BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 24 1961

ACUTE AND SUBACUTE CORONARY INSUFFICIENCY*

BY

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The term "acute coronary insufficiency" has become increasingly familiar since it was properly described as an entity by Master and his colleagues in 1947. It may be defined as a state in which the coronary circulation is insufficient to meet the full metabolic demands of the myocardium at rest, yet sufficient to prevent myocardial infarction. The modified title of this paper was chosen to emphasize the prolonged course of the illness in one-half of the patients. Thus in the 150 cases studied the illness was acute, lasting less than six weeks, in 50% ; subacute, lasting between two and six months, in 45% ; and chronic in 5%.

Characteristically this transient physiological state arises spontaneously during the course of ischaemic heart disease due to occlusive coronary atherosclerosis. Special forms of coronary insufficiency may be associated with paroxysmal tachycardia, paroxysmal atrial fibrillation or flutter, severe haemorrhage or shock, asphyxia, hypertensive crises, ruptured aortic cusp, spirochaetal aortitis, severe anaemia, and several other conditions ; but these are beyond the scope of this paper. I am concerned here entirely with coronary insufficiency as it occurs in ischaemic heart disease.

My immediate purpose is to draw greater attention to this syndrome and its frequency, to redescribe its clinical features for the benefit of those who are still unfamiliar with it, to offer factual data concerning its natural course, and especially to record the results of anticoagulant therapy.

Material

The analysis is based on a consecutive series of 150 cases seen over a period of about 10 years at the National Heart Hospital, at the Brompton Hospital, and in private practice. The diagnosis was made from the clinical history, negative physical signs, characteristic electrocardiogram, and absence of laboratory data denoting fresh infarction. In most cases attacks of angina were witnessed and in many an electrocardiogram was also recorded when pain was present.

The average age of these 150 patients was 56, and the male:female sex ratio was just under 3:1. The total duration of ischaemic heart disease when the patient was first seen averaged 3.7 years, previous cardiac infarction had occurred in 25%, and the electrocardiogram provided conclusive proof of ischaemic heart disease in 87%.

*Presented at the joint meeting of the British and Canadian Medical Associations in Edinburgh on July 21, 1959.

Prevalence

The true incidence of coronary insufficiency is difficult to determine. Some idea of its prevalence, however, may be gathered from the following data:

1. In a consecutive series of 1,000 cases of ischaemic heart disease seen privately over the past 10 years the presenting feature was acute or subacute coronary insufficiency in 10%, simple angina pectoris in 30%, fresh cardiac infarction in 24%, and old cardiac infarction with or without angina pectoris in 36%.

2. According to Mounsey (1951), one-quarter of all cases of acute cardiac infarction have warning symptoms indicating a preliminary state of acute coronary insufficiency. In a consecutive series of 100 cases of cardiac infarction under my care the major attack was preceded by a state of acute coronary insufficiency for an average period of 3.3 weeks in 45%. In two-thirds of this group the warning period did not exceed three weeks. Information is not available concerning the frequency of acute coronary insufficiency preceding sudden death from acute cardiac infarction.

3. Conversely, 22% of 50 cases of acute or subacute coronary insufficiency that were treated conservatively in the present series developed frank cardiac infarction within two months of the day the diagnosis was made (first consultation).

Pathology

There was virtually no necropsy evidence concerning the pathology of acute coronary insufficiency in the present series. Most deaths followed the clinical development of cardiac infarction, and this was proved at necropsy in seven instances, the infarction being due to coronary thrombosis.

Sudden death from ventricular fibrillation during acute coronary insufficiency occurred in only 2.6% of 150 cases, and a post-mortem examination was not carried out in these four cases.

Seven patients died after a prolonged period of subacute or chronic insufficiency (three months to two years), and, although advanced occlusive coronary disease with old thrombosis and cardiac infarction was usually found at necropsy, there were two instances in which neither thrombosis nor previous infarction could be demonstrated.

The clinical data, however, support the view that acute coronary insufficiency is due to coronary thrombosis without infarction. In the present series the onset was sudden in 81%, gradual deterioration of previous angina pectoris over a period of three to six months

occurring in only 19%. Even more convincing was the fact that 20% of the series not only developed acute coronary insufficiency abruptly, but did so at a time when they seemed to be in perfect health, entirely free from symptoms, and with no previous history of angina pectoris. It is difficult to believe that anything short of coronary thrombosis could so impoverish the coronary circulation so suddenly.

Until reliable necropsy data become available, it is reasonable to assume that cases with an abrupt onset have had a fresh coronary thrombosis, and that cases with angina pectoris which gradually deteriorates until it reaches a state of coronary insufficiency at rest may be attributed to progressive occlusive atherosclerosis alone.

The Clinical Syndrome

Characteristically, as just stated, the onset of acute coronary insufficiency is sudden, a state of normal health (20%) or of relatively mild angina of effort, with or without a previous history of cardiac infarction, changing abruptly to one of almost total incapacity. Although the pain is usually provoked by all the familiar triggers, including changes of temperature, a meal, getting into bed at night, or getting up in the morning, as well as by trivial effort and excitement, it may also occur spontaneously when the patient is sitting quietly in a chair reading the paper, or may wake him repeatedly from sleep.

The attacks tend to be prolonged, often lasting between 10 and 30 minutes, but are usually shortened by trinitrin. Sometimes, however, trinitrin brings indifferent relief. Indeed, if more than two tablets of trinitrin are consumed one after another, because of this indifferent relief, the pain may increase and in more than one instance syncope has resulted.

These unprovoked attacks of angina pectoris occur at varying intervals over a period of days, weeks, or months. In some cases the patient is remarkably well in the intervals between the attacks, being able to walk freely on the level without discomfort, and in rare instances even strenuous effort fails to provoke pain.

That the pain is cardiac, however atypical its behaviour, is usually obvious on account of its central position in the thorax, its radiation to the arms or jaws, and its constricting or oppressive quality. In the great majority there are no abnormal physical signs, although the blood-pressure may be raised if taken during an attack of pain, and closure of the aortic valve may be delayed (reversed split second sound).

The electrocardiogram, however, is diagnostic in 80% of the cases, showing widespread ischaemic depression of the S–T segment when recorded at rest between attacks. In the present series a further 8% showed evidence of previous cardiac infarction only, and in 12% the graph was strictly normal. An ischaemic graph taken during an attack of pain confirms the diagnosis of angina pectoris, but, of course, does not then prove a state of acute coronary insufficiency.

A diagnosis of acute coronary insufficiency denies evidence of cardiac infarction. Thus there is no fever, leucocytosis, or rise of the erythrocyte sedimentation rate; the C-reactive protein test is negative; and both the serum glutamic oxalacetic transaminase level and the lactic dehydrogenase activity remain normal.

It must be admitted, however, that the physiological situation in these cases is critical, and that the gap between acute coronary insufficiency and cardiac infarction is narrow. After prolonged attacks minor degrees of necrosis may occur and cause transient or repetitive T-wave inversion in serial electrocardiograms, and perhaps slight changes in the laboratory data mentioned. These should be regarded as borderline cases.

Course

The natural course of acute coronary insufficiency was studied in 50 patients treated conservatively. These patients received rest, a low-calorie and low-fat diet, trinitrin as required, and often pentaerythritol tetranitrate in doses of 10–30 mg. t.d.s.

As stated in the introduction, the duration of acute coronary insufficiency is less than six weeks in 50% of the cases, but in the other 50% the illness proves to be subacute or chronic. Thus it lasted for two to three months in 30% of the present series, from four to five months in 15%, and for appreciably longer than this, even up to two or three years, in 5%. The duration of acute or subacute coronary insufficiency was little influenced by treatment when the course was not terminated by cardiac infarction or death.

Cardiac infarction occurred within two months of the onset of acute coronary insufficiency in 11 of these 50 untreated patients. Eight of them died. Seven other patients died when in a state of subacute or chronic coronary insufficiency: two from cardiac infarction, two abruptly, two in their sleep, and one from cerebral thrombosis. Thus the total mortality was 30%.

When the course was favourable attacks of pain gradually abated, and after a variable interval patients usually regained their previous state of health.

The after-histories of the 35 patients who survived the attack of coronary insufficiency may be summarized as follows: 10 could not be traced; nine died in an average period of four years either from cardiac infarction, suddenly from angina pectoris, or after they had relapsed into a state of coronary insufficiency; six had a recurrence of acute coronary insufficiency or developed subsequent cardiac infarction within five years (usually within one year); one relapsed into a state of chronic coronary insufficiency and is still alive; seven are relatively well with mild or moderate angina of effort; and two are symptom-free. Thus only 26% of the survivors are known to have done relatively well for an average period of five years (range three to seven years); a similar percentage are dead and 20% have suffered further coronary episodes.

If we assume that the untraced patients fared similarly to those that were followed up, then roughly one-third of the initial survivors are dead, one-third have had recurrent coronary episodes, and one-third are relatively well. This is a sinister record for an average period of about five years. It must also be remembered that many cases of acute coronary insufficiency are not classified as such because they are not seen until they have already developed cardiac infarction.

Anticoagulant Treatment

A series of 100 patients with acute coronary insufficiency were treated with phenindione ("dindevan"), or occasionally with ethyl biscoumacetate ("tromexan") or nicoumalone ("sinthrome"), and the more severe cases also received two or three initial injections of 12,500 units of heparin intramuscularly

over the first 24 hours. The initial dose of phenindione was 50 mg., repeated 12-hourly for five doses. Subsequent doses varied according to the prothrombin time, which was maintained between 2 and 2½ times the control time (ratio 2–2.5 : 1).

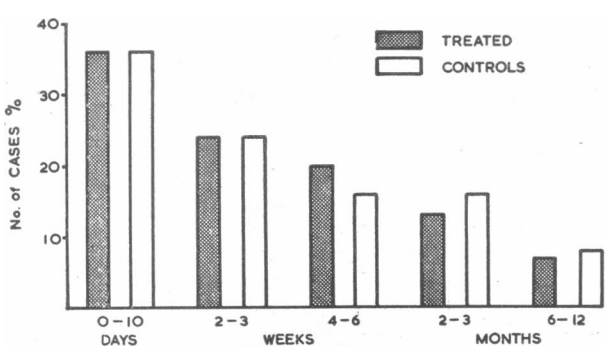
In the earlier cases treated between 1947 and 1953 anticoagulant therapy was nearly always withheld when the patient had recovered from the coronary insufficiency episode, but was always continued for a minimum of six weeks. Since then, however, an increasing number of these patients have remained on permanent anticoagulant therapy, and this is now routine practice.

The results of anticoagulant treatment in this series of 100 cases were compared with those obtained in 50 similar controls. During the first two years of the period of study alternate patients with acute coronary insufficiency received anticoagulant therapy, and alternate patients served as controls. It soon became obvious, however, that the controls were faring worse than the treated cases, and it became morally difficult not to offer all patients the protection that anticoagulant treatment seemed to give. Thus the last 30 patients in the control group were not chosen at random, but for some particular reason, such as a recent history of peptic ulcer, previous haematemesis, a tendency to spontaneous bruising, geographical difficulty, prejudice on the part of the general practitioner or other consultant concerned in the case, or for some other reason of this sort. In all other respects, however, the cases in the control group were precisely the same as those treated. Table I shows that the average age of the patients, the sex ratio, the total duration of ischaemic heart disease, the frequency of cases seen within the first three weeks, and the frequency of ischaemic depression of the S–T segment of the electrocardiogram were virtually identical in the two groups. Previous cardiac infarction and intermittent claudication occurred a little more commonly in the treated patients.

Perhaps the most important condition in making a comparison of this kind is that the time interval between the onset of acute coronary insufficiency and the day

TABLE I.—*Coronary Insufficiency in 100 Cases Treated with Phenindione and 50 Controls*

	Treated Cases	Controls
Age	56	56
M : F sex ratio	2·9 : 1	3 : 1
Total duration ischaemic heart disease (years)	3·7	3·8
Duration of coronary insufficiency:		
Average (weeks)	4·3	5·4
Up to 3 weeks	60%	60%
Previous infarct	29%	18%
Claudication	12·5%	7%
Ischaemic E.C.G.	80%	75%
Old C.T. only	8%	9%
Normal E.C.G.	12%	16%



Duration of coronary insufficiency when first seen.

the patient was first seen should be the same in each group. The Chart shows that the percentage of treated and untreated cases seen within 10 days of the onset, within two to three weeks, within four to six weeks, and at longer intervals. It will be seen that in respect of these time intervals the two series were remarkably similar.

The results of anticoagulant therapy are compared with those of conservative management in Table II, and may be summarized as follows: (1) The mortality of

TABLE II.—*Acute Coronary Insufficiency in 100 Cases Treated with Phenindione and 50 Controls*

Results	Treated Cases %	Controls %
Good	75	32
Infarct within 2 months	3 (2 died)	22 (16 died)
,, after withholding anticoagulants	2 (1 ,,)	
Chronic coronary insufficiency	9 (3 died)	22 (8 died)
Cerebral thrombosis	0	2 (died)
Ventricular fibrillation	0	4 (,,)
Deteriorated and anticoagulated		4
Untraced	9	14
Minimum mortality	6	30

treated cases was one-fifth that of the controls. (2) The percentage of cases that failed to improve and finally entered a state of chronic coronary insufficiency when treated with anticoagulants was one-third of the number that behaved in this way when not so treated. (3) Cardiac infarction within two months of starting treatment was seven times less common in the group given anticoagulants than in the group managed conservatively (3% compared with 22%). (4) When cardiac infarction occurred while the patient was under observation for acute or subacute coronary insufficiency, the mortality was 66% and was similar in both groups. (5) Neither cerebral thrombosis nor ventricular fibrillation occurred in the treated cases, but accounted for three deaths in the controls. (6) Two of the treated patients developed cardiac infarction within a week or two of anticoagulants being withheld. (7) Good results, the patients returning to work and leading a useful life with or without relatively mild angina pectoris, occurred more than twice as often in cases treated with anticoagulants as in the controls (75% compared with 32%).

These results bear out preliminary impressions gained from a smaller series reported 12 years ago (Wood, 1948), and are in harmony with the experience of Nichol (1950), who reported two infarcts in a series of 41 cases of acute coronary insufficiency treated with anticoagulants (no controls). Beamish and Storrie (1960) treated 85 cases with anticoagulants, and only two of them developed cardiac infarction; of their 15 controls infarcts occurred in all but one, and 11 proved fatal. In a series of 158 similar cases observed by Levy (1956), all of which were managed conservatively, frank cardiac infarction developed in 23.4%. The total mortality in his series was 32.3%, 15.8% dying from ventricular fibrillation and 16.5% from cardiac infarction. Thus as many as 70% of his patients who developed cardiac infarction died. These figures relating to the natural course of this unstable and dangerous state are remarkably similar to those reported here.

Subsidiary Treatment

Bed rest and a diet low in calories and animal fat formed a routine part of the treatment. A cardiac bed or special armchair was used when patients tended to have angina when lying flat. One patient was often

forced to stand to obtain relief from pain. Sedatives were given as required, and pethidine was sometimes administered in the early stages when pain was severe.

Contributory factors, such as diabetes mellitus, hypertension, and obesity, were corrected so far as was possible. Cases with serious hypertension, however, were not included in the series analysed.

The only coronary vasodilators that were used in this study were trinitrin, p.r.n., and pentaerythritol tetranitrate, in the form either of "peritrate" (10 mg.) or of "myocardol" (30 mg.), in doses of one or two tablets three times a day, one hour before meals.

Adverse blood lipid patterns that did not respond to diet alone were countered with 40–50 oz. of corn oil daily or with nicotinic acid, the dose of which was gradually increased from 100 mg. t.d.s. to 500 t.d.s., if well tolerated. Such treatment was rarely given unless the serum cholesterol remained obstinately high, between 350 and 700 mg./100 ml., and was uninfluenced by the decision to give anticoagulants or not. Neither triparanol ("MER-29") nor oestrogens were used in this series.

During 1958 iproniazid ("marsilid") proved helpful in relieving intractable cardiac pain in states of coronary insufficiency, but did not influence the fundamental course of the disease (Towers and Wood, 1958). The hypotensive, anabolic, hepatotoxic, and neuromuscular side-effects of iproniazid, however, limited its use. During the last two years other mono-amine oxidase inhibitors relatively free from these side-effects have been tried, particularly isocarboxazid ("marplan"), but on the whole they have been less effective. It is repeated for emphasis that these substances do not alter the fundamental course of the disease. They are best used temporarily, to overcome undue suffering when the patient is incapacitated, and should usually be withheld before he returns to work, for masking angina pectoris may be dangerous.

Summary

The clinical features and natural course of acute coronary insufficiency are described.

The results of anticoagulant therapy in 100 cases are compared with those of conservative management in 50 cases.

Cardiac infarction developed within two months in 3% of the treated cases and in 22% of the controls.

The mortality of treated cases was one fifth that of the controls.

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A new edition of *Introductory Manual on the Control of Health Hazards from Radioactive Materials* has now been published in the Medical Research Council's regular series of Memoranda. As the preface to the volume indicates, it is essentially an introductory manual intended mainly for the guidance of those concerned with the manipulation of radioactive materials in laboratories and elsewhere. Publications dealing in greater detail with various aspects of hazards from radiation are mentioned in the text and in the bibliography. (H.M.S.O., M.R.C. Memorandum No. 39, price 1s. 9d. net.)

MORTALITY FROM PRIMARY TUMOURS OF BONE IN ENGLAND AND WALES

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The suggestion that small doses of radiation might be capable of inducing cancer has stimulated interest in the incidence of some of the rarer forms of the disease. In particular, it has been suggested that the very small amounts of radium and other radioactive substances which are located in the skeleton might be responsible for some cases of bone tumour, and that the incidence of such tumours might vary from one geographical area to another, depending upon the radioactivity of local food and water supplies (Marinelli, 1958). Experiments have shown that large doses of radioactive substances will regularly cause bone tumours in a high proportion of animals (Brues, Lisco, and Finkel, 1946; Finkel, 1956), and observations on patients given deep *x*-ray therapy (Vaughan, 1956), and on persons exposed to radium therapeutically or in the course of their work (Martland, 1931; Aub, Evans, Hempelmann, and Martland, 1952; Looney, Hasterlik, Brues, and Skirmont, 1955; Looney, 1956) have demonstrated that ionizing radiations can also cause bone tumours in man. It does not follow, however, that a similar effect will be produced by smaller doses, and it is possible that very small doses will not produce any risk of cancer at all.

The maximum effect of small doses can be estimated by assuming (1) that the effect is proportional to the dose, and (2) that the total natural incidence of cancer is attributable to natural background radioactivity. This method was used by the United Nations Scientific Committee on the Effects of Atomic Radiation (1958) to estimate the maximum amount of bone cancer which might be due to the ingestion of very small quantities of strontium-90 and of other radioactive substances; but they thought it reasonable to assume that not more than 10% of primary bone tumours could be attributable to natural radioactivity. They assumed that the annual incidence of primary bone tumours was between 5 and 10 cases per million persons per year, and they therefore made their calculations on the basis that "a natural radiation level of 9 rem per 70-year human lifetime" would give rise to between 5 and 10 cases per million persons in a 10-year period.

One of the many difficulties in making this type of calculation is that there is no accurate measure of the incidence of bone tumours. The disease is rare and data collected from cancer registries relate to too short a

*Since the completion of the work Dr. Mackenzie has died.