learned by the patient who avoids it altogether, and it requires skilled psychological techniques to help the patient to undergo the required learning. In both alcoholism and obesity it has been found that self-help groups of sufferers are often able to achieve more than the physician can with the individual patient, and a recent controlled trial from the Institute of Psychiatry in London showed that socially cohesive groups of agoraphobics benefited more from a communal flooding experience than did non-cohesive groups. Other methods of behaviour therapy such as desensitization have been disappointing, but clearly the whole field of behaviour therapy requires more investigation, particularly combined with physical treatments.


### Scombroid

Intoxication after eating fish was named ichthyosarcotoxism by Halstead and reported by him to comprise six distinct clinical entities associated with different groups of fish. One of these groups is the suborder Scombroidi, which includes tuna and mackerel, though other less familiar genera seem to be responsible more often for poisoning. Numerous outbreaks have been reported from Japan, where raw fish is often eaten.

Recent interest has been aroused by a large outbreak last year in the U.S.A., affecting 232 persons from four states who had eaten commercially canned tuna fish from two lots produced by one canner. The incubation period ranged from 15 minutes to three hours with a mean of 45 minutes, and the symptoms, which lasted up to eight hours, included nausea, vomiting, abdominal cramps, diarrhoea, flushing, headache, urticaria, and a burning sensation in the mouth. Hospital treatment was not required, and there were no deaths. Assays on nine samples of the suspected fish showed histamine levels ranging from 68 to 280 mg/100 g of fish muscle, as compared with a normal of 3 mg/100 g.

It seems that the toxic entity in this disease is composed of histamine (resulting from the enzymatic decarboxylation of histidine by certain organisms), saurine (named after "sauri"), a dried fish delicacy associated with scombroid poisoning but not yet defined chemically), and possibly other compounds. Of organisms capable of forming histamine from histidine, Kimata reports that *Proteus morgani* has been most commonly cultured from incriminated raw fish.

Ienitsea states that fish, fish products, and some types of cheese may develop large amounts of histamine, but that histaminolytic bacteria probably break it down. Shewan mentioned a taboo on the consumption of mackerel in certain localities in Scotland; this was thought to be due to the presence of histamine, which may be produced in quantity when these fish are stored at temperatures above 8°C.

Closer scrutiny is needed of the relationship between spoilage organisms and their toxic byproducts. Enumeration of the various organisms in raw fish and open-pack cooked fish suspected to cause this scombroid type of food poisoning would be useful, together with careful examination of stool samples. The outbreak of scombroid fish poisoning in the U.S.A. is said to be the first reported from commercially canned fish. It would be interesting to know whether similar incidents can be recalled in Britain.

### An Artificial Pancreas?

Insulin was first used in the treatment of diabetes in 1922. Many routes for its routine administration have been attempted but only subcutaneous injection has stood the test of time. It is remarkably free from serious side effects: sepsis and allergy are rare, and minor local reactions or fat atrophy are common but not dangerous. Only hypoglycaemia remains both disagreeable and at times hazardous, and anything which could eliminate it would be welcome. A system of insulin delivery on demand is needed; pancreatic transplantation, islet transplantation, or a mechanical artificial pancreas are the methods for achieving it.

Pancreatic transplantation has been performed successfully, but the mortality is high and even in the U.S.A., where most experience has been obtained. There were in 1973 only two long-term survivors from 32 operations. This price is clearly too high for the theoretical advantage of halting the progress of diabetic complications in some patients, and certainly too high as an exchange for insulin injections. Admittedly many of the pancreatic transplants were performed in conjunction with renal transplants in patients with advanced renal failure: even then the mortality remains much greater than for renal transplant alone.

Islet transplantation looks more promising and has been successful in diabetic rats. The techniques are still experimental, and problems of rejection have yet to be overcome. Relatively large amounts of embryonic islet tissue are needed, and the methods of organ culture, with alteration of immunogenicity, are still being developed. The development of an artificial pancreas sounds an exciting alternative.

An artificial pancreas system consists of a glucose sensor, which rapidly determines the concentration of blood or tissue glucose and which controls an insulin infusion apparatus. Techniques for continuous monitoring of glucose concentrations have been developed over many years. The most refined glucose sensor is a glucose-oxygen fuel cell, only 12×12×2 mm in size. It has been implanted subcutaneously in animals and has responded to blood glucose changes for up to 117 days. Most systems depend on continuous flow of blood through a glucose analyser, which at its best requires a blood flow of 0.05 ml per minute with a delay of 3½ minutes before the blood glucose reading is recorded. Using this system, workers in Toronto have linked the blood glucose...
recorder to a mini-computer which regulates insulin or glucose infusion pumps. They tested the system in pancreaticectomized beagles and showed that glucose tolerance could be made normal with physiological amounts of insulin. They then examined its effectiveness in three unstable diabetic patients and succeeded in controlling blood glucose levels within very narrow limits at almost physiological levels, avoiding serious swings in either direction, for some 10-12 hours. Insulin infusion rates varied, but once blood glucose levels had been lowered to the normal range the infusion rate was often below 100 milliunits per minute. The total amount of insulin infused after stabilization was less than that usually needed by subcutaneous injection.

The artificial pancreas is a magnificent technical achievement and an elegant research tool for further investigation of carbohydrate metabolism. Already interesting observations have been made. Insulin requirements are reduced by continuous intravenous insulin infusion; and the rates used in Toronto were comparable to the 50-100 milliunits per minute described recently for the treatment of diabetic ketoacidosis. These observations corroborate experimental evidence showing that serum insulin levels obtained in this way are sufficient to achieve maximal hypoglycaemic activity. It is also interesting that the biphasic insulin response seen during glucose tolerance in normal subjects has been mimicked by the artificial pancreas, and this observation again raises the possibility that absence of this response could be important in both the evolution of diabetes and perhaps its complications.

The artificial pancreas brings us one step nearer to the diabetics' dream of eliminating injections and hypoglycaemia. However, years of development will certainly be needed for its miniaturization and implantation, and even then it seems unlikely to have universal application.

4 Cahill, G. F., et al., Diabetes, 1972, 21 (suppl. 2), 703.
8 Sonksen, P. H., et al., Clinical Science and Molecular Medicine, 1973, 45, 633.

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**Weight Loss and Coronaries**

The effects of obesity on the incidence and prognosis of coronary artery disease remain uncertain. Few would dispute that angina of effort is often improved by reduction in weight. Obesity is less socially acceptable than in the past—the bottoms of Rubens and the thighs of Titian are no longer fashionable—but for a doctor to advise that a task so difficult as weight reduction may improve the outlook in coronary disease requires convincing evidence that the treatment is likely to be effective.

Ancel Keys and his colleagues suggested that neither relative weight nor obesity assessed by skinfold thickness had any significant effect on future coronary heart disease if the effects of increased age, serum cholesterol, blood pressure, and smoking were discounted. More recently, however, research at Framingham, Massachusetts, has shown an apparent close correlation between changes in weight and changes in four atherogenic risk factors. Ashley and Kannel analysed the results of a 16-year follow-up of 5,209 adults examined every two years. Of these, 85% had attended every possible examination during the study period and less than 2% were totally lost to follow-up. Relative weights (the ratio of weight to the median weight for sex and height) were calculated and changes in relative weight were correlated with changes in serum cholesterol, systolic blood pressure, blood uric acid, and blood glucose.

Close correlations were found between changes in weight and changes in cholesterol and systolic blood pressure. These correlations were closer in men than in women, showed no trend with different age groups, and the initial relative weight seemed to have little influence. Comparison of changes in uric acid and relative weight showed similar features, but the correlation was less close. Changes in blood glucose correlated least well with changes in weight—but still significantly so—and these changes did vary with the degree of adiposity at the initial examination.

As the Framingham authors point out, the finding that these four qualities (all of which bear a statistically significant relationship to the incidence of coronary disease) tend to rise with weight gain and fall with weight loss is not new. From their previous results and their present data they attempt to predict, using multiple logistic equations, the effects of weight change on the incidence of coronary disease. They claim that for each 10% reduction in weight in men there should be about a 20% decrease in coronary incidence, and for every 10% increase in weight a 30% increase in coronary incidence. These effects are expected to be somewhat less pronounced in women and in older persons. The paper gives no account of the reasons for changes in weight nor where weight reduction had taken place is there any information about how this was achieved nor about whether it was accompanied by increased exercise or not.

Considerable caution is necessary before these important conclusions can be accepted wholeheartedly. The report is preceded by a leading article which indicates the potential statistical hazards of multiple logistic equations. Possibly much more open to criticism is the implied assumption that the prognosis for those who have had previously raised serum cholesterol, systolic blood pressure, blood glucose, or uric acid can be considered comparable, once these qualities have been reduced, to the prognosis for those in whom these potentially atherogenic risk factors have never been raised. Proof of the effects of weight reduction in diminishing the incidence of coronary disease can be assessed only by clinical experiment, a difficult thing to achieve in view of the numbers necessary. The authors themselves stress these reservations and merely claim, reasonably enough, that correcting overweight might improve an individual's prognosis.

There can now be little doubt that an increase both in serum cholesterol and in triglycerides predisposes to overt and early appearances of the clinical manifestations of coronary artery disease. A prospective study in Stockholm found that the occurrence of new events from coronary artery disease were linearly related to increased plasma triglycerides and cholesterol and smoking but not to an increased weight/height index.

Coronary artery disease accounts for about half the male deaths in the United States, with the incidence in Britain lagging little behind. Understandably many enthusiasts have advocated different lines of prevention and treatment, but none to date has been shown convincingly to be successful—with the possible but important exception of reducing cigarette smoking, which does appear to decrease the incidence of sudden death. The most attractive suggestions are to increase...