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EDITORIAL

ABOUT OBESITY

Obesity, like smoking, affects so many scientific and medical men personally that there is some difficulty in viewing the subject dispassionately. First of all it should be recognized as a serious disease. Jean Mayer, whose review of the Etiology of Obesity is the inspiration for this article, considers it to be perhaps the 'Number-One Public-Health Problem' in Western countries at the present time. Secondly it should be realized that man has no immunity from the workings of the Second Law of Thermodynamics. If he takes in more calories than he needs, he will gain weight; as Mayer says, 'in the development of 100 per cent of the cases of obesity, there must be excess intake'. There are no known exceptions. It is really remarkable how accurately the mechanism of appetite does control the constancy of weight in a large number of people.

Mayer considers in some detail what these mechanisms are that control the appetite. It seems beyond doubt that there is an 'appetite' centre in the hypothalamus. Destruction of parts of the ventro-median nuclei leads to obesity, while more lateral lesions cause anorexia. Over the last several years Mayer and his associates have elaborated the 'glucostatic' theory of regulation of food intake. They argued that the central nervous system, which is known to be dependent upon a continued supply of glucose in the blood, might maintain 'glucoreceptors' which are sensitive to fluctuation in available blood glucose. Hunger thus becomes one of the mechanisms by which the central nervous system ensures its own homeostasis.

Injection of glucose, fructose and epinephrine caused temporary raising of blood glucose and lowered the food intake correspondingly. Injections of sucrose and fat emulsion were without effect. More remarkable was the effect of injections of glucose upon alloxan-diabetic hypophysectomized rats. These animals were deprived of their mechanisms for recovery from hyperglycaemia. Three daily injections of glucose, maintaining continuous hyperglycaemia, caused death of the animals from inanition in spite of the presence of food in the cage.

Mayer and his associates reasoned further that the

VAN DIE REDAKSIE

OOR VETSUG

Vetsug, net soos die rookgewoonte, raak so baie van ons wetenskaplikes en medici persoonlik, dat dit ietwat moeilik sal gaan om hierdie onderwerp onpersoonlik te bespreek. Eerstens moet dit as 'n gevaarlike siekte beskou word. Jean Mayer, wie se hersiening van die *Etiology of Obesity* hierdie artikel geïnspireer het, beskou dit as die ‚Number-One Public-Health Problem' in die Westerse lande vandag. Tweedens moet ons besef dat die mens geen immuniteit teen die werking van die Tweede Wet van Termodinamika het nie. As hy meer kalorieë opneem as wat hy nodig het, sal hy gewig optel; soos Mayer sê, ‚in the development of 100 per cent of the cases of obesity, there must be excess intake'. Geen uitsondering is bekend nie. Dit is werklik opvallend hoe akkuraat die aptytmeganisme die gewigskonstantheid in 'n groot aantal mense beheer.

Mayer oorweeg taamlik breedvoerig die meganisme wat die aptyt reël. Dit ly geen twyfel dat daar 'n ‚aptyt'-sentrum in die hipotalamus is nie. Vernietiging van dele van die ventromediaankern lei tot vetsug, terwyl meer laterale letsels aptytverlies veroorsaak. Gedurende die afgelope paar jaar het Mayer en sy medewerkers die ‚*glucostatic*'-teorie van die voedselopname-reëling verwerk. Hulle het geredeneer dat die sentrale senuweestelsel—bekend vir sy afhanklikheid van 'n onafgebroke toevoer van glukose in die bloed—miskien ‚*glucoreceptors*' in stand hou, wat sensitief is vir skommelinge in die beskikbare bloedglukose. Honger word dus 'n meganisme waardeur die sentrale senuweestelsel sy eie ewewig behou.

Inspuitings van glukose, vrugtesuiker en epinefrien het 'n tydelike verhoging van die bloedglukose en 'n dienooreenkomstige verlaging van die voedselopname veroorsaak. Inspuitings van sukrose en vet-emulsie het geen effek gehad nie. Nog merkwaardiger was die uitwerking van glukose-inspuitings op alloksaandiabetiese rotte wie se hipofise verwyder was. In hierdie diere was die meganisme vir die herstel van hiperglisemie ontneem. Drie daaglikse inspuitings van glukose, wat sonder onderbreking die hiperglisemie volgehou het, het daartoe gelei dat die diere as gevolg van uitputting gevrek het, ten spyte daarvan dat daar kos in die hok was.

Mayer en sy medewerkers het verder geredeneer dat die aptytsentrum in die brein nie sensitief was nie vir die werklike bloedglukose-hoogte nie, maar eerder vir die beskikbaarheid van die bloedglukose—dit moet eers oor membrane gaan om die gluko-ontvangerselle binne te dring, en dit veronderstel integriteit van fos-

appetite centre in the brain was not sensitive to the actual level of blood glucose, but rather to its availability—it first must cross membranes to enter the glucoreceptor cells, and this implies the integrity of phosphorylation. Hence in diabetes mellitus the sufferer may be hyperphagic despite a high blood-glucose level. To test this theory one would like to estimate the utilization of glucose in the hypothalamus itself. Since this is impossible in man, measurements of arteriovenous glucose differences (called 'λ glucose') were adopted as indices of glucose utilization.

Large numbers of experiments on man confirmed the postulated alterations of λ glucose varying inversely with appetite. The relationship was found to hold normally, on subnormal diets, in diabetes and hyperthyroidism, after cortisone administration, and after insulin. It was also applied to various types of experimental obesity.

This scheme of glucostatic control of appetite is simple and attractive, but it must be pointed out that it is by no means proved and it has not everywhere found favour. In any event it is plain that the physiological mechanism of regulation of food intake is exceedingly complicated and correspondingly vulnerable.

Conditions which increase appetite without corresponding increase in energy expenditure are therefore those which lead to obesity. The first factor to be considered is the genetic one. Obesity due to a dominant gene occurs in a yellow strain of mice. The proximate cause of their obesity is unknown, though they favour a high food-intake and low level of activity. Another genetic obesity in mice is the 'hereditary obese-hyperglycaemia syndrome', controlled by an autosomal recessive gene. These enormously obese animals show no increase in oxygen consumption over non-obese controls. Unlike the state of affairs in human obesity, where subjects have 'normal' basal metabolism, the basal metabolic rate of these mice, referred in the usual way to surface area, may be less than 50%. Their food intake is only some 25% greater than that of the non-obese litter-mates, but they are 50 to 100 times less active. Their calorie intake, then, although little above normal, is still enormously greater than their metabolic need.

These obese mice are interesting also for another reason—they develop progressively severe hyperglycaemia and glycosuria. Strangely enough, high-fat diets tend to cause loss of weight, while high-protein diets increase weight and increase the severity of the diabetes. From a variety of evidence, Mayer and his associates have suggested that the obese animals secrete an excess of glucagon from overactivity of the alpha cells of their pancreatic islets. This would account for their hyperglycaemia and insulin-resistance. The basic biochemical lesion is said to be a slowing down of the process of oxidation of acetate to carbon dioxide and water.

Interesting as these mice undoubtedly are, with their superficial resemblance to human obese diabetics, it must be doubtful whether there is any basic analogy.

Mayer, J. (1953): Physiol. Rev., **33**, 472.

forilering. Dus is dit moontlik dat 'n suikersiektepasiënt aan verhoogde-voedselopname kan ly ten spyte daarvan dat sy bloedglukose hoog is. Om hierdie teorie te toets, sou 'n mens graag die gebruikmaking van glukose in die hipotalamus sigself wou skat. Aangesien dit by die mens onmoontlik is, is die meet van arterioveneusglukose-verskille (genoem 'λ glukose') as indeks van glukosegebruikmaking aanvaar. Die gepostuleerde veranderings van λ glukose met omgekeerde veranderings van aptyt is deur baie eksperimente op die mens bevestig. In gevalle van suikersiekte en oormatige skildklierwerking is gevind dat—met subnormale dieëte—die verhouding normaal bly ná toediening van kortisoon en insuline. Dit was ook by verskeie tipes van eksperimentele vetsug gebruik.

Hierdie plan vir glukostatiese beheer van aptyt is eenvoudig en aantreklik, maar daar moet op gelet word dat dit nog glad nie bewys is nie, en dat dit nie orals byval gevind het nie. Dit is in elk geval baie duidelik dat die fisiologiese meganisme van voedselopname-reëling baie ingewikkeld is en dienooreenkomstig vir kritiek vatbaar is. Toestande wat die aptyt verhoog sonder om die energieverbruik ooreenkomstig te verhoog, lei tot vetsug. Die erflikheidsfaktor is die eerste wat oorweeg word. Vetsug te wyte aan 'n dominante geen kom in 'n geel ras van muise voor. Die onmiddellike oorsaak van hulle vetsug is onbekend, alhoewel hulle geneig is tot 'n hoë voedselopname en 'n lae peil van aktiwiteit. 'n Ander tipe erflike vetsug in muise is die *'hereditary obese-hyperglycaemia syndrome'*, wat deur 'n resessiewe outosoom-geen beheer word. Hierdie enorme vetsugtige diere toon geen verhoging van suurstofverbruik in vergelyking met nie-vetsugtige kontrolediere nie. Anders as in die geval van menslike vetsug waar die pasiënte se basale metabolisme normaal is, kan die basale metaboliese koers van hierdie muise, soos gebruiklik verwys na oppervlaktegebied, minder as 50% wees. Hulle voedselopname is slegs sowat 25% groter as dié van hul werpselmaats wat nie aan vetsug ly nie, maar hulle is sowat 50-100 maal minder aktief. Hulle kalorieopname derhalwe, alhoewel bietjie bo normaal, is nogtans geweldig groter as hul metaboliese vereiste.

Ook om 'n ander rede is hierdie vetsugtige muise interessant—progressief ontwikkel hul swaar hiperglisemie en glikosurie. Eienaardig genoeg is dieëte ryk aan vet geneig om gewigsverlies te veroorsaak, terwyl dieëte nut hoë proteiengehalte die gewig vermeerder en die hewigheid van die diabetes laat toeneem. 'n Verskeidenheid van bewyse het Mayer en sy medewerkers op die gedagte gebring dat die vetsugtige diere 'n oormaat van glukagon afskei as gevolg van ooraktiwiteit van die alfaselle van hul alvleesklier-eilandjies. Dit sal hul hiperglisemie en insuline-weerstand verklaar. Dit word beweer dat die basiese biochemiese letsel 'n vertraging van die oksidering van asetaat na koolsuurgas en water is.

So interessant soos hierdie muise met hulle oppervlakkige ooreenkoms met vetsugtige suikersiektepasiënte ongetwyfeld is, moet dit betwyfel word of enige basiese analogie bestaan.

Mayer, J. (1953): Physiol. Rev. **33**, 472.

NOVOBIOCIN

Much interest has been aroused by the new antibiotic, novobiocin, largely on account of its activity against staphylococci and other organisms which are or have become resistant to the commonly-used antibiotics, and also because of the high concentrations of novobiocin in the blood that have been achieved. Active research is still proceeding. An interesting line is the investigation of the apparent identity or relationship of some antibiotics obtained from different organisms.

Novobiocin is well known under its trade names of Albamycin (Upjohn Co.), Cathomycin (Merck) and Cardelmycin (Pfizer).

In vitro[1] studies of novobiocin indicate especially high activity against *Staphylococcus aureus* and effectiveness against *Streptococcus haemolyticus*, *Streptococcus viridans* and *Diplococcus pneumoniae*, as well as several other gram-positive organisms. Of the gram-negative organisms, the most susceptible have been found to be *Proteus vulgaris*, *Pasteurella multocida* and *Klebsiella pneumoniae*. The drug was similarly highly effective against induced infections *in vivo* with these organisms. Lubach[2] tested 182 strains of *Staphylococcus aureus* and only one strain failed to be inhibited by 1·0 μg./ml. of novobiocin. The majority of the tested strains were inhibited by considerably lower concentrations of the drug and were highly resistant to the commonly used antibiotics.

Novobiocin is bactericidal rather than bacteriostatic.[3] No cross-resistance with any other antibiotics was observed.[4] While resistance may develop *in vitro*, it usually occurs in a stepwise, penicillin-like manner instead of the rapidly increasing type noted for streptomycin.

When a therapeutic dose of novobiocin is administered orally to dogs or man, absorption is rapid, with peak blood-levels reached in 2-4 hours.[5] Unusually high blood-levels are maintained over a 24-hour period, which may be due to the loose binding of novobiocin by serum proteins and the reabsorption of antibiotics excreted by the liver. The blood levels are reported as being 10-50 times as high as that attained by equal doses of other antibiotics when therapeutically active amounts are administered. Novobiocin is well distributed throughout the body tissues and fluids but is usually not detected in the cerobrospinal fluid. Excretion studies show that about one-third of the antibiotic is excreted in the faeces *via* the bile. Approximately 3% is detected in the urine.

The April issue of *Antibiotic Medicine* contains 8 reports of the results of the clinical use of novobiocin. Most of the authors gave oral doses of 1-2 g. per day to adults. Children received 15 mg. per kg. per day. Transient generalized skin-reactions occurred in 0·5% of cases who received 1·0 g. per day. No serious side-effects such as staphylococcal enteritis or moniliasis were recorded.

Staphylococcal infections in particular responded readily. Martin *et al*[6] found novobiocin highly effective in the treatment of 4 of 5 patients with staphylococcal septicaemia. All 5 cases of staphylococcal enteritis responded, as well as 3 of 4 cases of skeletal-system infections.

Pyogenic infections of the skin, due mainly to staphylococci and streptococci, responded well[7].

Morton *et al*[8] treated 41 cases of soft-tissue infections with novobiocin in conjunction with surgery; the incidence and magnitude of the surgical procedures were reduced. Limson and Romansky[9] treated 30 cases of bacterial pneumonia; all the patients recovered, despite the existence of severe complicating conditions in 12 of them.

Satisfactory results were obtained in a number of cases of urinary infections due to susceptible strains of *Proteus vulgaris* and *E. coli*, though the latter is relatively insensitive to novobiocin.[10]

Further clinical studies are necessary to determine all the possibilities of novobiocin, but at this stage it appears to be a very useful antibiotic to use in the treatment of infections due to staphylococci, streptococci, pneumococci and proteus organisms.

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