shock has been produced by mere dissection of the sciatic nerve, which would be quite innocuous under deep ether anaesthesia. In my experiments I have found that cocainization of the carotid sinuses and the vagi enhances the depressor responses, but the exact significance of this point I have not yet made out.

This variety of shock, together with that produced by loss of carbon dioxide, is probably what has hitherto been known as primary shock—a state well recognized to be fundamentally different from secondary wound shocks by workers such as Cowell, Bayliss, Dale, and Wallace. But the experiments which I have just quoted suggest that this variety of shock may be more important in accident cases and in the operating theatre than is generally supposed. In relation to operations an interesting piece of work has recently been published by Richet and Dublineau, showing that the vaso-dilator centre seems to develop a preliminary higher excitability under anaesthetics. It seems likely that the pressor mechanisms become anaesthetized before the depressor mechanisms.

Now a very interesting point is that experimentally, under apparently similar states of anaesthesia, depressor shock cannot always be demonstrated. This time last year I had no difficulty in producing it; indeed, my attention was drawn to it by the fact that on many occasions I produced it accidentally by operations which are usually innocuous. On the ground of these experiments which appeared so certain I decided to give this lecture its present title, but when I began to prepare for it in detail in September and October I found myself totally unable to produce shock in this way. It was rather disconcerting. The results were so clear-cut in February and September that I decided to wait for a few months. Now I am relieved to find that I can produce the depressor shock easily again, but as yet I have not been able to define exactly the circumstances under which it arises. The difference may be due to the seasonal variability in the sympathetic system of cats or may be solely a question of exhaustion by cold. This is, however, by no means solely a purely experimental point, but one of clinical importance, because it is found that some patients are much more easily shocked than others, and that fear, emotion, and cold, which stimulate the sympathetic and may cause exhaustion of the suprarenals, are definitely looked upon as aggravating causes (Fraser).

Mixed Shock.—From what has been said it is almost obvious that in some instances the varieties of shock must overlap—for example, chemical shock may supervene on nervous shock; indeed, it may almost be assumed that it will if a nervous shock is allowed to persist, because oxygen want will of itself lead to tissue death and capillary dilatation.

CONCLUSION

The whole clinical problem now requires to be completely reinvestigated in the light of modern experimental facts, with a view to finding methods for diagnosis of the different varieties. A large amount of the existing literature is completely valueless. I do not pretend that what I have said is in any way final, and a large number of the facts are not new; all I hope is that it may serve as a simple basis from which systematic clinical study may be made. But I think you will agree that a fuller knowledge of the experimental facts makes the general approach to the subject easier.

I have omitted those methods of producing shock which I do not think are related to surgical practice, and (as I said at the beginning of the lecture) I have also deliberately omitted a large number of facts regarding shock. Many are secondary to the fall of blood pressure, acidosis, loss of muscle tone, lowered metabolism, etc. I have done so because I want to make it quite clear that a

number of clear-cut varieties of shock exist experimentally. Clinically they have not been differentiated except very crudely as primary and secondary, although, as I have indicated, there is every reason to believe that distinct varieties exist. To the physiologist and biochemist may be left the problem of how best to deal with histamine, a solution to which is one of the most important requirements of modern surgery. But meantime we also want in relation to shock a better clinical surgery capable of making a more adequate differential diagnosis—not the dramatic surgery of the operating theatre, but the unexciting and unremunerative study of the patient in bed, the work which is too often left to anybody willing to do it, the surgery which involves a careful study of available experimental data, which would be a stepping-stone to a new surgery. If more surgeons came into the physiological laboratories and saw the different varieties of shock for themselves, there would be a much better appreciation of the facts, and soon we should have the clinical investigations which are so desirable.

SUMMARY

Experimental shock may be divided into several distinct varieties which, apart from that produced by haemorrhage and cardiac failure, may be divided into chemical and nervous.

The chemical variety is typified by histamine shock experimentally and clinically by a delayed shock associated with gross destruction of tissue. This variety is enhanced by anaesthetics.

The nervous varieties may result from physical damage to the vasomotor centre or its efferent paths, from afferent impulses leading to loss of carbon dioxide (acapnia), or from inhibition of the centre. Acapnia and inhibition account for the shock which follows immediately on injury. Shock dependent on afferent impulses is prevented by deep anaesthesia and reduced by morphine. The chemical and nervous varieties may coexist and enhance each other.

INSULIN AND GLUCOSE IN THE TREATMENT OF HEART DISEASE

WITH SPECIAL REFERENCE TO ANGINA PECTORIS

BY

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The past twenty years have witnessed an increasing interest in the therapeutic nutrition of the heart. The fact that digitalis is the outstanding means of combating serious heart disease and failure is indisputable, but in certain types of heart failure, particularly those associated with normal rhythm, this drug confers but slight or transient benefit. Attention has therefore become focused upon intensive glucose administration as a supporting measure, or sometimes a last resort. Dangerous states of circulatory insufficiency often occur in the second half of life when arterial, and specially coronary, degenerations have frequently set in, and in such circumstances it is reasonable to suppose that an increased content of nutritive material in the blood should be beneficial. It may well be also that a relative failure of carbohydrate utilization from endocrine causes may constitute part of the disability in chronic myocardial disease. Furthermore, the continued overaction of the heart and the enhanced basal metabolic rate in congestive failure demand ample supplies of carbohydrate, which may not be forthcoming unless special provision be made.

One of the earliest reports on glucose therapy was published before the war by Goulston,¹ who recorded definite benefit resulting from oral glucose administration in cardiac failure. These observations were confirmed by Budingen,² who claimed that glucose therapy supplemented the action of digitalis. Intravenous administration of glucose has been employed by Klewitz and Kirchheim,³ who reported subjective improvement both in patients suffering from chronic heart failure and in anginal syndromes. These observers also found, by animal experimentation, that alternation of the heart could be relieved by addition of glucose to the perfusion fluid; their records received support from the work of Edwards and Page,⁴ who were able to produce alternation in the course of experimental hypoglycaemia in dogs, and to relieve this arrhythmia by the subsequent provision of glucose. From the clinical standpoint the disappearance of alternation during glucose therapy has been recorded by Kisthinos and Gomez,⁵ and Loeper, Lemaire, and Mougeot.⁶ Loeper and Lemaire⁷ brought forward clinical evidence to suggest that the action of digitalis, strophanthin, and quinidine is augmented by the daily administration of 50 grams of sugar. The intravenous injection of glucose solution has been claimed by Marvin⁸ to be of value in the treatment of paroxysmal cardiac dyspnoea. Both this condition and alternation must be regarded as expressions of grave myocardial damage or stress, and the fact that they may be relieved by glucose administration would suggest either that a relatively inadequate nutrition was previously available, or that a superfluity of glucose in the myocardial irrigation is in some way remedial.

GLUCOSE-INSULIN THERAPY

The advent of insulin in 1922 opened up new possibilities in the treatment of cardiovascular diseases, and as early as 1924 the potentialities of glucose-insulin therapy were envisaged by Pick.⁹ Two years later Osato¹⁰ published an account of the favourable effect of such treatment upon six patients suffering from congestive failure. More recently Kisthinos and Gomez⁵ have found that although sugar administration often provokes diuresis in heart failure, benefit may accrue even when this does not occur. These authors applied the remedy to patients who had been under treatment with digitalis on previous occasions, and they concluded that glucose had a direct action upon the heart muscle, and that, with or without insulin, it might be efficacious in failure when other remedies had been unsuccessful. They observed the abolition of bigeminy in one case, and considered that insulin therapy might be usefully applied even when failure was of thyrotoxic origin. Rimbaud, Balmès, and Anselme-Martin¹¹ treated twenty-one patients with congestive failure with glucose and insulin. They found that in "irreducible failure" this method could produce valuable results, either alone or in conjunction with digitalis, but that little if any benefit was to be expected in thyrotoxic myocardial disease. The technique in their investigations was as follows: five units of insulin subcutaneously, followed in fifteen minutes by 50 grams of glucose or laevulose by the mouth, daily. If no benefit ensued in five days the doses of insulin and sugar were doubled, and the treatment continued for ten or twelve days. Similar methods have been adopted by Macchioro,¹² Weiner,¹³ Jorge and Sobrinho,¹⁴ and Loeper, Lemaire, and Degos¹⁵ with corresponding results. The electrocardiographic changes in patients treated by insulin and glucose for heart disease have been studied by Mathieu, Colleson, and Simonin.¹⁶ Among ten patients suffering from chronic myocardial disease, of whom three also had renal impairment, they found a shortening of the QRS complex and increasing amplitude of the R wave in all

leads. In two instances the reappearance of T waves previously absent was observed. These changes were noticed after periods of treatment varying from eight to twenty-one days.

It has been said concerning new remedies that it is insufficient for the introducers to record benefit or cure in 100 per cent. of their cases: confirmatory investigations must also give positive results in other hands. The reports reviewed above constitute an important body of evidence suggesting that glucose-insulin therapy is valuable in heart disease and failure. There is, however, no consensus of opinion in this matter. Carusi¹⁷ has found no beneficial results from the treatment of failure by glucose and insulin. Moreover, Lasch¹⁸ has formed the opinion that these remedies are not only useless in this sphere, but also possibly harmful.

ANGINA PECTORIS AND PANCREATIC EXTRACTS

It was observed by Hetenyi¹⁹ that the insulin treatment of diabetics who also suffered from angina pectoris sometimes resulted in relief from the anginal attacks. The application of this finding to the treatment of non-diabetics with angina pectoris was made by Ambard, Schmid, and Humbert,²⁰ who reported a case in which attacks had ceased after treatment with insulin and glucose. Beale²¹ has observed a comparable instance in which anginal attacks ceased after injection of small doses of insulin, while Bickel²² has reported a similar result using insulin and glucose. Vaquez has extended these investigations to the treatment of related conditions such as peripheral arterial disease, but has obtained inconstant results, which he attributed partly to variations in the content of pancreatic extracts other than insulin in the preparations he employed. These results led him, in collaboration with Giroux and Kisthinos,²³ to use a de-insulinized pancreatic extract (angioxyl) prepared according to the researches of Gley and Kisthinos.²⁴ He found that in fourteen out of twenty cases of angina pectoris treated with injections of angioxyl no further attacks occurred. The therapeutic action of angioxyl has been subsequently investigated by Woolf, Findlay, and Dessen,²⁵ and Nuzum and Elliot.²⁶ Their results were in general agreement with those obtained by Vaquez, Giroux, and Kisthinos.

It appears from the account given by Vaquez of his investigations that he attributes the influence of insulin on the cardiovascular system to the hypotensive substances that it contains in greater or less amount. If one takes the view that anginal pain is of aortic origin and is precipitated by excessive pressure in the aorta it is naturally attractive to view the action of insulin in this light; further, since it has been frequently demonstrated that a transitory elevation of blood pressure accompanies some attacks of angina pectoris, it follows that substances producing a reduction of blood pressure will relieve some sufferers from angina pectoris. More and more evidence is accumulating to show that anginal pain in general arises not in the aorta, but in the heart muscle, and is attributable essentially to deficiency in coronary blood or blood flow rather than to alterations in blood pressure. Granting this coronary hypothesis, the results obtained by Vaquez are readily explicable on the ground that hypotensive substances produce a fall in blood pressure by virtue of generalized arterial dilatation in which the coronary arteries share.

GLUCOSE-INSULIN THERAPY IN ANGINA PECTORIS

Few diseases are more variable in their response to treatment than angina pectoris. Every physician must recall certain patients who, despite every care in investigation, management, and treatment, have failed to experi-

ence diminution in frequency or severity of attacks. Further, the course of the disease is commonly one of unexplained exacerbations, modifications, and remissions, even in the absence of any treatment whatsoever. Angina pectoris thus belongs to the group of maladies in which spontaneous changes for better or worse render the assessment of the value of any particular remedy extremely difficult. In these circumstances any medicament or method of treatment which gives a prospect of possible benefit deserves consideration and trial. It is for this reason and in the hope that other clinicians may apply the method described below that I venture to publish the following case reports. Certain investigations that have been made by myself and others into the metabolic and cardiographic aspects of the problem of cardiac nutrition will be discussed subsequently, but it may be mentioned here that insulin and glucose were applied to the treatment of angina pectoris in the belief that a defect of carbohydrate combustion in the heart muscle is at the root of anginal pain, and in the hope that by this means normal glycogen utilization in the heart might be promoted and the pain thus avoided.

During the past year upwards of forty patients suffering from angina pectoris have been considered from the standpoint of treatment by insulin and glucose. For reasons put forward above, and since it was required to assess the value of the treatment, it was considered advisable to treat only patients who fulfilled certain rigid criteria: (1) the patients were suffering from undoubted coronary syndromes; (2) they were subject to frequent attacks, usually several attacks in a week or daily attacks; (3) the attacks were of at least one or two months' duration; (4) the clinical condition at the time of treatment was static—neither improving nor deteriorating. In most of the patients one or more remedies had already been tried without avail—rest, vaso-dilators, sedatives, etc.

The circumstances and technique of treatment were also definitely decided upon. The patients continued taking any remedies that they had previously been taking. They continued in the same regime of work or rest during, as before, treatment. Records of frequency, severity, and duration of attacks were kept for the period prior to, during, and after treatment. The method consisted in giving five units of insulin before breakfast and before the evening meal, each dose being followed by 30 grams of glucose taken with the meal. This treatment was administered over periods varying from two weeks to seventeen weeks. In certain patients otherwise suitable for treatment, practical difficulties prevented the application of this systematic technique. In such cases the treatment was not instituted.

CASE REPORTS

Case 1.—Male, aged 57. Arteriosclerosis; angina pectoris. Onset in January, 1932, of left supramammary pain on effort. Pain relieved by five to ten minutes' rest. The frequency of the attacks increased to one daily. Diuretin, trinitrin, luminal, and rest in bed had all failed to prevent attacks. Without altering in any way the mode of life, insulin treatment was started in June. Within one week he was free from definite attacks, although slight mammary pain occurred occasionally on effort. He was kept on the treatment for seventeen weeks, and at the end of this time his effort tolerance had very much improved; very slight mammary pains occurred occasionally on effort, the duration being "a minute" as compared with the previous duration of about fifteen minutes. In October he discontinued the treatment, continuing the same regime, and within a week he had had two severe anginal attacks. Insulin treatment was reinstated, and he has remained well since.

Case 2.—Male, aged 52. Hypertension; angina pectoris; chronic bronchitis and emphysema. This patient had been under treatment for the lung condition for one year when he began to notice "numbness" and oppression in the centre

and left side of the chest and in the left arm. These symptoms were concisely related to effort and always relieved in a minute or so by rest. In July, 1932, after two months of unchanging symptoms, insulin treatment was instituted, the patient continuing his usual mode of life exactly. After six weeks the symptoms were much less easily evoked and much less intense. After thirteen weeks he was completely free from symptoms, and has remained so since discontinuance of insulin and glucose on October 11th.

Case 3.—Female, aged 43. Syphilitic aortitis; aortic incompetence; chronic bronchitis. For three and a half years the patient had experienced attacks of pain in the left of the sternum, spreading down the inner side of the left arm and forearm. Pain usually related to exertion, but sometimes on getting up in the morning. Duration fifteen to twenty minutes; relieved by rest. Despite two and a half months in bed in hospital, patient constantly woke with pain and had two or three slight attacks during the day, trinitrin, iodide, and mercury giving no relief. At this stage insulin and glucose treatment was started. For one week slight pain was felt while washing in the morning, but during the following month the patient remained completely free from pain, except for one bout at the onset of an attack of tonsillitis. Some oedema which had appeared prior to treatment rapidly disappeared, and the patient was discharged fit to be up and about her home. For the first months after her discharge insulin treatment was discontinued; she wrote, "The pain all came back down the left arm, but after starting the injections, in about a week the pain went again," and she has been free since.

Case 4.—Male, aged 70. Hypertension and arteriosclerosis; aortic atheroma; angina pectoris. In the summer of 1930 onset of attacks of pain just to the right of the mid-sternum; always brought on by exertion, with a tendency to radiation across the sternum and up to the throat. Relief from rest and amyl nitrite. Sedatives, diuretin, trinitrin, and glucose alone gave a slight relief, and he was still getting attacks most days when insulin treatment was started. He continued with it for six weeks. At the end of this period he was able to walk four miles without getting pain, whereas fifty yards had previously been sufficient to induce an attack. Very slight pains occurred occasionally, but although he has discontinued the insulin for six months his great improvement is maintained.

Case 5.—Male, aged 56. Syphilitic aortitis. For eighteen months prior to admission to hospital there had been oppression over the lower third of the sternum on effort. There had also been nocturnal attacks in which the patient awoke with pain spreading across the left costal margin, amyl nitrite giving relief. He was admitted with some oedema of the legs, and in four weeks up to the end of October he had four nocturnal attacks. Insulin and glucose treatment was then instituted, and thereafter, up to the time of his discharge, five weeks later, he had only one attack of pain, and has felt very marked subjective improvement.

Case 6.—Male, aged 48. Angina pectoris; recent cardiac infarction; angina decubitus. The patient, whose father died of angina pectoris, was well until eighteen months ago, when he began to notice pain at the upper third of the sternum during exertion. Early in February, 1933, he had an extremely severe attack at night lasting six hours, which almost certainly represented an acute coronary occlusion. After that he remained in bed for four weeks, and was troubled nearly every night with attacks of sternal pain and oppression, which would awaken him from sleep and compel him to sit up. Various remedies had given no relief, and for the first ten days of March he was given five units of insulin and two heaped tablespoonfuls of glucose daily. No further nocturnal attacks were experienced after the first day of this treatment, nor have they recurred since it was discontinued.

DISCUSSION

I have recently drawn attention²⁷ to a group of conditions in which diffuse parenchymatous myocardial damage exists independently of any disease of the coronary system. Examples of these states are general malnutrition or starvation, hypoglycaemia, myxoedema, and severe diabetes. The evidence that perversion of myocardial

function accompanies these disorders of malnutrition consists in a characteristic deformity of the electrocardiogram, which shows depression of the RT interval or inversion of the T wave in one or two or all leads. It is clear that an important distinction has to be drawn between these changes (which are throughout in the direction of depression or inversion) and those produced by focal myocardial damage as in coronary sclerosis. In the latter condition the changes produced in Lead I are in general opposite in sense to those produced in Lead III. In all of the above-mentioned nutritional disorders the electrocardiographic abnormality disappears when the metabolic fault is rectified.

In a discussion of the electrocardiographic changes occurring during the control of severe diabetes, I have indicated in collaboration with R. A. Hickling,²⁸ that a defect of nutrition underlies these electrical phenomena, and that deficient glycogen utilization is probably the important factor. Reasons have also been given in these publications for the belief that defective glycogen utilization is the cause of the electrocardiographic abnormalities in the other conditions of disordered metabolism already mentioned. Allusion to the fact that disturbances of general glycogen metabolism, as in diabetes and hypoglycaemia, may give rise to anginal pain has been made elsewhere,²⁷ and the significance of these facts was then fully discussed. But if anginal pain has a basis of deficient glycogen utilization in some instances, it seems likely that this factor may play a part in anginal syndromes brought about by local ischaemia, as in coronary spasm or sclerosis. Further, the recent work of Lewis²⁹ has thrown important emphasis upon the metabolic origins of anginal pain in contradistinction to anoxaemic factors. The attempt to inhibit anginal pain by the administration of glucose and insulin was the natural outcome of the foregoing researches and considerations.

CONCLUSION

It is here suggested that such influence as ordinary insulin exerts upon heart disease in general is by virtue of insulin *per se*, as distinct from the effect of incidental hypotensive substances contained in the pancreatic extract. Reference has been made to the considerable body of clinical reports bearing witness to the efficacy of glucose-insulin therapy in chronic heart disease and congestive failure. The fact that opinion is not unanimous suggests that selection of cases is necessary upon a basis hitherto unrecognized, but does not throw serious doubt upon the value of this therapeutic measure. It will be observed that the use of insulin and glucose in the treatment has not been empirical, but is based upon the belief that the promotion of glycogen utilization in the heart may prevent the accumulation of substances producing anginal pain.

But there are almost certainly other factors concerned. If insulin benefited patients with arterial disorders entirely by its effect on glycogen utilization (or even by a hypotensive action as Vaquez suggests) it might be expected that the results would be immediate and at once maximal. This is not found to be the case. For example, in Cases 1, 2, and 3 already described, the frequency and severity of attacks progressively diminished over periods of one to several weeks. It is clear that freedom from attacks is *per se* beneficial, but it cannot be doubted that the facts and arguments presented indicate that insulin has a further effect upon functional efficiency and nutrition of the coronary arteries. It is well known that accumulations of fat in the deeper layers of the intima constitute one of the earliest stages of atheroma. When such fatty deposits are accompanied by cell necrosis, the degenerative process is, as Aschoff³⁰ has stated, irremediable. On

the other hand, the accumulations of fat in the early atheromatous processes are removable, as has been shown by Anitschkow and Chalutow³¹ in dieting experiments. It is here suggested that the removal of such fat is part of the action of insulin in angina pectoris. Evidence in support of this view is forthcoming from the work of Himwich and Spiers,³² who have shown in experiments upon dogs that injections of insulin cause reduction in plasma fat. Insulin promotes glycogen utilization, and by virtue of this effect stimulates the proper combustion of fats. Such an action on the coronary arteries would explain the cumulative benefit sometimes seen in the course of treatment by insulin and glucose.

SUMMARY

1. The evolution of glucose and glucose-insulin therapy in cardiovascular disease is reviewed.
2. While there is evidence that these methods are of value in congestive heart failure, it appears that glucose-insulin therapy is likely to be of special benefit in arterial, and particularly coronary, syndromes.
3. An account is given of the successful treatment by insulin and glucose of patients suffering from intractable angina pectoris, and six case reports are given.
4. Reasons are given for believing that anginal pain is related to faulty carbohydrate metabolism in the heart. It is held that insulin acts immediately by its stimulating effect upon glycogen metabolism in the heart and progressively by promotion of the combustion of fat, this process leading to resolution of early atheromatous changes in the coronary arteries.
5. A technique for the application of glucose-insulin therapy in angina pectoris is described, and it is suggested that this method deserves careful and extended trial.

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