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EDITORIAL

DIABETES COMPLICATING CORTICOID THERAPY

When corticotropin was first available Conn[1] found that all of 3 healthy subjects became temporarily diabetic after receiving doses of 75-100 units for 10-14 days. As a result of this finding corticotropin and cortisone were considered to be potent diabetogenic substances. Subsequent experience has shown that they are not. It is only rarely that non-diabetic patients become diabetic when treated with corticotropin or cortisone in the usual dosage range.[2–4] This 'steroid diabetes' is apparently only temporary and disappears when corticotropin or cortisone is withdrawn. Similarly, in experimental animals, corticotropin is not a potent diabetogen.

Rats can be made diabetic only if forcibly fed in addition[5] and only for as long as the hormone administration is continued. The carbohydrate tolerance of dogs is not affected by large doses of cortisone, even if the animals are first partially depancreatized.[6] Guinea-pigs are probably the most sensitive animals.[7] Sprague[8] indicates the variability of the response to corticoids in man by citing 3 cases. In the 1st, no impairment of glucose tolerance was found on repeated examination after more than 100 mg. of cortisone had been given for over 200 days. In the 2nd, the 2-hour level was high in a tolerance test performed after 7 days, but was normal 18 days after cortisone had been stopped. In the 3rd, glycosuria and a high fasting blood-sugar level appeared after 6 days on corticotropin; yet these abnormalities disappeared even while the hormone therapy was being continued.

W. P. U. Jackson reports that among patients whose cases were studied at the Massachusetts General Hospital only very few became diabetic on corticoid therapy, and in most of these the disorder was minor or temporary only. Three were initially known to be prediabetic or very mildly diabetic. One of these developed frank diabetes after 10 days of corticotropin; one developed the same under treatment with cortisone, but later

VAN DIE REDAKSIE

SUIKERSIEKTE-KOMPLIKASIES BY BEHANDELING MET KORTIKOÏEDE

Toe kortikotropien vir die eerste maal beskikbaar gestel is, het Conn[1] bevind dat 3 gesonde persone, na 'n dosis van 75-100 eenhede toegedien oor 10-14 dae, almal tydelik suikersiekte ontwikkel het. Op grond hiervan is dit toe gemeen dat kortikotropien en kortisoon kragtige diabetogeniese stowwe is. Latere ondervinding het egter bewys dat dit nie die geval is nie. Dit gebeur selde dat nie-diabetiese pasiënte suikersiekte ontwikkel as gevolg van behandeling met *gebruiklike* dosisse kortikotropien of kortisoon.[2–4] Hierdie ‚steroïede suikersiekte' blyk slegs tydelik te wees en dit verdwyn wanneer kortikotropien en kortisoon onthou word. Ook in die geval van proefdiere veroorsaak kortikotropien nie suikersiekte nie.

By rotte kan suikersiekte veroorsaak word slegs gepaard met gedwonge voeding[5] en vir net so lank as die hormoon toegedien word. Kortisoon in groot dosisse beïnvloed nie 'n hond se koolhidraatdulding nie, selfs al word die milt eers gedeeltelik verwyder.[6] Marmotjies is miskien die mees sensitiewe diere.[7] Sprague[8] se aanhaling van drie gevalle toon die verskillende reaksies van die mens op kortikoïede aan. Aan die eerste is meer as 100 mg. kortisoon oor 'n tydperk van meer as 200 dae toegedien, maar herhaalde ondersoek na die behandeling het geen belemmering in die glukosedulding getoon nie. By die tweede het 'n duldingtoets na 7 dae 'n aansienlike 2-uurhoogte getoon, maar 18 dae nadat kortisoon onttrek was, was dit normaal. Glikosurie en 'n aansienlike vastende bloedsuikerhoogte het by die derde na 6 dae onder kortikotropien verskyn. Hierdie abnormaliteite het egter verdwyn selfs terwyl die kortisoonterapie nog voortgeduur het.

W. P. U. Jackson rapporteer dat slegs 'n klein persentasie van die pasiënte wie se gevalle by die *Massachusetts General Hospital* bestudeer is, suikersiekte as gevolg van kortikoïedterapie ontwikkel het. By die meeste van hierdie gevalle was die aandoening slegs van 'n ligte of verbygaande aard. Dit was van die begin af bekend dat 3 van hierdie gevalle òf vatbaar was vir suikersiekte òf alreeds die siekte in 'n baie ligte graad gehad het. Na 10 dae van behandeling met kortikotropien het die eerste definitiewe suikersiekte ontwikkel; dit het ook met die tweede wat onder kortisoonbehandeling was, gebeur. Die glikosurie en oormatige

even while therapy was continued the glycosuria and hyperglycaemia disappeared; while the 3rd had no glycosuria after 134 days of high-dosage ACTH therapy. As many as 7 out of 12 patients with skin disorders developed impaired sugar-tolerance; other factors concerned may have been the very large doses of corticotropin used and the positive family-history of diabetes in 4 of the 7 cases. Two patients with Addison's disease became actually diabetic when cortisone was used. It has been claimed that patients with Addison's disease are unduly sensitive to the metabolic effects of cortisone.[17, 18] However, cortisone-induced diabetes must be a very rare complication of this disease. Such a situation has not arisen at the Peter Bent Brigham Hospital[19] despite the wide experience at that centre. Nevertheless one should watch for the development of diabetes if doses of around 50 mg. a day are used in cases of Addison's disease. Another important danger lies in the use of cortisone or ACTH in established diabetics; in these cases retinopathy may appear for the first time or become intensified. One such patient was seen in Jackson's series. There are insufficient data to be sure whether there is any extra danger in treating a pregnant woman, who would already have a high glucocorticoid production.[20, 21] From experimental observations, wariness would seem indicated, especially if there is any suggestion of prediabetes in the previous history.

The time during which ACTH or cortisone continued to be administered before diabetes ensued varied widely in this series, from 4 days in a case of Addison's disease to 2 years in one of pemphigus. In 3 other cases the period was 11 months, 8 months and 2 months. Thus one can never be sure that hyperglycaemic complications may not develop at any time during corticoid therapy. A similar phenomenon is the diabetogenic effect of pregnancy, which may be manifested only after repeated pregnancies.

TYPE OF DIABETES PRODUCED BY CORTICOID HORMONES

It is generally agreed that corticoid-induced diabetes differs from ordinary diabetes in 3 principal features:[1,4,9] (1) in being reversible, (2) in being insulin-resistant, and (3) in the rarity or mildness of ketosis. The observations reported by Jackson are in accord with (1). Furthermore, impairment of carbohydrate tolerance actually lessened or disappeared in 2 cases while cortical hormone was being continued at the same dosage or, in 2 others, at a lower dosage. This rather unexpected finding may be related in part to improvement in the patient's general condition and in the basic disease. Thus it has been claimed that untreated rheumatoid arthritis can of itself produce a lowering of carbohydrate

glisemie het egter verdwyn selfs voor die behandeling gestaak is. By die derde het daar geen glikosurie na 134 dae van ACTH-behandeling, in groot dosisse, voorgekom nie. Uit 'n groep van 12 pasiënte met velaandoenings het nie minder as 7 'n belemmerde suikerweerstand ontwikkel nie. Die uitermate groot dosisse kortikotropien, en die feit dat by 4 uit die 7 gevalle daar 'n definitiewe suikersiekte-geskiedenis in die familie was, mag hierdie persentasie beïnvloed het. Twee pasiënte wat aan Addison se siekte gely het, het akute suikersiekte ontwikkel met die gebruik van kortisoon. Dit word beweer dat pasiënte met Addison se siekte buitengewoon gevoelig is vir die metaboliese uitwerkings van kortisoon.[17, 18] Suikersiekte wat as gevolg van kortisoonbehandeling ontstaan, is waarskynlik 'n baie seldsame komplikasie by Addison se siekte. Ondanks groot ondervinding het so 'n geval nog nie in die Peter Bent Brigham-hospitaal[19] voorgekom nie. As gevalle van Addison se siekte met dosisse van ongeveer 50 mg. per dag behandel word, moet hul egter dopgehou word vir die ontwikkeling van suikersiekte. Die gebruik van kortisoon of ACTH in bevestigde gevalle van suikersiekte behels nog 'n ander belangrike gevaar: in sulke gevalle mag retinopatie òf vir die eerste keer verskyn, òf vererger word. Jackson het so 'n geval in sy reeks teëgekom. Daar is nie genoegsame gegewens om vas te stel of hierdie behandeling ekstra gevaar inhou vir 'n swanger vrou wie se gluko-kortikoïedproduksie alreeds hoog is nie.[20, 21] Proefondervindelike waarnemings skyn versigtige behandeling aan te beveel, veral as daar enige prediabetiese geskiedenis bestaan.

Die ontwikkeling van suikersiekte is in hierdie reeks deur grootliks wisselende tydperke van kortisoon- of ACTH-behandeling voorafgegaan. In 'n geval van Addison se siekte was dit 4 dae; by blaarkoors 2 jaar. In 3 ander gevalle het die periode (voor die ontwikkeling van suikersiekte) respektiewelik 11, 8 en 2 maande beslaan. Hierdie gegewens bewys dat daar nie met sekerheid verklaar kan word op watter tydstip gedurende kortikoïedbehandeling hiperglisemiekomplikasies kan intree nie. Die diabetogeniese uitwerking van swangerskap is 'n soortgelyke verskynsel—dit mag eers na herhaalde swangerskappe voorkom.

SOORT SUIKERSIEKTE BEWERKSTELLIG DEUR KORTIKOÏED-HORMONE

Dit word algemeen aangeneem dat die soort suikersiekte wat bewerkstellig word deur kortikoïede in 3 opsigte van die gewone verskil.[1, 4, 9] Dit is (1) omkeerbaar, (2) teen insulien bestand en (3) ketose is lig of seldsaam. Jackson se waarnemings klop met eersgenoemde hoedanigheid. In 2 gevalle onder kortikohormoonterapie, in dieselfde dosisse, het belemmering van die koolhidraatdulding selfs verminder of verdwyn. Dit het ook gebeur in twee verdere gevalle waar daar 'n laer dosis toegedien was. Hierdie ietwat onverwagte bevinding mag gedeeltelik te danke gewees het aan die verbetering in beide die algemene toestand en die grondliggende siekte. Dit was derhalwe beweer dat onbehandelde rumatiese gewrigsontsteking op sigself 'n vermindering in die koolhidraatdulding kan mee-

tolerance,[10, 11] and cortical hormones may counteract this by their action on the primary disease.

Insulin-resistance (or insulin-insensitivity) was not noted in this series, inasmuch as large doses of insulin were not required for control. Even in cases of established diabetes there was need for little more than the dosage used before the treatment with corticoids. Nor was any case of iatrogenic-corticoid diabetes severe (except in the special instances of diabetes occurring in Addison's disease).

The characteristic impairment of glucose metabolism produced by corticoid hormones is shown in the tolerance curve by a high or even rising level of the blood sugar 2 and 3 hours after the glucose has been given, with a normal fasting blood-sugar. It is interesting that this is also the characteristic type of alteration of sugar tolerance found in Cushing's disease.[12]

SIGNIFICANCE OF FAMILY HISTORY IN THE ETIOLOGY OF DIABETES

The high incidence of diabetic relatives in the families or the affected patients in Jackson's series (6 out of 10) must be considered in conjunction with similar reports by Sprague[8] (who found this in 2 out of 4) and Bookman[4] (who found 4 out of 5, while the 5th had had previous glycosuria). This incidence of a positive family-history for diabetes in 63% of the combined series is far above the percentage of the non-diabetic population with one or more relatives affected, given by various authorities as 1-10% (Joslin[13]). One is drawn to the theory that corticoid therapy brings out a diabetic syndrome only in persons who are already predisposed. In other words, the normal functional reserve of the anti-diabetic mechanisms—mainly the pancreatic beta cells—is sufficient to deal with ordinary corticoid dosage, but in some persons there is an inherent partial defect of carbohydrate metabolism, which is rendered evident by the stress of corticoid administration.

When one further considers the prediabetic obstetric syndrome, consisting mainly in the production of large babies and stillbirths many years before the development of overt diabetes,[14, 15] one is led more and more to agree with Colwell[16] that 'the course of diabetes begins at birth' and is made manifest by the various stresses to carbohydrate metabolism which occur during the life span.

The beta cells of the pancreas, with insulin as their weapon, are fighting a lone battle for hypoglycaemia against an array of diabetogenic forces derived from the alpha cells, the pituitary, the thyroid, the adrenal cortex, and the medulla. Whether the addition of exogenous corticotropin or cortisone leads to hyperglycaemia depends on whether the extra antagonist is sufficient to overpower the pancreatic beta-cell reserve.

1. Conn, J. W., Louis, L. H. and Wheeler, C. E. (1948): J. Lab. Clin. Med., **33**, 651.
2. Wilson, D. L., Frawley, T. F., Forsham, P. H. and Thorn, G. W. (1950): Proc. Amer. Diabetes Assoc., **10**, 25.
3. Sprague, R. G. *et al.* (1950): Arch. Intern. Med., **85**, 199.

bring.[10, 11] Die uitwerking van kortikohormone op die primêre siekte mag hierdie vermindering teenwerk.

Omdat groot dosisse insulien nie vir kontrole nodig was nie, het hierdie reeks nie 'n weerstand teen (of ongevoeligheid vir) insulien getoon nie. Selfs in gevalle van bevestigde suikersiekte was nie veel meer as die dosis wat wel gebruik was, nodig vóór behandeling met kortikoïede nie. Behalwe die uitsonderlike gevalle van Addison se siekte vergesel van suikersiekte, was daar nie 'n enkele geval van iatrogeniese kortikoïedsuikersiekte wat werklik ernstig was nie.

Die kenmerkende belemmering van glukose-metabolisme veroorsaak deur kortikoïedhormone word op die duldingkurwe aangetoon deur 'n hoë of selfs stygende bloedsuikerhoogte 2 en 3 uur na die toediening van die glukose, met normale vastende bloedsuiker. Dit is interessant dat hierdie kenmerkende soort wisseling van suikerweerstand ook in Cushing se siekte voorkom.[12]

DIE BETEKENIS VAN FAMILIEGESKIEDENIS IN DIE OORSAAKLEER VAN SUIKERSIEKTE

Die hoë voorkomssyfer van suikersiekte in die families van geaffekteerde pasiënte in Jackson se reeks (6 uit 10) moet tesame met soortgelyke verslae deur Sprague[8] en Bookman[4] oorweeg word. Sprague het dit by 2 uit 4 gevind, en Bookman by 4 uit 5—die vyfde het vantevore glikosurie gehad. Verskillende gesaghebbendes gee die persentasie van die nie-diabetiese bevolking (met 1 of meer diabetiese familielede) as 1-10 aan (Joslin[13]), en dus is die voorkoms van diabeties-positiewe familiegeskiedenis in 63 persent in die gekombineerde reeks hierbo ver bo die gemiddelde. Die teorie dat kortikoïedterapie 'n simptomegroep van suikersiekte slegs by persone wat reeds daartoe neig bewerkstellig, lyk aanneemlik. Die funksionele reserwe van antidiabetiese meganismes — hoofsaaklik die beta-selle van die milt — kan m.a.w. 'n gewone dosis kortikoïede behartig. By sommige persone is daar egter 'n aangebore gedeeltelike defek in die koolhidraatmetabolisme wat na vore kom onder kortikoïedbehandeling.

Prediabetiese kraamsimptome, soos groot of doodgebore babas baie jare voordat suikersiekte openlik voorkom,[14, 15] maak Colwell[16] se stelling dat ‚die verloop van suikersiekte reeds by geboorte begin' steeds meer aanneemlik. Dit openbaar sigself as gevolg van die verskeie inspannings geverg deur koolhidraatmetabolisme gedurende die lewensloop.

Met insulien as wapen veg slegs die beta-selle van die milt teen die diabetogeniese invloed van die alpha-selle, die hipofise, die skildklier, die bynierskors en die murg om die suikerinhoud van die bloed normaal te hou. Die ontwikkeling van 'n oormatige hoeveelheid suiker in die bloed mag as gevolg van bykomstige, uitwendige kortikotropien of kortisoon voorkom, maar dit kan slegs gebeur as die bykomstige ‚vyand' sterk genoeg is om die milt se beta-sel reserwe te oorweldig.

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19. Laidlaw, J. C. (1953): Personal communication.
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21. Gemzell, C. A. (1953): *Ibid.*, **13,** 898.

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POLIOMYELITIS VACCINE

The Salk vaccine, which was the subject of the 1954 Field Trial in the United States, contains the product of the action of formaldehyde solution on virulent strains of poliomyelitis virus. More than 400,000 school children were inoculated with this vaccine, and when the Summary Report of the Evaluation of the Field Trial[1] disclosed no untoward results in these children it was generally accepted that the vaccine might be used with safety, though some virologists in Britain and elsewhere were not entirely convinced. This confidence was soon shaken by some subsequent events.

The authorities did not delay in making the Salk vaccine available for the vaccination of children throughout the United States, and the number of children inoculated soon ran up to 5 million. Amongst these, 100 developed poliomyelitis shortly after inoculation, and it seemed likely that in 60-80 of them the disease was the result of the inoculation.[2] The manufacture of the vaccine has been entrusted to several laboratories, and the distribution of the cases suggested that it was the vaccine from a particular laboratory, and perhaps one other, that was at fault. The only conclusion that can reasonably be drawn is that the vaccine contained residual live virus, whether owing to faulty technique or an inherent defect in the method of preparation.

Great interest has been displayed all over the world in the Field Trial and the subsequent large-scale use of the vaccine in the United States; and trials of vaccine prepared according to the Salk formula were projected in the United Kingdom. However, last month the Ministry of Health decided to postpone these trials and in the meantime work is to be begun to ascertain the distribution of polio immunity in the population of London. This was announced on 15 July by Dr. G. S. Wilson, Director of the Public Health Laboratory Service, who also stated that the Medical Research Council had started experiments to find a safer vaccine. For this purpose a special unit is being set up in Fajara, in Gambia, British West Africa. Dr. Wilson said there were many things about the Salk vaccine which his service did not like. He spoke of the difficulties of being quite sure that virulence was destroyed by the formaldehyde used, and referred to the narrow margin of safety between ineffectiveness and danger. He said it was difficult to avoid the conclusion that formaldehyde as used in this vaccine could not be relied on completely to kill the virus; the human child was a more effective test than any they had in the laboratory. These were the reasons why they wondered whether it would ever be possible to make a vaccine of the Salk type quite safe.[2]

Dr. Wilson went on to say that opinion not only in England but, he believed, in the United States, was that a vaccine prepared from living attenuated virus was more likely to fulfil their requirements than a dead virus. The most successful vaccines that had been developed in the past had been of the attenuated living type. There were strains of that nature available, but he did not think the search for polio vaccines was likely to be a short one.[2]

In South Africa, where there have been distressing outbreaks of poliomyelitis, much research on the subject has been carried out, and at the Johannesburg laboratories of the Poliomyelitis Research Foundation large stocks of a vaccine of the formalin-killed type have been

prepared and are available. A decision whether this vaccine should be brought into use for the protection of the child population has been awaited for some months, and a committee of experts, comprising virologists and other pathologists and public-health medical officers, appointed to advise on polio prophylaxis, has had the matter under consideration. In view of the incidents in America it may be taken that the vaccine will not be passed for use in South Africa until its safety is assured. The Secretary for Health (Dr. du Pré le Roux) announced last week: 'There will be no inoculation of children in South Africa with anti-polio vaccine of the Salk type until the whole position has received further study'.[3]

A further meeting of the advisory committee has been called and may have been held by the time this issue of the *Journal* is published.

Speaking on 22 July,[4] Dr. James Gear, Director of Research of the Poliomyelitis Research Foundation, referred to the highly virulent Mahoney strain of polio virus which was incorporated in the Salk vaccine and said that this strain had not been used in the vaccine made at the laboratories of the Foundation. He said that scientists in the United States, England, Denmark and Sweden were of opinion that a safe vaccine could be produced by the use of non-virulent or mild strains, which if not entirely killed in the processing would have no ill effects when injected under the skin. Safety tests had been made more stringent, and safer vaccine would be available in the coming year. Dr. Gear remarked that in Denmark 500,000 children had been vaccinated against poliomyelitis without untoward results, and in Canada 800,000, and that neither country had been diverted from its immunization programme by the incidents in America.

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