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PRO-INSULIN—A BREAKTHROUGH?

Steiner and his colleagues, in several recent publications,[1-5] have produced evidence for the existence of a protein-precursor in the biosynthesis of insulin. This has been found in the cells of insulin-secreting adenomas, in adult rat pancreas, in crystalline preparations of bovine, porcine and rat insulin, and, most recently, in the blood and urine of 5 human subjects, including a healthy volunteer and patients with insulinoma, untreated ketotic diabetes and maturity-onset diabetes. This pro-insulin is separated from ordinary insulin by fractionation through a Sephadex G-50 column in molar acetic acid. Probably the same substance has been isolated by Elliott *et al.*[6] and Roth *et al.*,[7] who termed their product 'big insulin', but who used procedures different from those employed by Steiner's group.

Pro-insulin is a single-chain polypeptide of molecular weight about 9,000, as against 6,000 for insulin. In effect, it contains 33 extra amino acids which link the C-terminus of the B chain with the N-terminus of the A chain. The beginning of the molecule is the normal amino-acid sequence of the B chain from the N-terminus, and the end is the normal amino-acid sequence of the A chain.

Pro-insulin is converted into insulin in the B cells, presumably by a trypsin-like enzyme, though the exact mechanism is not known.

Pro-insulin—and likewise 'big insulin'—is immunologically similar to insulin, but has negligible biological activity. Consequently, if pro-insulin is a normal constituent of the circulating blood, it follows that *some* of the insulin measured by immunoreactive procedures is not true insulin and is biologically inactive; though, of course, it may possibly be converted into insulin in tissues other than the pancreas. Perhaps, therefore, some conditions in which insulin resistance has been postulated because of glucose intolerance or lack of hypoglycaemia despite high immunoreactive insulin levels may really be explained by the presence of excessive quantities of pro-insulin which are being measured as insulin. Pro-insulin may act against insulin by a mechanism of competition for binding sites on effector tissues. The lack of conversion of pro-insulin to insulin may be a causative factor in some types of diabetes.

1. Steiner, D. F. and Oyer, P. (1967): Proc. Nat. Acad. Sci. (Wash.), **57**, 473.
2. Steiner, D. F., Cunningham, D., Spigelman, L. and Aten, B. (1967): Science, **157**, 697.
3. Steiner, D. F. (1967): Trans. N.Y. Acad. Sci., **30**, 60.
4. Steiner, D. F. and Clark, J. L. (1969): Proc. Nat. Acad. Sci. (Wash.), (in the press).
5. Rubenstein, A. H., Cho, S. and Steiner, D. F. (1968): Lancet, **1**, 1355.
6. Elliott, R. B., O'Brien, D. and Roy, C. C. (1965): Diabetes, **14**, 780.
7. Roth, J., Gordon, P. and Pastan, I. (1968): Paper read at the 60th Annual Meeting of the American Society of Clinical Investigation.

MEDIESE OPLEIDING

Die heersende dokters-tekort is 'n saak waaraan al hoe meer aandag gegee word. Daar word op alle vlakke besef dat hierdie tekort eerder gaan vererger as verbeter tensy drastiese stappe geneem word om meer dokters op te lei. Allerhande voorstelle is reeds gemaak,[1] en dit is duidelik dat die saak nie maklik opgelos kan word nie. Voorlopig moet ons aanvaar dat die opleiding van halfgekwalifiseerde geneeshere nie in die nabye toekoms prakties gaan wees nie en dit is onwaarskynlik dat die Geneeskundige Raad ooit sal instem om sulke dokters te erken. Daar is dus slegs twee uitweë uit die probleem; iedere bestaande mediese skool moet meer geneeshere per jaar oplei, of daar moet meer skole gestig word.

Laat ons eers die opleiding by bestaande skole ondersoek. Reeds 10 jaar gelede is daarop gewys dat die tyd wat aan die verskillende vakke bestee word gedurende die kliniese jare nie altyd met die student se benodighede tred hou nie.[2] Hy ontvang bv. 'n hele jaar se gereelde lesings oor psigoses en slegs een of twee lesings oor neurose, en tog kan die gemiddelde praktisyn verwag om nie meer as 2 of 3 psigoses per jaar in sy praktyk raak te loop nie. Die hoë insidensie van neurose is welbekend. Ten spyte daarvan dat hierdie gegewens reeds 10 jaar gelede gepubliseer is, is daar tot dusver nog geen stappe geneem om die wanverhouding te verbeter nie. As eerstejaar student kon ons nooit begryp waarom ons plantkunde so intensief moes bestudeer nie; veral nie die tipe plantkunde wat te doen het met die noukeurige klassifikasie van blaarvorms en dies meer nie. Ons is toenertyd aangesê om maar voort te gaan en dat ons later, met meer kennis, sal besef hoe belangrik dié studie tog vir die geneesheer is. Na 17 jaar in die praktyk wonder ons nog steeds welke belang die kartelrant van 'n blaar vir die huisarts het, en ons twyfel sterk of ons kennis van die sweetgaatjies van 'n sonneblom ooit iets bygedra het tot enige van ons diagnoses. Had ons destydse lektore hulle daarop toegespits om ons iets te leer van die plante wat wel mediese waarde het, soos *Digitalis purpurea* of *Datura stramonium*, sou ons nog iets van waarde uit hierdie eindelose plantkunde klasse kon put, maar dit skyn asof praktiese toepassingsmoontlikhede nie een van die belangrike oorwegings is gedurende die pre-kliniese jare nie.

Bostaande is des te meer onrusbarend as mens die gedurige gekla van studente en lektore aanhoor oor die ontoereikende tyd wat hulle tot hul beskikking het om die werklik belangrike basiese vakke soos anatomie en fisiologie te leer. Welke oordeel moet mens vorm van die logika van 'n aangebode leerplan wat 'n volle jaar aan plantkunde bestee en wat geen kursus in mediese statistiek aanbied nie? As bostaande feite versigtig in oënskou geneem word wonder mens werklik of die 6-jaar opleiding geregverdig is. Sou 5 jaar nie voldoende wees as al die dwaalspoortjies toegekamp word nie? Hoeveel ure word nie verkwis op lesings oor die mees obskure operatiewe tegnieke wat uiteindelik slegs deur die super-spesialis toegepas gaan word? Mens wonder soms of sodanige lesings gegee word met die welsyn van die voorgraadse student in gedagte of om die ego van die nuut-afgestudeerde spesialis 'n stootjie te gee. Die argument dat die huisarts tog moet weet wat gedoen kan word, hou nie steek nie. Hy moet weet wat moontlik is, ja, maar hy hoef nie te weet hoe om dit te doen nie. Indien hy later wil gaan spesialiseer sal hy in ieder geval dieselfde paadjie weer meer noukeurig moet volg.

As al hierdie tydverkwistende faktore uit die weg geruim

word sal dit bes moontlik beteken dat die kursus òf verkort kan word, òf meer studente ingeneem kan word. Hoe dit ook sy, die grenslose verveling wat met nuttelose lesings gepaard gaan sal die arme student gespaar bly.

Hoewel die omset van die bestaande skole indien moontlik vergroot moet word, bly dit noodsaaklik dat ons meer mediese opleidingssentrums in die lewe moet roep. Die fasiliteite is daar, ons moet slegs skouer aan die wiel sit en die nodige organisasie instel. Met die toenemende industriële ontwikkeling het die hospitale verbonde aan die verskillende mynkomplekse in so 'n mate ontwikkel dat daar nou oorgenoeg onderwysmateriaal beskikbaar is, mits die nodige toestemming tot gebruik van hierdie pasiënte vir opleiding verkry kan word. Met die oog op die dringende landsbehoefte behoort ons nie te skroom om sodanige toestemming op die hoogste vlak te reël nie. Leerkragte is daar genoeg, mits die betrokke universiteite gewillig sal wees om hulle 'n behoorlike salaris te betaal. Hopelik het die tyd nou aangebreek dat ons na eeue, ja bykans jaarduisende, uiteindelik sal besef dat die geld wat aan goeie leerkragte betaal word een van die beste beleggings is wat 'n volk kan maak.

Ons hoop om binnekort 'n nuwe morbiditeitsstudie as bylaag tot die *Tydskrif* te publiseer en ons vertrou dat die universiteitsowerhede hierdie keer gewillig sal wees om dit die aandag te skenk wat dit verdien en om nie bang te wees om selfs ingrypende veranderinge in die leerplan aan te bring as die feite duidelik toon dat dit vir almal ten beste sal wees nie.

1. Tobias, P. V. (1968): S. Afr. T. Geneesk., **42**, 1240.
2. Van Biljon, P. J. (1957): *Ibid.*, **31**, 397.

AN ANTENATAL EVALUATION OF INCREASED RH-ANTIBODY STIMULATION*

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Since the recent discovery that Rh-negative mothers can be protected against Rh immunization by the passive administration of anti-D gammaglobulin,[1,2] considerable attention has been focused on the incidence and effect of foeto-maternal bleeds occurring at delivery. Evidence is also available to show that foetal red cells often find their way into the maternal circulation during pregnancy, indicating that it is possible that antigenic stimuli for Rh-antibody formation can be expected before, as well as after, the delivery of an Rh-positive infant.[3-7]

Even though investigators employ different methods for the antenatal detection of foetal red cells, there has always been close agreement that the frequency of positive findings increases during the final months of pregnancy. While not every foeto-maternal bleed necessarily constitutes an active process of iso-immunization (because individual differences in the mechanism of antibody formation can be expected), it nevertheless raises the problem that antenatal haemorrhage from the foetus to the mother can initiate or further the intensity of antibody stimulation. It is therefore possible to postulate that recorded antenatal variations in antibody specificity, nature of immunoglobulin involved, or simple antibody titre differences can be considered as evidence that renewed foetal bleeds have taken place.

In this section of a three-part report, results of an investigation are presented to show that Rh-antibody follow-up studies performed throughout pregnancy can often clearly reveal the frequency of transplacental haemorrhage and its effect on foetal wastage. Although past observations have consistently suggested that the initial development of Rh immunization occurs as a result of the trauma of parturition, it is also shown that such events can occur as a consequence of foetal bleeds during pregnancy.

MATERIALS AND METHODS

All Rh-immunized mothers analysed in this study were examined from the first trimester of pregnancy onwards. In no instance were mothers included in whom the production of Rh antibodies might have been the result of previous Rh-incompatible blood transfusions, and only Rh-incompatible mother-infant combinations were examined.

For the evaluation of Rh-antibody titres the standardized method of indirect antiglobulin titration was used.[8] The importance of thorough washing of Rh-sensitized cells to avoid contamination by human serum before adding antihuman globulin reagent is emphasized. The necessity for this mode of testing, particularly for establishing consistent titration results, was recently confirmed by Gibbs and Camp.[9]

Since the frequency of antenatal episodes of Rh immunization is known to differ in Rh-negative mothers who become immunized by foetal Rh-positive red cells,[10] the question of when and how often these mothers do show increased episodes of antibody production is important. To determine these variations it is necessary that the investigator first resolves the accuracy of his indirect antiglobulin titration procedure. Table I shows that within the range of one dilution tube nearly 20% of inaccurate results can be recorded for the same samples of blood when tested by two investigators. For a 2-dilution-tube difference the percentage of error is narrowed to 5%. The absence of titration inaccuracies exceeding 3 dilution tubes is significant in that an observed increase of this magnitude can confidently be regarded as a renewed episode of immunization. Assuming that titre differences of 3 dilution tubes or more can also imply that transplacental passage of Rh-incompatible foetal red cells has taken place, then it should also be possible to assess how often such occurrences generally take place during pregnancy.

TABLE I. ACCURACY IN EVALUATION OF RH-ANTIBODY TITRES BY STANDARDIZED INDIRECT ANTIGLOBULIN METHOD WHEN DETERMINED BY 2 INVESTIGATORS (BLIND TEST)

134 samples of Rh antibodies examined

Titre differences	*First investigator % error*	*Second investigator % error*	*Average variation % error*	*Accuracy in predicting increased episodes of Rh immunization when variations exceed*
Three dilution tubes	0·0	0·0	0·0	100%
Two dilution tubes	6·7	5·9	6·3	93·7%
One dilution tube	15·6	17·9	16·7	83·3%

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