidingspatroon met dié wat by gesonde persone gevind word, ooreengekom het. By die 4 gevalle waar daar geen afname was nie, was die verhouding minder as een. Terwyl die vertolking wat hierdie navorsers aan hulle bevindinge heg, baie behoedsaam is, is dit moontlik dat hierdie proefneming mag toon dat dit op 'n praktiese wyse van nut is, des te meer daar hormoonbeheer vir die eindstadium van borskanker 'n gevestigde entiteit is.

corresponding regression rate (Pearson *et al.* 51% of 41 cases;⁶ Kennedy 64% of 28 cases⁷) they do not share the 'Swedes' success over the duration of the period of regression. In neither series was the average regression of longer duration than 7½ months. Even so, the Guy's Hospital team consider that their hypophysectomized patients survived on the average 4 months longer than the adrenalectomized ones. In fact, Atkins and his colleagues in their careful comparison of the results of the two procedures seem to favour hypophysectomy, although they emphasize that the operation has no statistical superiority over adrenalectomy.

Which case should be submitted to operation? And to oophorectomy with adrenalectomy, or to hypophysectomy? As the *Lancet* writes, 'There is still no satisfactory means of predicting which patients with breast cancer will respond to adrenalectomy or to hypophysectomy.'⁸ Luft *et al.* suggest that older patients, particularly post-menopausal women, are less likely to respond satisfactorily. Similarly, metastases in the liver or brain with a relatively long-standing growth are said to be of bad prognostic significance. Therapeutic castration is believed to give a good indication of the likely effect of hypophysectomy; if the patient responds to oophorectomy, she is likely to do so to hypophysectomy. But these are only clinical pointers, and specific indications for operation have been hard to determine. Until recently the pathologist could give little useful information. There is no correlation between counts of mitotic cells and response to treatment. Excretion of oestrogen and gonadotrophin in the urine is unaffected. Calcium urinary levels are useful only if osteolytic metastases are present—a fall in the level with an injection of oestrogen and a rise with cortisone suggests that the tumour is hormone-dependent, and that adrenalectomy would be of benefit. Earlier this year the clinical pathologist at Guy's Hospital drew attention to a significant clinical phenomenon that may well prove the key to the selection of cases for operation. Merivale *et al.* have studied the fractions of total neutral 17-ketosteroids in the urine of 15 cases with breast cancer, before and after operation (either hypophysectomy or adrenalectomy with oophorectomy). In these cases the ratio of 11-deoxy-17-ketosteroids to 11-oxygenated (or -hydroxylated) -17-ketosteroids was estimated. In the 11 cases which had benefited clinically by the operation, this ratio was found to be greater than 1, and the excretion pattern resembled that found in healthy subjects. In the 4 cases where no remission occurred, the ratio was less than one. Whilst the interpretation that these workers place upon their findings is very cautious, it is possible that this test may prove to be useful in a practical way. This is the more so since hormonal control of terminal mammary cancer is an established entity.

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A NEW DERMATOME

The problem of burns looms relatively larger as the hospital stay of other surgical conditions becomes reduced. The average time spent in hospital by cases of herniotomy, appendicectomy and cholecystectomy is usually less than one week, and even an ulcer-gastrectomy need rarely keep a patient in bed for more than the same time, but the burn—more often than not in a child—occupies a bed for weeks and months. Anything, therefore, that can be done to reduce this time will be amply rewarded not only by prevention of suffering, but also in reduction of hospital charges. Late sequelae such as contractures will also be reduced because the sooner healing is achieved, the less fibrosis will develop; once the wound is covered with skin, fibrosis is halted and rehabilitation can commence.

The surface of the average burn or scald is composed of areas of varying severity whose exact position it is not possible to predict in the first few days. Scattered over most burnt areas are islets of surviving epithelium and this damaged epithelium offers very little resistance to further injury and is easily completely destroyed by infection which develops on the burnt areas and effectively kills these islets. In the recent past the main aim of therapy, once the initial state of shock and the later stage of fluid and protein loss are safely passed, has been to prevent infection and so to preserve these islets.

Since epithelium grows centrifugally, even a light peppering of skin soon coalesces, and very large areas can quickly be covered. This is the explanation of the rapid healing of

large areas of burnt skin that are occasionally reported in advertisements of proprietary ointments; the depth of the burn has been superficial, the many islets have coalesced and healing has taken place.

But with all the care to prevent infection a large number of cases are referred to hospital and occupy beds. It has long been recognized that the best dressing for these areas is autogenous skin applied as soon as the infection is under control. Many practitioners, in relatively isolated areas, are well aware of this, but have not been able to acquire the skill and experience necessary to cut these thin split-skin grafts. To overcome this difficulty, mechanical dermatomes of greater or lesser complexity have been invented and described from time to time. Davies and Davies, on this page of the *Journal*, describe a new dermatome which has several advantages. It is inexpensive, simply constructed, portable and safe and requires practically no skill or experience to ensure a good cut. With very little skill in cutting Thiersch grafts it will allow a practitioner, operating in any small hospital, when he feels that a burnt area is ready to be grafted, to cover the granulations with strips of skin and to feel relatively sure that within 14 days healing will be complete. The instrument works on the principle of the barber's hair-clipper. A standard safety-razor blade, which is easily replaced, moves a few millimeters from side to side to achieve the cut. The use of this instrument should have a noticeable effect in shortening the stay in hospital and reducing the morbidity in these difficult cases.