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BIOCHEMICAL JOTTINGS ON HUMAN DISEASE

Diabetic Ketosis

Many diabetic patients pass into coma as a result of some complicating factor, such as infection or injury, superimposed on a longstanding ketotic state. Recovery of the patient depends on the expeditious return of his cellular metabolism to within the normal range. The following remarks may be helpful to medical practitioners who have to manage difficult diabetic patients.

From the biochemical point of view certain cellular constituents are of prime importance, and if the concentrations of these in the body are not put right the patient's convalescence will be halted.

Hydrogen ions. The patient in diabetic coma, with very rare exceptions, is suffering from grave metabolic acidosis. Excessive quantities of hydrogen ions accumulate in the body, both in the extra- and intracellular compartments, mainly owing to the overproduction of aceto-acetic and β hydroxybutyric acids by excessive fatty acid degradation in the liver. The gravity of the acidosis can be gauged approximately by the lowered bicarbonate concentration and pH of the serum and by the titratable acidity of the urine. The latter provides a rough index, if renal distal tubular function is not impaired, of the pH of the intracellular compartment, of which the tubular cells can be regarded as a small sample. It is still not generally appreciated that intracellular proteins provide the greatest buffer capacity in the body, and in diabetic ketosis intracellular proteins, including enzymes, are heavily laden with protons, which have displaced other cations such as potassium and magnesium from binding sites.

Glucose uptake and further metabolism is markedly inhibited in acidosis, which, if severe, can also by itself lead to peripheral circulatory failure and coma.[1] pH correction is therefore urgent, and the acidosis should be the first metabolic disturbance in diabetic ketosis to be rectified. From the concentration of bicarbonate ions observed in the patient's serum, it is possible to calculate roughly the quantity of sodium bicarbonate needed to raise the bicarbonate concentration in the extracellular compartment to the lower end of the normal range. Thus, if the observed bicarbonate concentration is 10 mEq./l., there is a deficit of 14 mEq./l. If we assume that the extracellular compartment (whole blood volume + interstitial fluid) comprises 30% of the body weight, a 70-kg. person will need $70\times30/100\times14$ mEq.$=294$ mEq. of sodium bicarbonate to correct the base defect in the extracellular compartment. The equivalent weight of $NaHCO_3$ is 84 G.: thus approximately 25 G. are needed quickly and should be administered intravenously as a M/6-isotonic-solution. Further bicarbonate can be given from time to time as hydrogen ions are removed from the intracellular space, by the reaction $H^+ + HCO'_3 \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$. Since this space accounts for approximately 45% of the total body mass, 70 - 80 G. of sodium bicarbonate may be needed before the pH of all the patient's tissues are brought back to normal.

Bicarbonate is the rational therapy for correction of metabolic acidosis, since it supplies bicarbonate ions with which protons can react immediately. The use of sodium lactate can hardly be justified because (1) the conversion of lactate to bicarbonate imposes an additional metabolic load along a pathway possibly already inefficient, viz., lactate→pyruvate→acetyl coenzyme A→carbon dioxide (formed during aerobic oxidation of intermediates of the citric acid cycle)→carbonic acid (mediated by carbonic anhydrase)→bicarbonate ions, (2) the last stages can be written as follows: $CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO'_3$ and are readily reversible, otherwise carbonic acid could not form a buffer system. It is clear that the formation of bicarbonate ions from lactate, or indeed, from any other carbon compound fully oxidized to carbon dioxide, must be accompanied by the production of an equivalent number of hydrogen ions. No net gain of bicarbonate is possible unless and until the renal tubular cells are able to exchange protons for sodium or other cations. The renal tubular cells are already fully extended by the established keto-acidosis. On both counts, therefore, sodium bicarbonate is to be preferred. It can be appreciated how, in renal failure, sodium lactate might give rise to so-called lactic acidosis.

The dangers of overenthusiastic treatment with sodium bicarbonate hardly need stressing. Metabolic alkalosis can by itself directly affect enzyme systems and indirectly may cause losses of potassium ions from the distal renal tubular cells, which, if prolonged, can lead to gross potassium depletion in the body; this in turn, presumably through the need for potassium of dephosphophosphorylase, pyruvate kinase, creatine phosphokinase and other enzymes, can interfere with carbohydrate metabolism to produce a state indistinguishable from insulin-deprived diabetes mellitus.

By the administration of sodium bicarbonate much of the patient's dehydration and peripheral circulatory inadequacy will be corrected. If needed later, additional sodium chloride can be given, but it should not be given before correction of the metabolic acidosis, since, when 1 litre M/6 sodium chloride (166 mEq. Na^+ and Cl') is administered, 25 mEq. Cl' are retained and reduce correspondingly the concentration of bicarbonate ions which can be made available for pH adjustment.[2] 5 litres of isotonic saline will diminish the base excess by 125 mEq., roughly 6 mEq./l serum bicarbonate—a severe restriction on the quantity of bicarbonate which can be introduced for its buffering action at a time when the need is most urgent.

Glucose and insulin. It is possible to rectify the extracellular acidosis quickly and turn to the problem of investigating the underlying disturbances in carbohydrate, lipid and protein metabolism. In practice this means the

facilitation by insulin of the uptake and metabolism of glucose in skeletal and heart muscle, liver, and adipose tissue. Although it is said that aceto-acetic acid is the preferred energy source of heart muscle, and 2,500 cals. of energy can be supplied by this organic acid before overt ketosis appears, nevertheless so long as the glycogen stores in liver and other cells are depleted, ketosis will continue.

Glucose must be induced to pass rapidly inside the cells to provide energy for production of adenosine triphosphate and other high-energy compounds required for lipogenesis and protein synthesis—to provide a store of glycogen and abate the mobilization of lipids and breakdown of fatty acids to acetyl coenzyme A and keto-acids. In the days or weeks before the diabetic patient passes into coma, his tissues have been drained of glycogen, proteins (including enzymes), lipids and coenzymes such as nicotinamide adenine dinucleotide, phosphopyridoxal, and other vitamins, ions such as potassium and magnesium and phosphate, and many other essential cellular constituents. The objective is to reverse all those changes, and if adequate quantities of vital substances are not provided, the anabolic process will be impeded. Success, too, is often contingent upon adequate treatment of complications such as infection or injury, which stimulate the production of cortisol, an insulin antagonist. Irrespective of the blood glucose concentration, glucose and insulin should be given far in excess of the normal requirements of a patient resting in bed, since most of the glucose will be utilized for endergonic processes of protein synthesis and lipogenesis. M/3 glucose solution is approximately isomolar with blood; it is advisable that glucose should be given simultaneously with insulin—1,500 mg. of glucose/100 ml. of blood means only 10 G. of circulating glucose, which in a normal person would, as single energy source, last only 20 minutes and require less than 1 unit of insulin.

Frequent blood and urinary glucose determinations should be carried out to provide an indication of the response to treatment and of the rate of glucose utilization, and to ascertain whether, in the early stages especially, the blood glucose concentration is being safely maintained in the 300 - 500 mg./100 ml. range. Such hyperglycaemia increases the rate of intracellular uptake of glucose and lessens the risk of sudden hypoglycaemia.

With response to treatment, ketosis, as judged by Rothera's and Gerhardt's tests, is usually corrected within 24 hours. Since a large proportion of the keto-acids is excreted as β hydroxybutyrate in advanced ketosis,[3] and, since β hydroxy butyrate does not produce coloured products with the Rothera and Gerhardt reagents, these colour tests do not provide a reliable index of the gravity of severe ketosis (urinary titratable acidity is better) although they are most useful in revealing the presence or absence of abnormal quantities of aceto-acetic acid in the urine. Correction of ketosis by appropriate treatment is truly shown by a negative Rothera test, since the overproduction of β hydroxy butyrate stems from accumulated aceto-acetic acid, and falls away as the metabolic pool of the latter declines to normal.

Potassium and phosphate. From the profound metabolic disturbances which together constitute diabetes mellitus, as much as 40% of the body potassium may have been lost in the urine; contributive causes are the intracellular acidosis, disappearance of intracellular binding sites especially on proteins catabolized for gluconeogenesis, impaired active transport through cellular membranes, and loss in association with excreted organic acids. Taking the intracellular mass as being 45% of total body weight and the intracellular concentration of K^+ as 92 mEq./l.[4] the losses from a patient of 70 kg. B.W. would be $70 \times 45/100 \times 92 \times 40/100$ mEq.=1,140 mEq.=approximately 44 G. of potassium ions. This is the quantity of potassium ions which, in actual practice, could be needed to replenish the intracellular compartment during convalescence from an episode of diabetic coma. This is, indeed, a formidable quantity of ionic potassium and it must be passed through the relatively diminutive extracellular space, the serum concentration at all times being maintained within a narrow range, either hypo- or hyperpotassaemia being rapidly lethal to cardiac muscle. The greatest danger to the diabetic patient probably lies in one's failure to sustain the serum potassium concentration in the face of a rapid uptake of glucose, since each molecule of glucose gives rise to a number of ester phosphates all of which readily attract potassium ions. A serum potassium concentration below 2 mEq./l. is a threat to the life of the patient.

This trouble can usually be successfully prevented by giving potassium in a solution with glucose by mouth, 4 G. of K_2HPO_4 and 100 G. of glucose per litre. If the serum concentration of potassium is desperately low, the calculated shortfall below 3 mEq./l. needed in the extracellular fluid can be given intravenously as so-called cell repair fluid, but with sodium lactate replaced by sodium bicarbonate. This preparation has the following approximate composition: Na^+ 57, K^+ 25, Mg^{++} 6, HCO'_3 25, Cl' 50, HPO_4^{--} 12·5 mEq./1, Administration of the appropriate quantity of potassium dihydrogen phosphate, KH_2PO_4, has been found to be a smoothly effective way of correcting metabolic alkalosis accruing from overzealous bicarbonate therapy.

Another constituent for which rejuvenated cells make great demands is inorganic phosphate. Each molecule of glucose fully metabolized to carbon dioxide provides enough energy to be stored in the conversion of 62 molecules of adenosine diphosphate to adenosine triphophate (ATP), i.e., 62 phosphate ions are required. Since the active transport of glucose into the cells is dependent on ATP, the continued provision and ingress of inorganic phosphate is obligatory. An early prompt response to insulin may peter out owing to phosphate lack. A recent patient was found to have a serum inorganic phosphorus of only 0·4 mg./100 ml. Dipotassium hydrogen phosphate given orally in liberal quantities—60-70 G. of phosphorus in all—rapidly overcame the apparent block. It is interesting that this situation does not invoke mobilization of phosphate ions from bone. This same patient had previously survived a critical period when the serum potassium concentration had plumbed to 1·5 mEq./l.

The lesson to be learned is this: if thousands of units of insulin are being given to the patient in an attempt to increase his cellular uptake of glucose, when we know that hundreds of units are vastly in excess of theoretical requirement, then we should look first for evidence that the acidosis has been properly corrected, without alkalosis, and

that the supplies of potassium and inorganic phosphate are being maintained at the appropriate level. It is probable that many instances of insulin resistance are due to elementary errors of this kind rather than to specific insulin antibodies.

Magnesium. Magnesium, like potassium, is mainly an intracellular ion, and the quantity found in the body—2,000 mEq.—is roughly two-thirds of that of potassium.[5] Although magnesium is known to be an essential cofactor for a great number of important enzymes concerned with energy metabolism, including glucokinase, galactokinase, pyruvate kinase, the dehydrogenases of glucose 6 phosphate, 6 phosphogluconate, pyruvate, isocitrate and α ketogluterate, pyridoxal phosphokinase, adenosine triphosphatase and many others, magnesium depletion[6] does not appear to be a recognizable complication of diabetic ketosis. Since some loss would appear inescapable, the normal practice is to give the patient magnesium ions orally in the cell repair fluid, which contains 6 mEq. of Mg^{2+}/l.

Amino acids, vitamins, hormones. Following closely in the wake of glucose-insulin therapy must follow those other essential dietary substances needed for fullest cellular activity.

Amino acids in a suitable form, such as casein hydrolysate (5% w/v with 5% w/v glucose), should be given liberally to allow rapid synthesis of proteins, enzymes, nucleotides and nucleic acids, and generous quantities of vitamins should likewise be made available for their important role of coenzymes. To attain a satisfactory positive nitrogen balance as early as possible is the rational aim of therapy. The contribution which the protein anabolic steroids, e.g. nor-androstenolone, can make remains a subject for intensive study.[7]

All things considered, the difficult diabetic still presents as a most formidable challenge to the biochemist.

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DIE MISBRUIK VAN SIEKTEVERLOF

Een van die lastige en delikate probleme wat gereeld deur geneeshere en administrateurs van gesondheidsdienste gehanteer moet word, is die probleem van die misbruik van siekteverlof. Dit is 'n probleem wat soms ernstige afmetings aanneem en wat met mening en krag aangepak moet word as ons wil voorkom dat daar twyfel ontstaan oor die integriteit van mense wat betrokke is by hierdie aspek van ons openbare lewe.

Op die persoonlike vlak gebeur dit gedurig dat mense hul geneeshere nader met die versoek om korter of langer periodes van siekteverlof aan hulle toe te staan, wat dan gebruik word vir persoonlike doeleindes anders as siekteverlof. En as die geneeshere onwillig is om ‚saam te speel' is daar dikwels die dreigement dat ‚daar 'n ander dokter is wat my sal help'. Hierdie soort optrede stel geneeshere dikwels voor 'n moeilike situasie—nie omdat hulle nie weet wat die regte ding is om te doen nie, maar omdat dit 'n onaangename situasie is om te hanteer.

Probleme van hierdie aard ontstaan op 'n baie groter skaal waar ons te doen het met groter groepe van werkgewersorganisasies. In 'n onlangse brief wat gerig is aan die Registrateur van die Suid-Afrikaanse Geneeskundige en Tandheelkundige Raad, skryf die Direkteur van die Transvaalse Departement van Werke, byvoorbeeld: ‚Ek is oortuig daarvan dat daar sekere klasse van werknemers in hierdie Administrasie is (hoofsaaklik bouwerkers) wat hul jaarlikse siekteverlof-voorregte misbruik. 'n Hele aantal sorg dat hulle, kom wat wil, elke jaar al die dae waarop hulle vir siekteverlof geregtig is, af neem. Ek is seker dat sommige van my distriksbeamptes die prooi is van deskundige misleiers. Selfs die feit dat ons daarop staan dat 'n mediese sertifikaat vir een dag se siekte getoon moet word, het die toestand van sake, wat baie ontstellend is, nie verbeter nie.'

Die feit van die saak is dat die werknemers, na wie hierbo verwys word, die hele saak met 'n verkeerde gesindheid benader. In plaas van om siekteverlof te beskou as 'n voorreg waarvan gebruik gemaak kan word in tye van siekte, reken hulle dat hulle al die dae waarop hulle geregtig is vir siekteverlof *moet* neem—en dit dan vir gewone verlof. Hierdie praktyk is natuurlik sowel dwaas as oneerlik.

Uit die brief van die Direkteur van Werke, waarna ons hierbo verwys het, blyk dit verder dat gedurende die jaar wat op 30 Junie 1963 geëindig het, nie minder nie as 1,003 werksdae verloor is, net in een distrik, as gevolg van ‚siekteverlof'. In 'n ander distrik is afwesigheid vir ‚siekteverlof' en ‚beserings' op diens verantwoordelik vir 21·3% van die redes vir afwesigheid, en ‚beserings' op diens kom soms soos epidemies voor.

'n Soortgelyke toestand van sake kom skynbaar ook in die Spoorweë voor—op grond van die verklaring wat die Algemene Bestuurder van die Spoorweë op 30 Julie 1963 voor 'n byeenkoms van die Federale Raad van Spoorwegpersoneelunies gemaak het.

Die toestand van sake wat ons bedryf het, is onbevredigend en ongewens. Uit 'n nywerheidsoogpunt beskou, kan ons land dit nie bekostig nie. En uit 'n mediese en publieke gesondheidsoogpunt beskou, kom dit neer op wanpraktyk van 'n ernstige aard. Ons wil hier in alle erns op ons kollegas 'n beroep doen om mekaar te ondersteun in 'n poging om hierdie praktyke uit te wis. Ook wil ons vertrou dat die breëre publiek ons sal help om die wanpraktyk te voorkom sodat daar geen verdere benadeling van die beeld van ons mediese dienste hoef te wees nie