

## EDITORIAL : VAN DIE REDAKSIE

## LACTIC ACIDOSIS AND DIABETES

In two recent articles Huckabee<sup>1,2</sup> has described some mechanisms which may be responsible for 'hyperlactic-acidaemia'. The accumulation of lactic acid after severe muscular exercise or acute anoxia has long been known. As clinical problems, Huckabee reported on two groups of patients with raised blood lactic acid levels and severe metabolic acidosis. In the first group there was either severe anoxaemia of recent origin or peripheral bleeding. The carbon dioxide (CO<sub>2</sub>) tension in arterial blood was raised in these cases. The second group of patients showed no evidence of circulatory or respiratory failure, but had severe hyperpnoea, tachycardia and dyspnoea. They became progressively more stuporose and died within 12 days. A variety of underlying diseases was present in these nine patients, but there was no obvious common clinical denominator.

Daughaday *et al.*<sup>3</sup> have now described three patients with severe non-ketotic metabolic acidosis in association with diabetes. The nitroprusside test on undiluted plasma and on urine was negative in all cases; this may reasonably be taken to indicate that acetoacetic acid could not have been a major factor in the acidosis. In the two cases in which measurements were made, the blood lactic acid levels were found to be very greatly raised (by a factor of more than 10), the pyruvate levels were raised to a much smaller extent, the bicarbonate levels were correspondingly low, and the arterial pH was 7.19 in the case in which it was measured. The plasma potassium levels were high, but the blood sugar levels were comparatively moderately elevated (538; 435 and 260 mg. per 100 ml. in two similar episodes in the same patient; and 646 mg. per 100 ml. in the third case).

From the case reports,<sup>3</sup> the patients would appear to have been less dehydrated than is usual in diabetic coma. Only one was actually 'in coma', the other two were noted as 'agitated and confused'. Deep, 'acidotic' breathing was observed, as would be expected. All four episodes in the three patients responded rapidly to insulin and replacement fluids containing sodium bicarbonate, in this way differing from Huckabee's non-diabetic lactic-acidotic patients.

The cause of the accumulation of lactic acid in these cases remains obscure. Normally, of course, the diabetic can handle lactate perfectly satisfactorily, even when in coma. One patient was an alcoholic and under the influence of alcohol when he entered hospital. Daughaday *et al.*<sup>3</sup> suggested that this might have played some part in producing the acidotic syndrome, and discussed the biochemical possibilities. None of the patients was taking diguanides.

Daughaday *et al.* emphasized the importance of careful laboratory confirmation of the nature of the metabolic acidosis in a diabetic. They suspected that many patients with non-ketonic acidosis might also lack elevated plasma ketones and might actually have lactic acidosis. In these cases it is plain that sodium bicarbonate should be used rather than sodium lactate in the treatment of the acidosis.

There is another occasional cause of lactic acidosis in diabetes—it may appear during the use of the oral diguanide, phenformin ('insoral'). Walker and his colleagues<sup>4-6</sup> observed the appearance in some patients of ketoacidosis without elevation of the blood sugar. In some a large fall in plasma bicarbonate occurred—these were almost always juvenile-type diabetics. In general, however, a tendency to acidosis, with resting hyperlactataemia and hyperpyruvataemia, was found in all types of phenformin-treated patients. Furthermore, Walker *et al.* observed a greater elevation of blood lactate and pyruvate levels after exercise than occurred in normal control or insulin-treated subjects. Phenformin thus appeared to be associated with ketoacidosis and with lactic acidosis, without hyperglycaemia being a necessary accompaniment of either.

Certainly, any severe or important degree of acidosis caused by phenformin appears to be virtually confined to the juvenile type of diabetic, so that the drug is relatively safe in the adult-onset group. However, Gottlieb *et al.*<sup>7</sup> have reported the case of a 49-year-old woman whose diabetes had been well controlled by phenformin (200 mg. daily) for two years. She went into coma without apparent precipitating cause, with circulatory collapse, a blood sugar level of 532 mg. per 100 ml., and severe acidosis without ketonuria. She was later found to have a somewhat raised blood lactate level, and it seemed probable that the 'large amount of unmeasured serum anion' present during the comatose phase was lactic acid. The patient recovered rapidly under treatment with insulin and intravenous bicarbonate.

We should probably not be unduly alarmed by these occasional reports of severe ketoacidosis from phenformin. This drug should, in general, be restricted to the adult-onset type of diabetic, and it might be advisable to make periodic tests for the presence of urinary ketones as well as sugar.

1. Huckabee, W. E. (1961): *Amer. J. Med.*, **30**, 833.
2. *Idem* (1961): *Ibid.*, **30**, 840.
3. Daughaday, W. H., Lipicky, R. J. and Rasinski, D. C. (1962): *New Engl. J. Med.*, **267**, 1010.
4. Walker, R. S. and Linton, A. L. (1959): *Brit. Med. J.*, **2**, 1005.
5. Walker, R. S. and Hannah, R. (1961): *Diabetes*, **10**, 275.
6. Walker, R. S., Linton, A. L. and Thomson, W. S. T. (1960): *Brit. Med. J.*, **2**, 1567.
7. Gottlieb, A., Duberstein, J. and Geller, A. (1962): *New Engl. J. Med.*, **267**, 806.

## NAVORSINGSPATRONE

Van die aansienlike aantal studente wat jaarliks na ons universiteite kom met die hoë ideaal om 'n naam in wetenskaplike navorsing te maak, word selde weer iets gehoor

en 'n mens mag wel wonder wat van hierdie mense en hul ambisies word. As daar enige 'resepte' vir navorsing bestaan, is dit belangrik dat ons daarvan kennis moet dra



sodat ons aan die beginner die regte leiding en denkrigting kan verskaf. Die beskeie verklaring van 'n direkteur van navorsing, dat so iets soos 'n direkteur nie bestaan nie omdat navorsing aan hom direksie gee, is welbekend. Dit is ook interessant dat so baie van ons ouere wetenskaplikes steeds sekere aspekte van hul eerste aanvanklike probleem bestudeer. Die keuse van die onderwerp is derhalwe vir die beginner van die uiterste belang, en insig in die kandidaat se aanleg en bekwaamheid vir 'n bepaalde studierigting kan van groot waarde wees.

Riley<sup>1</sup> beskryf interessante navorsingspatrone. Die student kies sy eie onderwerp. Hoe onuitvoerbaar of onbuigsaam die probleem aanvanklik mag lyk, word dit deur die adviseur en student saam tot sy empiriese vorm afgetakel, sodat die student 'n duidelike beeld van die aard en omvang van die probleem in gedagte het. Die ideale onderwerp is een wat deur 'n regstreekse 'ja' of 'nee' beantwoord kan word; wat feitelike informasie inhou en wat tot verdere spekulasie aanleiding kan gee. Navorsing begin in eenvoud. Die student kan daaraan herinner word dat Louis Pasteur 'n hele, nuwe skeikundige vakgebied geopen het deur die rasemiese tartrate van mekaar te skei met behulp van eenvoudige apparaat soos 'n hand-lens en 'n naald. Die beginner wat 'n hele laboratorium vir sy navorsing nodig het, maar wat nie in staat is om sonder die hulp van 'n rekenmasjien 'n eenvoudige berekening te doen nie, moet met versigtigheid bejeën word.

Die algemene patroon verloop dan soos volg: Eers kom daar knaende twyfel of sekere van die aanvaarde stellings heeltemal korrek is. Dit is 'n gesonde begin van enige navorsing. Dan die vraag: Is daar 'n alternatiewe hipotese? Die een moontlikheid na die ander word deur die student eers in sy gedagte ontleed en oorweeg en later self beproef in die hoop om 'n intelligente antwoord te vind. In wese is dit die kern van navorsing: die moeilike taak van dink en uitprobeer waarvoor daar geen plaasvervanger is nie. Sels genieë word aan grenselose dinkwerk onderwerp sodat wanneer 'n oplossing uiteindelik gevind word, dit 'n Archimedes beweging om nakend uit sy bad te spring met die woorde: 'Eureka!—Ek het dit!' Die onderbewussyn van die mens is gedurig besig om problematiese feite te hergroepeer, te rangskik en te herskommel totdat hulle in 'n nuwe patroon inval wat dan skielik tot die bewussyn

deurdring. Terwyl hy in 'n Londense bus moes wag, het die chemikus, Kekule, skielik koolstof se heksagoniese konfigurasie voor hom gesien. Daarná word die nuwe of gemodifiseerde hipotese deeglik getoets en deur eksperimente bewys, en in die vorm van 'n wetenskaplike publikasie opgeskryf. Die ware feite van die eksperiment word aantreklik weergegee en op 'n oortuigende wyse gepresenteer, nie noodwendig in die volgorde waarin die eksperimente uitgevoer is nie, maar soos dit vir die leser die verstaanbaarste is.

Die vraag word dikwels gestel watter milieu die mees bevorderlik is vir 'n persoon wat begerig is om navorsing te doen. In teenstelling met suiwer navorsingsinstitute blee die universiteit in hierdie opsig 'n belangrike posisie: Dáár is 'n aanhoudende stroom van jong energieke studente met nuwe oorspronklike idees ten opsigte van die werk wat hulle doen, en hulle kom gedurig in aanraking met mense wat 'n groot verskeidenheid van beroepe beoefen. Geeneen van ons kan sê nie: 'Ek sal môre-oggend 'n goeie idee hê!' Idees kies hulle eie tyd. 'n Persoon met 'n idee moet daaraan begin werk terwyl dit nog vuurwarm is. Apparaat moet tot sy beskikking wees om tydelike modelle te bou en desnoods fondse om vir hom hier en daar 'n stukkie apparaat by te koop. Vryheid van handeling is vir die geskikte kandidaat op die duur die mees geslaagde weg. Voltydse navorsing aan 'n navorsingsinstituut kan senutergend wees. Tensy die persoon of instansie dit gelukkig tref om op 'n golf van sukses te ry, kan 'n gevoel van onvoldaanheid ontstaan wanneer eksperimente misluk en teorieë verkeerd blyk te wees. Ons universiteite bied hier 'n gulde geleentheid aan vir hul doserende personeel van wie onderrig sowel as navorsing verwag word. Die soliede, betroubare weg van die onderwys gee aan die persoon die gevoel dat hy sy plek in die samelewing volstaan en vrywaar hom van die spanning en stagnasie wat die werk van voltydse wetenskaplikes dikwels versuur en vertroebel. Deur sy navorsingswerk bou die wetenskaplike vir homself 'n reputasie op wat, alhoewel dit stadig en tydsaam in verloop is, tog op die duur sy kompensasies het.

Einstein het eenmaal gesê: 'Om 'n ontdekking te organiseer is maklik, as dit eers gemaak is'.