Drug Treatment of Disease

CORONARY ARTERY DISEASE: PART I

BY

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ANGINA PECTORIS

The most important aspect of the treatment of angina is adjustment of the patient's way of living in order to reduce the frequency and severity of attacks. Treatment by drugs is only of secondary importance. More can be achieved by thoughtful rearrangement of the patient's daily routine and activities than by the administration of drugs. The family doctor with his knowledge of the patient's responsibilities is often best able to offer this advice. Reduction of the patient's physical activity will be necessary. Frequently this can be attained by advising small changes such as giving up the use of a bicycle, never hurrying, avoiding hills, and moving the patient's bedroom to the ground floor. Sometimes a change of occupation may be necessary, or retirement may even have to be recommended. On the other hand, unduly severe and artificial restrictions are not advisable, and patients should be encouraged to find out the limits of their exercise tolerance and then to keep within these limits. Every patient requires individual assessment and advice.

Regular periods of rest are essential to the patient with angina. A good night's rest of nine or ten hours, with at least eight hours' sleep, should be obtained, and, if necessary, a hypnotic can be prescribed for this purpose. A complete day in bed at the week-end is often helpful. Patients must endeavour to make it an invariable rule to rest for 20 or 30 minutes after every meal, and heavy meals should always be avoided. For the anxious, restless, worried, and over-active patient, phenobarbitone $\frac{1}{2}$ gr. (30 mg.) can be very valuable twice or three times daily.

Many patients with angina are too heavy. Reduction of obesity, therefore, is important. With the patient's co-operation it can be achieved by a low-calorie diet, and this often leads to improvement of exercise tolerance; dextroamphetamine sulphate and thyroxine are unnecessary and undesirable for weight reduction, since they can produce tachycardia and increase the work of the heart. Smoking should be discontinued. In a few patients angina may have been precipitated or aggravated by anaemia, and will disappear or decrease once the anaemia is corrected.

In a minority, myxoedema can contribute to the development of angina. The administration of thyroid $\frac{1}{2}$ gr. (30 mg.) once or twice daily, or L-thyroxine sodium 0.05 mg. daily, may reduce the incidence of pain, probably by increasing the cardiac output and coronary blood flow. Patients with myxoedema are difficult to manage, since too much thyroid can increase the myocardial demands for oxygen more than the coronary blood flow, with resulting ischaemia of the myocardium and aggravation of angina. Often there is an optimum level of thyroid above or below which angina may occur.

When during a period of a week or two patients develop increasingly frequent episodes of angina, at first on effort and later at rest, a myocardial infarct may be impending. Such patients should be regarded as needing

emergency treatment, and, despite their protests of indispensability, admitted to hospital or a nursing-home, where they must be kept strictly in bed. Anticoagulants often appear to have a protective action in these cases (Nichol *et al.*, 1954), and they should be administered for at least three weeks after the episodes of spontaneous pain have ceased. Anticoagulant therapy will be considered in detail in a subsequent article on the drug treatment of myocardial infarction.

It has been emphasized that the drug treatment of angina is of less importance than the general management of the patient. Nevertheless, drugs which relieve anginal attacks should be prescribed to allow of a reasonable amount of activity which otherwise could not be accomplished. Moreover, many patients feel reassured by the administration of a pill, and accordingly their angina often improves. There are many drugs available for the treatment of angina but only a few are of proved therapeutic value.

Nitrites and Nitrates

Short-acting Preparations

Glyceryl Trinitrate.—This is the most widely used and generally beneficial of this group of drugs. In the majority of patients the sublingual administration of 1/130 gr. (0.5 mg.) will relieve an acute episode of angina within two or three minutes or prevent its development when taken in anticipation of an acute attack. Occasionally as much as 1/65 gr. (1 mg.) is necessary to relieve a single episode of pain. Glyceryl trinitrate is also available in the strengths of 1/100 gr. (0.65 mg.), 1/120 gr. (0.54 mg.), and 1/200 gr. (0.32 mg.), and unless otherwise specified it is dispensed in a chocolate base. If chocolate is disliked, glyceryl trinitrate can be obtained in any of these strengths in a base of lactose and glycerine as a white tablet. As its action is short, lasting no longer than 30 to 45 minutes, the dose can be repeated many times each day according to the patient's requirements. Some patients will consume 200 tablets in a week, while others may not require more than 1 or 2. Some, by modifying their way of life, need none at all. The administration of glyceryl trinitrate is commonly associated with peripheral vasodilatation and often with a headache and pounding in the head. Patients with severe angina seldom complain of these side-effects, but if they are troublesome a dose of 1/200 gr. (0.32 mg.) may still relieve angina yet be associated with only minimal side-effects. Patients should always carry an adequate supply of glyceryl trinitrate. The tablets lose potency during the course of a year, and should be kept in sealed bottles, away from the light and in a cool place.

Amyl Nitrite.—This is an effective short-acting volatile nitrite. It is not advocated as a practical treatment of angina, since it is unnecessarily strong and is administered by inhalation; the noise of breaking the glass container, the pungent smell, and the violent facial flush are embarrassing in public. It acts in 10 to 15 seconds but lasts only for 2 or 3 minutes. It has been superseded by glyceryl trinitrate.

Long-acting Preparations

The long-acting drugs in this group are usually disappointing in reducing the incidence or severity of angina but are worthy of trial. There are several in current use, but only two can be recommended.

Pentaerythritol Tetranitrate.—This preparation is of value only in a small percentage of patients, probably less than 20%, but should be given a trial. It is marketed as "mycardol" 30-mg. tablets, and as "peritrate" 10-mg. tablets. It is equally effective sublingually or orally. Oral doses of 30 mg. four times daily an hour before meals are valuable for the patient who experiences pain after a heavy meal, but larger doses may cause dyspepsia. Its action begins after 30 minutes and lasts about 4 hours.

Erythrol (Erythrityl) Tetranitrate.—This preparation is more or less comparable in action to pentaerythritol tetranitrate when given orally in doses of 15 mg. three or four times daily, and is effective in a minority of patients. If before each meal a tablet is allowed to dissolve slowly in the mouth, a greater proportion of patients obtain relief from this preparation than when it is swallowed (Riseman *et al.*, 1958). Its sublingual administration is accompanied by mild peripheral vasodilatation. Its action of 6 hours is valuable, but its continued use sometimes causes a headache.

Other Nitrites and Nitrates.—Sodium nitrite, mannitol pentanitrate, mannitol hexanitrate, and triethanolamine trinitrate biphosphate have little effect and are not recommended in the treatment of angina.

Iproniazid

This is a derivative of isoniazid and is a powerful inhibitor of amine oxidase. Its action in suppressing angina is not yet understood. It probably reduces the appreciation of pain by the cortex (it also relieves the pain of rheumatoid arthritis and carcinomatosis), and it produces a mild euphoria. It potentiates the action of noradrenaline and may, therefore, stimulate coronary vasodilatation. At a dose of 50 mg. three times daily, iproniazid ("marsilid") produces relief from angina in a majority of patients (Cesarman, 1958; Towers and Wood, 1958), and would therefore seem to be a useful drug. Unfortunately it is associated with many serious side-effects, such as jaundice and liver damage (which may be fatal) and stimulation of the autonomic system. The frequency of these toxic effects greatly limits the therapeutic value of the drug. It may, however, have a part to play in severe and intractable angina in helping the patient over an ischaemic episode; in these circumstances iproniazid therapy should be covered by concurrent tests of liver function.

Antithyroid Agents

Atherosclerotic coronary arteries are often unable to supply sufficient blood for the normal myocardial demands for oxygen, and myocardial ischaemia may result. If the myocardial requirements of oxygen could be restricted, then the reduced blood supply might be adequate. Thyroidectomy, thiouracil (Raab, 1945), and radioactive iodine (Blumgart *et al.*, 1956) have been used to reduce myocardial metabolism, and in a majority of patients reduction of the incidence and severity of angina has followed. Patients who may be expected to gain the greatest benefit from artificial myxoedema are those in whom intractable angina has been present for a year or longer. It is not advised for patients who can be

kept moderately active and comfortable by other means. Naturally, patients with angina are often intolerant of the accompanying mental retardation and distressing features of myxoedema, and this form of therapy should be kept as a late resort.

Administration of antithyroid drugs to reduce myocardial metabolism allows easy control of the degree of induced myxoedema, and is less irrevocable than thyroidectomy or radioactive iodine. However, these derivatives do not induce hypothyroidism in every euthyroid patient, and when effective they must be continued for the rest of the patient's life. At any time during such treatment there is danger of agranulocytosis and other reactions to the drug. Carbimazole 20 mg. three times daily, propylthiouracil 600 mg. daily, or methylthiouracil 600 mg. daily can be given to induce artificial myxoedema. If it is decided that the patient may benefit from artificial myxoedema, radioactive iodine is probably the method of choice. If the initial dose of radioactive iodine is insufficient, additional doses may be given, and, if the patient cannot tolerate the hypothyroid state, it can be alleviated by the administration of thyroid. It is unwise to give radioactive iodine to patients in the terminal stages of the disease, since between five and six months intervene before the maximum benefit can be expected.

Miscellaneous Drugs

There is no satisfactory evidence that khellin, xanthine derivatives, testosterone, or alpha-tocopherol (vitamin E) have any practical therapeutic value in the treatment of angina.

CORONARY ATHEROSCLEROSIS

The dietetic and drug treatment of coronary atherosclerosis is still in the experimental stage and is based on an assumption which is at present unproved. It is that reduction of a high blood level of cholesterol might be associated with inhibition or even regression of atherosclerotic lesions in the coronary arteries. This assumption is based on experimental and epidemiological evidence which suggests that there is a positive and direct relation between the height of the blood cholesterol and the extent of atherosclerotic lesions. The aetiological significance of this relationship and the nature of hypercholesterolaemia are under constant investigation at present, and this is not the place to consider the arguments.

At present it should be emphasized that neither inhibition nor regression of atherosclerotic lesions has yet been demonstrated in man on any regime designed to lower hypercholesterolaemia, but obviously it is difficult to obtain such evidence. Even if atherosclerosis can be retarded, this does not necessarily indicate that reduction of hypercholesterolaemia will improve the prognosis in patients who have already developed clinical features of coronary atherosclerosis. Thus, there is at present no justification for the introduction of any drug or dietetic regime as a routine for patients with ischaemic heart disease.

Reduction of the level of blood cholesterol should be confined to patients who are known to have hypercholesterolaemia, particularly young patients with a strong family history of vascular disease. The principle of the dietetic regimes at present recommended is the reduction of animal fats (saturated fatty acids) with the substitution of vegetable fats (unsaturated fatty

acids) (*British Medical Journal*, 1958). Various drugs have been advocated in order to lower a raised level of serum cholesterol or to reduce the absorption of cholesterol, but there is no therapeutically acceptable drug yet available nor is there any general agreement on the advisability of these procedures.

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PSYCHOSOMATIC DISORDERS IN CHILDREN*

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Let me suggest that to speak of psychosomatic disorders, if it implies that certain nameable clinical entities can be so classified, is inaccurate and dangerous—dangerous to clear thought and harmful to our patients. I do not, of course, mean that Psyche and soma are never collaborators or partners in the production of either ill-health or good health. Of course they are. It can even be argued that every state of health is due to such collaboration. This is, I suppose, the central tenet of Christian Science, and, though most of us cannot accept it in full, we have, I take it, been driven by irrefutable facts a long way from the materialist front-line of half a century ago.

Allergy and Psychosomatosis

But, while fully admitting that, in my own phrase, Psyche has a finger, and sometimes a fist, in every clinical pie, I still wish to press the point that it is entirely fallacious to make a list of disorders or diseases, whether in children or adults, and term them "psychosomatic." Asthma, urticaria, eczema, rheumatoid arthritis, toxic goitre, ulcerative colitis, duodenal ulcer, and many more disorders or physiological perversities should no more be called psychosomatic than allergic. Their highest common factor is, surely, inherited disposition. They could, not unreasonably, be termed "constitutional," but, like all human affairs, they are due not to one but to a multiplicity of interacting causes.

"In the world of concrete fact," wrote Arthur Balfour (1925), "nothing occurs through the action of a single cause, nor yet through the simple co-operation of many causes, each adding its own unqualified contribution to the total effect, as we picture horse helping horse to draw a loaded dray. Our world is a much more complicated affair."

"Psychosomatosis in childhood" or "children in psychosomatic disorder" should be my title, and I beg you to believe this is not a mere verbal quibble. Let me illustrate.

Susan T., said to have begun to wheeze a little at 5 months, had fairly severe asthma at the age of 10 years in 1938. Asthma was at that time widely regarded as an "allergic disorder," so, though both her mother and I were decently sceptical, to the allergist of the day we had to go. With a mere side-glance at her clinical history, he plunged at once into skin tests, pronounced her sensitive to tomatoes, feathers, horse-hair, pollen, and other things, and advised avoidance of many foods, special pillows and mattress, and a desensitizing course of injections. Her mother and I, in consultation, discovered the flattest contradictions between the skin tests and clinical experience, changed her pillow but forbore to desensitize, and suffered her to continue to eat tomatoes and ride and groom horses, which she did with perfect impunity. We both thought her trouble, at bottom constitutional, was provoked by emotional tensions which we could see and name but not remove.

I shall come back to her case, but my present point is simply that the acceptance of asthma as an allergic disorder threatened to land this child in tiresome deprivations and painful treatment, unsoundly based, likely to fail, and very expensive. Her subsequent history, which I followed for many years, was good; would it have been better if, asthma being psychosomatic, search had been made for forgotten emotional trauma or buried complex instead of for an allergen? I take leave to doubt. Allergy exists, psychosomatosis exists; but let us beware of applying the corresponding adjective to clinical pictures.

"A rash on the hands," it has been well said by Bowers (1958), "might look the same whether caused by 'dettol,' diesel oil, 'distaquaine,' or divorce"; and "on the face almost identical appearances may be given by sensitivity to cosmetics, chrome salts, or just conscience"; and, again, "a nurse may not show her sensitivity to streptomycin until she has some emotional upset."

If pressed I suppose I must concede that facial tics, habit spasms, and the like are, at least at onset, always psychogenic; here is perhaps a psychosomatic disorder diagnosable at sight. But is not soma here a mere indicator, related to Psyche as the railway signal is to the signalman? Psychosomatosis surely demands a more equal and intimate partnership. I think my thesis stands.

How, then, can we know psychosomatic disorder when we meet it? Not, I think, from any static picture, presented at a given moment, but only from the course of events, as learnt by history and observation. The blindness of three blind mice may be psychosomatic, and negative ophthalmoscopy may suggest that it is, but the only sure means to diagnosis in these cases is to see how they run.

Thirty years ago, at the Shadwell Children's Hospital, I saw a child whose constant involuntary movements seemed to me then—and I think would still seem—indistinguishable from true rheumatic chorea. Only when they ceased on admission to hospital but recurred on discharge, and this sequence was several times repeated, was I convinced that the disorder was psychogenic, and the lady almoner discovered for me ample reasons in the child's home. Later I took her into my own house to work in the kitchen and pantry. She proved temperamental, but, sure enough, she never dropped a cup. I know her still, courageously holding down a responsible job despite extreme myopia and retinal detachment.

Only the *course* reveals the psychosomatosis and the diagnosis can be made only by deduction. One more

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