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SERUM INSULIN-LIKE ACTIVITY—SOME INTERESTING APPLICATIONS

At present there are three main methods in use for estimating the insulin-like activity (ILA) of circulating plasma. In one, the change in glucose uptake or glycogen deposition by isolated rat diaphragm is measured. In the second, the change in glucose uptake or the carbon-dioxide production in the rat epididymal fat pad is observed. The third method is an immuno-assay, depending basically upon competition between insulin from different species for protein-binding sites. Advocates of this third method claim that it measures the true amount of circulating insulin and is thus far more accurate than the biological insulin-like-activity assays.[1]

In certain circumstances the two methods of biological assay give very different results. In particular, with the rat-diaphragm assay technique normal levels of ILA have been observed in serum or plasma from untreated adult-onset-type diabetic patients, but very low levels in the serum of patients with the severe, youth-onset form of diabetes.[2] Using the rat-epididymal-fat-pad assay, *elevated* levels of insulin activity have been found in the sera of patients with untreated, recently discovered diabetes of *both* adult-onset and youth-onset forms.[3] These apparent discrepancies led to the suggestion that insulin antagonists might exist which are effective on muscle but ineffective on adipose tissue. This idea has been largely confirmed by the finding that a plasma-albumin antagonist is, in fact, ineffective on fat, but clearly effective on diaphragm.[4]

Such findings plainly suggest that the onset of diabetes of *both* types is not related to an absolute deficiency of insulin, but rather to an excess of some anti-insulin factor, possibly of plasma-protein origin. This theory fits in nicely with the large, normal-looking pancreatic islets and beta-cells observed by pathologists in young people who have died shortly after the onset of diabetes. Unfortunately, however, the immuno-assay technique has not confirmed these results.[1] Although high levels of plasma insulin have been found in maturity-onset diabetics (especially with glucose loading), in juvenile diabetics the insulin concentration has been low or nil. So the problem rests at the moment.

Going back to an earlier stage in the natural history of diabetes, we might be led to wonder whether the phenomena associated with 'prediabetes' are also related to some insulin-antagonistic substance. If so, then presumably the pancreatic islets may be extra hard-working in their successful attempt to maintain normal blood-sugar levels. Recently Renold and co-workers,[5] using a bio-assay based on C^{14}-labelled glucose oxidation by the fat pad, have measured the ILA in 23 subjects who were classified as 'prediabetic' on the strong genetic evidence of both parents or an identical twin being diabetic in each instance. All measurements were made in the resting state, after an overnight fast. The 'prediabetics' had all shown entirely normal results in glucose-tolerance tests. Their 30 normal control subjects had a mean ILA of 25% serum of 83 microunits (μu) per ml., with a standard error of $\pm$ 6. The corresponding mean figure for the prediabetics was 203 μu, with a standard error of $\pm$ 23 and a top reading of 500μu. The difference between these means was highly significant. These findings suggest that prediabetics may produce excessive amounts of insulin, which is either partially unavailable to the tissues or counterbalanced by antagonistic factors.

Large and hyperplastic islets of Langerhans are well known to be present in the pancreases of stillborn infants of diabetic mothers. This fact suggested the possibility that excessive amounts of insulin might be circulating in such foetuses and that this insulin might be a contributory factor in the production of the large size of the babies at birth.[6] Baird and Farquhar[7] have recently performed intravenous (umbilical vein) glucose-tolerance studies on newborn infants of normal and diabetic mothers, with a remarkable outcome. The normals gave 'diabetic' results and the diabetics' infants gave very normal results. The mean K values (disappearance rates) were 0·84 and 3·9 respectively, with no overlap. Plasma ILA was also measured by the rat-diaphragm method, both in the fasting state and five minutes after the injection of the glucose load. In the fasting state there was no marked difference between the mean ILA in the two groups, but at five minutes the ILA was ten times higher in the diabetics' infants (700 μu per ml. as against 72).

These fascinating results suggest that the normal newborn infant (and presumably also the foetus-in-utero) has no need for insulin and does not produce it, whereas the diabetic's infant does produce it. We wonder whether the same is true for the large infant of the prediabetic, and what the mechanism is for the stimulation of this early pancreatic activity. There are sure to be many more exciting discoveries following further use of insulin assays.

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SUUR-BASIS TERMINOLOGIE

Die regulasie van die waterstof-ioonkonsentrasie beklee dié unieke plek in die geneeskunde en die fisiologie dat, hoewel fundamenteel redelik eenvoudig, die terminologie wat daaromheen ontwikkel het sake so gekompliseer het dat ons mekaar nie verstaan as ons dieselfde ding sê nie.

Die student het op skool reeds iets omtrent die proses

verneem en daarna is dit aan hom verduidelik met jaarlikse tussenposes deur chemici, biochemici, fisioloë, chemiese patoloë en, les bes, deur klinici. Die literatuur poog geensins om sake te vereenvoudig nie as ons bv. verneem dat ‚natriumchloried 'n potensieel-aansurende sout is',[1] en dat 'n ‚asidose deur intrasellulêre katioon, hoofsaaklik kalium, gebuffer word'.[2]

Daar is paradoksale stellings wat bly voortbestaan en in dieselfde skool deur verskillende leermeesters benadruk word. Studente sal meedeel dat die pH een van die strengste fisiologiese grense het, aangesien die grense waartussen lewe moontlik is tussen 7·0 en 7·8 lê. Daar is min wat besef dat, omdat pH 'n logaritmiese eenheid is, 'n eenheidsverskuiwing ooreenkom met 'n tienvoudige verandering in konsentrasie. As 'n normale pH as 7·4 voorgestel word, is die verdraagsaamheidsperke tussen 40 en 250%, 'n veel groter vryheid as wat bv. vir natrium of kalium verdra kan word.[6]

Die konsep van Brönsted en Lawry het veel gedoen om die terminologie terug te bring na die enigste logiese gebruik, nl. 'n chemiese definisie van 'n suur as 'n protonskenker en 'n basis as 'n waterstof-akseptor of 'n hidroksiel-vrysetter.

'n Navolgenswaardige stap is onlangs aan die Londenhospitaal se mediese skool geneem toe 'n fisioloog, 'n biochemikus en twee interniste die terminologie probeer vereenvoudig het vir gebruik in daardie skool.[3] Terminologie en konsepdefinisie sou na hulle mening die meeste verwarring opklaar, en hoewel mens oor kleiner punte van hulle definisies mag verskil, wil mens baie sterk saamstem dat die terme ‚alkali-reserwe', ‚anioon- en katioon-oormaat' en ‚CO_2-binding' verwerp moet word. Die meetbare parameters van 'n versteuring in H^+ioon konsentrasie is immers alleen die pH, die pCO_2 en die HCO_3-konsentrasie. Om alkali-reserwe en CO_2-binding te gebruik in plaas van bikarbonaatkonsentrasie (in milli-ekwivalente per liter) is oorbodig.

Om die term ‚metabolies' te gebruik om nie-respiratoriese asidose of alkalose aan te dui, is dubbelsinnig, en die meeste geneeshere het sekerlik al die term self in twyfel getrek.

Die terme ‚asidose' en ‚alkalose' is natuurlik ook nie akkuraat nie. Die klinikus verwys hiermee na die *rigting* van pH-verskuiwing, maar die pH kan normaal wees in die geval wat as bv. asidose bestempel is. Die burgerreg wat die terme verkry het, sou aandui dat hulle waarskynlik behou moet word vir die *primêre* verandering. Hoewel ons van mening is dat asidemie en alkalemie in gebruik moet kom vir afwykings van bloed-pH, teenoor asidose en alkalose vir normale pH met versteurde buffer,[4] meen genoemde skrywers[3] dat dit liefs vermy moet word, tensy sulke terme streng volgens definisie gebruik sou word.

Die groot probleem in die praktyk is hoe versteurings aan die klinikus oorgedra moet word. Die probleem lê by dié gevalle waar sekondêre veranderings ingetree het. Hoewel reeds tot 'n mate in gebruik, voel mens huiwerig om te praat van ‚kompensasie' omdat so 'n kompensasie nog steeds 'n abnormale bufferkonsentrasie behels. Die term wat hiervoor aanbeveel word is ‚sekondêre respons'.[3]

Dit sou baie help as die klinikus die moeite wou doen om gegewens op 'n diagram soos die van Nunn[4] of Astrup[5] te probeer vertolk. As 'n mens aanneem dat 'n E.K.G.-grafiek deur die meeste geneeshere aangeleer word, is daar geen rede waarom 'n aand nie bestee kan word om ook die pCO_2-, pH- en HCO_3-grafieke aan te leer nie.

As suur-basis regulasie (ook 'n swak benaming wat alleenlik op grond van burgerreg verduur word) gesien word as die regulasie van waterstof-ioonkonsentrasie, onderhewig aan die Henderson-Hasselbalch vergelyking, waar pCO_2 en bikarbonaat-konsentrasies die bepalende faktore is, verloor hierdie belangrike homeostatiese meganisme veel van sy oënskynlike ingewikkeldhede. Die onlangse monogram van Robinson,[6] wat 'n baie gelukkige kompromie tref tussen chemiese akkuraatheid en kliniese gebruik, is dus aangename leesstof, en die voorbeeld van Creese *et al.*[3] is sterk aan te beveel by alle opleidingshospitale.

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