would seem to be in those patients with acute lymphoblastic leukaemia who are no longer responsive to conventional treatment and yet have an adequate bone-marrow reserve. One further conventional drug should be available to maintain any remission obtained by rubidomycin. It would seem that rubidomycin offers the best chance of inducing a remission in acute myeloblastic leukaemia provided full supportive therapy is available.

New Treatments for Heroin Addiction

Recent reports[1-3] from New York describe the treatment of heroin addicts by maintenance with methadone—a long-acting opiate which can be taken orally. V. P. Dole and his colleagues found that with the blockade produced by a single daily maintenance dose of 100 mg. methadone patients became refractory to the euphoric action of 80 mg. or more of heroin, an amount equivalent to the drug contained in several illegal "bags" in New York. The results to date have been very promising in this disease known to have a poor prognosis. A group of relatively nonproductive heroin addicts, prone to relapse, were treated with methadone and showed social and vocational rehabilitation surprisingly quickly. However, the patients chosen were volunteers for the programme, who had long histories of addiction and were at an age when other factors, such as time and maturity,[4 5] might be expected to lead to an improved prognosis. At present there are very few heroin addicts in Britain who would have qualified for inclusion in Dole's series. A further difference is that the average heroin addict in New York probably uses only 80 mg. of heroin daily, compared with the 400 mg. which may be taken by the British addict, who is usually also taking cocaine.[6]

Methadone is legally and pharmacologically a narcotic. Its use can be abused and the drug can be sold on the black market. Any future use of methadone in the treatment of addicts would need to be so arranged that the possibilities of this abuse were reduced to a minimum.

The use of morphine antagonists in the treatment of heroin addiction may simplify this problem. Cyclazocine, an opiate antagonist and analgesic, is one of a series of *N*-substituted benzomorphan derivatives and was the first drug of this type to be used clinically.[7-9] W. R. Martin and his colleagues working at the Narcotic Addiction Research Unit at Lexington found that cyclazocine when taken orally produced a high degree of antagonism to the subjective effects of morphine. Physical dependence developed to the subjective effects of cyclazocine—similar to those produced by nalorphine—and there was cross tolerance between these drugs. Withdrawal of either nalorphine or cyclazocine produced an atypical abstinence syndrome. The fact that tolerance developed to the unpleasant effects of the narcotic antagonists without any diminution of the blocking effect on the euphorogenic and dependence-producing properties of morphine suggested the use of cyclazocine as an extension of the "drug-free environment" approach to treatment. Cyclazocine can provide a method of enforcing and maintaining a state of abstinence. A heroin addict taking a dose of 4 mg. cyclazocine daily is immune to the usual euphoric and systemic effects of a challenge dose of 15 mg. heroin.[10] The potential of cyclazocine for abuse is considerably lower than that of most narcotic drugs. Stabilized patients can be permitted considerably more latitude in their contact with treatment centres. Preliminary reports of clinical trials in New York confirm the possible future usefulness of this drug.[9]

The use of cyclazocine is still in the experimental stage. Maintenance on methadone has now been used in New York for three years. The follow-up of the group treated has been the most thorough reported so far, and the results the most promising. At a time when the Ministry of Health is starting to set up special outpatient clinics which will provide maintenance supplies of heroin for addicts[11] there is an urgent need for controlled trials of all forms of treatment of heroin addiction to decide whether or not long-term prescribing of heroin for an addict is ever justified, and whether these newer treatments will be as successful in the very different situation in England, where narcotics are still to be available on prescription for addicts.

Insulin Antagonism

An insulin antagonist is any substance which inactivates insulin. In theory it might interfere with the pancreatic synthesis and release of insulin; it might modify or combine with it in the circulation, or speed up its rate of degradation, or alter the response of the target organ to the hormone.[1] Not surprisingly, these various and complex factors are by no means fully understood. Caution is required before accepting much of the earlier work on serum antagonists because of the lack of precision of the bioassay procedures and because of the induction of artifacts from the methods of separating and extracting the serum.[2]

There is general agreement that after a few months all diabetic patients receiving exogenous insulin develop insulin-binding antibodies. They are found in the gammaglobulin fraction in the serum and are presumably formed in response to the small differences in the aminoacid sequences of beef and pork insulins from those of human insulin. A simplified method for assaying the antibodies has now been described.[3] To what extent antibodies to exogenous insulin necessitate giving more insulin than simple loss of the pancreas would require (30–50 units a day[4]) is debatable. But from the work reported recently by W. G. Oakley and his colleagues[5] it seems that the somewhat uncommon condition of sustained insulin resistance with daily requirements in excess of 200 units is usually but not invariably due to excessive formation of antibody. There is nothing to support the idea that autoimmune antibodies are formed to endogenous normal insulin.[6] Insulin is found in foetal and newborn serum and can be expected to induce immune tolerance.

The idea that insulin antagonists other than antibodies play a part in causing some forms of human diabetes has attractions. It has been repeatedly observed that in some diabetic patients the fasting level of insulin is raised and the insulin

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response to a glucose load is greater than normal.[6 7] The persistence of hyperglycaemia as a result of impaired insulin sensitivity is a continuing stimulus to secretion by the β cells. In contrast, in some young diabetics and in severe long-standing adult cases the insulin activity in the serum is very low,[8] and this could represent a later phase of islet cell exhaustion.

Is anything known of the nature of the possible antagonists? J. Vallance-Owen has found a substance in the serum of insulin-dependent diabetics which inhibits the stimulating effect on glucose uptake of adding insulin to the isolated rat diaphragm. It is also found after separation of the serum albumin fraction in obese and latent diabetics. Because it is not albumin itself he calls it the synalbumin antagonist,[9] and for various reasons has latterly proposed the interesting idea that it is the B chain of the insulin molecule itself.[10] The formation of the antagonist is dependent on pituitary and adrenal function.[11] Non-diabetic relatives may show antagonism in a way that suggests the factor is inherited as a Mendelian dominant.[12] A large proportion of non-diabetic patients who have had a myocardial infarct also show synalbumin antagonism. Both results imply that many more of the population are constituted as diabetics than show diminished glucose tolerance. Though Vallance-Owen's work may need confirmation[6] it supplies a satisfying hypothesis to explain some of the facts about the cause and the epidemiology of the disease.

It has long been known that anterior pituitary and adrenal hormones are antagonistic to insulin. Thus thirty years ago Houssay showed that a pituitary hormone identified subsequently as growth hormone by F. G. Young exerted a diabetogenic effect in the intact animal. P. J. Randle has put forward the important concept that this is because of an interrelationship between glucose and fat metabolism which he calls the glucose/fatty acid cycle.[13 14] In this scheme the uptake of fatty acids for oxidation by muscles inhibits their assimilation of glucose, and the insulin antagonistic activity of growth hormone is a consequence of its lipolytic action in raising the plasma level of non-esterified fatty acids. Adrenaline and cortisol act synergistically with growth hormone to produce a similar effect. Placental lactogen also acts like growth hormone[15] and may thus account for the rise in insulin requirement usually found in diabetic women during pregnancy. Studies in man have confirmed that increase in non-esterified fatty acids in the plasma results in impaired carbohydrate tolerance and antagonizes endogenous insulin.[1] While it is not proposed that over-secretion of growth hormone or cortisol is a common cause of diabetes, other unknown factors stimulating the release of fatty acids from adipose tissue might antagonize insulin and in time lead to glucose intolerance. This hypothesis neither excludes the additional importance of serum antagonists nor takes into account the possible importance of the rate of synthesis, release, and breakdown of insulin itself.

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Artificial Hearts

Successful homotransplantation of the heart will be considerably more difficult than homotransplantation of an organ which is composed of repetitive units, such as the kidney or the liver. Some of the problems encountered during the early work on implantable artificial hearts were reviewed in these columns two years ago,[1] and since then studies in large animals such as the calf[2 3] have shown that such a venture is now possible.

One of the major difficulties in developing an artificial heart is that it cannot be used intermittently like a haemodialysis unit. H. B. Shumacker and his colleagues have recently described their work towards developing a totally implantable, reliable mechanical heart.[4] They used an electrohydraulic pumping system with "ventricular" blood contained in two contiguous Silastic bladders, which were emptied alternately by the movement of fluid within an outer semi-rigid housing. This fluid space was connected by large-bore plastic tubing to a hydraulic pump and electric motor which were placed in the abdomen. It was found that autoregulation of the stroke output of this artificial heart according to the venous return resulted in a satisfactory flexible cardiac output. Normal pressures in both the pulmonary and systemic circulations were maintained, since these depend upon the normal vasoregulation of the peripheral vascular bed rather than on the heart itself. For this reason the pressure pulses produced by the artificial heart were found closely to resemble those produced by the healthy heart.

Thromboses and mechanical haemolysis have continued to be a major complication after the insertion of prosthetic valves into the human heart,[5] and this problem will also have to be solved for any valves that are to be incorporated in a complete artificial heart. Shumacker and his colleagues have designed one-piece silicone rubber valves which fold closed into a "C" or "S" shape for the inflow and outflow valves, respectively, and which open into a full circle. This design will permit the central flow of blood and should diminish both the turbulence around and the stagnation beyond the caged-ball valve—serious disadvantages which are unavoidable with the use of a central obturator. Thus the first heart model developed by Shumacker and his colleagues has not so far apparently been associated with thrombotic or haemolytic complications. Probably artificial hearts developed in the future will incorporate aortic valve homografts or heterografts. Another, and even better, possibility would be to replace the valves altogether by a roller or finger type of pump, which would maintain unidirectional flow by the compression of Silastic tubes.

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