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KETOGENESIS

The precise importance of 'ketone bodies' and their relationship to human carbohydrate and fat metabolism is still incompletely known. Interest in this subject has given rise to an enormous amount of biochemical work spread over more than 50 years. A recent review by van Itallie and Bergen[1] presents a most competent survey of present knowledge in this field. As a background for their discussion they point out that the ability of the human organism to maintain a carbohydrate reserve is limited to less than 400 G. Thus, in the average person, 90,000 calories may be stored as fat and only 1,500 as carbohydrate. Nevertheless approximately 120 G. of glucose a day are required to maintain the central nervous system, and additional quantities of carbohydrate are needed to support important functions in other parts of the body.

It is clear that when carbohydrate reserves become depleted the body must be able to draw on its fat stores promptly to maintain energy balance and to conserve carbohydrate for essential purposes. At the same time, mechanisms must be available for rapid manufacture of carbohydrate from non-carbohydrate precursors.

Ketogenesis is a normal function of the liver and the so-called ketone bodies are normal substrates for metabolism. The ketosis which occurs after exercise, for example, results from an accelerated production of these substances by the liver. The two ketone bodies, acetone and β-hydroxybutyric acid, are derived from the third one, acetoacetic acid, so that in considering ketogenesis we may limit ourselves to those factors which influence the synthesis of acetoacetate.

The normal oxidation of fatty acid in the liver produces acetoacetic acid. The fatty-acid molecule is progressively broken down by the splitting off of acetone fragments as acetyl coenzyme A (CoA). Acetyl CoA may condense with oxaloacetate to form citrate, which then enters the tricarboxylic-acid (TCA) cycle. Alternatively, two molecules of acetyl CoA can condense together to form acetoacetyl CoA which can then participate in lipogenesis, ketone-body formation or cholesterol biosynthesis. There is an enzyme in the liver which catalyses the splitting of acetoacetyl CoA to acetoacetic acid and CoA, but the reverse action can apparently not take place in liver tissue. Consequently, free acetoacetate tends to be formed in the liver, while in other tissues it remains bound to CoA.

It is possible that acetoacetate can also arise as a direct product of fatty-acid degradation in the liver. In any event acetoacetate is formed in the liver in association with the normal breakdown of fatty acid. If most of it arises from condensation of acetate fragments, as appears probable, then the rate of ketone production must depend largely on the ability of the liver to dispose of acetyl CoA by routes other than the formation of acetoacetate.

Van Itallie and Bergen point out that hyperketonaemia is most often found as a consequence of starvation, excessive fat intake, carbohydrate deprivation or diabetes mellitus. Hyperketonaemia also occurs in certain lactating ruminants, animals with phloridzin-induced diabetes and fasting pregnant animals. All these conditions probably have in common some degree of carbohydrate deficiency, increased fat utilization, and increased gluconeogenesis.

We may now consider the pathogenesis of ketosis in diabetes. Normally, glucose derived from ingested carbohydrate or by gluconeogenesis enters the liver cells and is phosphorylated to glucose-6-phosphate. Insulin in some way facilitates these steps. The glucose-6-phosphate can now be degraded by (1) the Embden-Meyerhof (EM) pathway *via* fructose and triose to pyruvate and then acetyl CoA, or (2) the pentose phosphate pathway *via* a 5- and a 7-carbon compound to fructose and triose, and then to acetyl CoA.

Two further points now need to be emphasized:

1. During the course of glucose catabolism in the pentose phosphate 'shunt', the reduced form of the coenzyme triphosphopyridine nucleotide (TPNH) is produced. This cofactor appears to be needed for the manufacture of fatty acids from acetate fragments. Reduced diphosphopyridine nucleotide (DPNH), which is formed during EM glycolysis, is also needed for fatty acid synthesis.

2. Before acetyl CoA can enter the TCA cycle and be further oxidized, it must condense with oxaloacetate, a compound that is normally derived almost entirely from carbohydrate. In the diabetic liver, phosphorylation of glucose is much reduced and glycolysis is diminished. Thus the supply of TPNH required for lipogenesis is reduced and the synthesis of fat from acetyl CoA is suppressed. Gluconeogenesis from amino acids is also greatly increased in the liver in a diabetic animal.

Exactly how ketosis occurs is still doubtful. One theory relates it primarily to an excessive release of fatty acids from adipose tissue, which occurs in acute diabetic states. The free fatty acid level in the plasma rises, and the degradation of fatty acids to acetyl CoA proceeds rapidly. More acetate units are produced than can be taken up into the TCA cycle and lipogenesis is inhibited. The only remaining pathway left to the liver is to throw out into the circulation the two carbon fragments as acetoacetate and its ketone products.

The 'oxaloacetate deficiency' theory is based on the concept that in diabetes a deficiency of phosphorylated glucose within the liver cell results in a deficiency of oxaloacetate. During the increased fatty acid breakdown that occurs in the diabetic liver, the amount of acetyl CoA exceeds the supply of oxaloacetate with which to condense. Consequently the 2-carbon fragments derived from fatty acid breakdown accumulate in liver cells and combine to form acetoacetic acid.

The third theory proposed to account for ketosis is related to excessive gluconeogenesis. Ketogenesis may be

linked to gluconeogenesis by a hydrogen transfer system that permits the hydrogen which is produced during fatty-acid oxidation to be used in the synthesis of glucose from 3-carbon precursors. The excess formation of acetyl CoA and hence of ketones may be a mechanism whereby hydrogen can be provided for the greatly accelerated gluconeogenesis that occurs in the acute diabetic state.

In conclusion it would seem certain that diabetic ketonaemia results from the formation of the ketone bodies by the liver at a rate exceeding the ability of other tissues to remove them. Large amounts of fatty acids are delivered to the liver at a time when the mechanisms of their disposal are reduced. These mechanisms include particularly the TCA cycle and the biosynthesis of fatty acids themselves.

1. van Itallie, T. B. and Bergen, S. S. (1961): Amer. J. Med., **31**, 909.

POLIOMIËLITIS SLUKENTSTOF

Volgens die voorlopige gegewens wat tot ons beskikking is, het die nasionale kampanje wat dwarsoor die land gevoer is in 1961 om poliomiëlitis slukentstof aan alle vatbare lede van die bevolking beskikbaar te stel, met 'n betreklike groot mate van sukses verloop. Ons hoop om die volledige resultate van dié onderneming eersdaags in die *Tydskrif* te publiseer.

In die tussentyd is dit uiters belangrik om met die inentingskampanje vol te hou op 'n roetine-basis. Aangesien die natuurlike reservoir van immuniteit deur die landswye inenting verwyder is, moet alle nuwe potensiële slagoffers (kinders wat gebore word en immigrante uit ander landstreke) van moontlike aanvalle van poliomiëlitis gevrywaar word deur profilaktiese inenting. Om hierdie doel te bereik, is die noue samewerking tussen alle lede van die mediese professie en van die publiek as 'n geheel, absoluut noodsaaklik.

In hierdie verband wil ons dus graag weer die aandag van ons lesers vestig op 'n brief wat deur die sekretariaat van die Mediese Vereniging ontvang is van die Sekretaris van Gesondheid, en wat in die *Tydskrif* van 22 September gepubliseer is. Die inligting in die brief wat vir ons doel ter sake is, is die volgende:

1. Die Departement van Gesondheid sal reëlings tref met plaaslike outoriteite om voorrade van die entstof, sonder koste en op versoek, beskikbaar te stel aan mediese praktisyns.

2. Die slukentstof en stroop sal beskikbaar gestel word met die verstandhouding dat die betrokke dokters wat dit ontvang, onderneem om aan die einde van elke kwartaal (d.i. aan die einde van Februarie, Mei, Augustus, en November) betroubare opgawes in te dien oor die naam, ouderdom, ras en geslag van die private pasiënte wat die entstof gedurende die kwartaal ontvang het, asook van die aantal dosisse van die slukentstof wat toegedien is. Hierdie besonderhede is nodig om die plaaslike outoriteite in staat te stel om elke kwartaal 'n volledige verslag aan die Departement van Gesondheid te stuur oor die aantal vatbare persone wat gedurende die betrokke tydperk in elke gebied geïmmuniseer is.

3. Die slukentstof kan aan kinders gegee word wat 3 maande oud en ouer is. Op grond van serologiese ondersoeke wat deur die Suid-Afrikaanse Instituut vir Mediese Navorsing gemaak is, is die blootgestelde ouderdomsgroepe van die verskillende bevolkingseenhede, soos volg:

Bantoes in die Bantoetuislande: 3 maande - 6 jaar.
Bantoes in ander gebiede, en Indiërs in die plattelandse gebiede van Natal: 3 maande - 9 jaar.
Asiate (uitsluitende diegene in die plattelandse gebiede van Natal), Blankes en Kleurlinge: 3 maande - 30 jaar.
Immigrante uit Wes-Europa en Noord-Amerika: 3 maande - 40 jaar.
Swanger vrouens: Enige ouderdom.

4. 'n Klein aantal persone wat nie in dié ouderdomsgroepe val nie, kan natuurlik tog poliomiëlitis kry. Die ouderdomsgroepe soos hierbo uiteengesit, moet dus dien om 'n algemene aanduiding te wees van die bevindinge van die serologiese ondersoeke.

5. Dit is baie belangrik dat babas van die ouderdom van 3 maande af en blootgestelde persone uit die hoër ouderdomsgroepe, wat nie gebruik gemaak het van die fasiliteite vir inenting gedurende 1961 nie, nou geïmmuniseer word.