now; and you can and must do without it. Religion must go: it has done you grievous harm."

At this the plain man drops his head and is silent.

The Biologist (continuing): "Only look at what I have to offer you in exchange for your soul. In the language of an old book which you seldom read and which is now obsolete, I will pull down your old barns and build you bigger and better ones; and I will fill them to the roof with 'goods' that our newest chemistry will provide—food, clothing, health, long life, ease, and pleasure. The loss of your soul is nothing to what you will gain."

The Plain Man: "What you offer tempts me. Many of us plain folk need these chemical goods badly. But the idea of life without soul frightens me; it would be so flat and cold and dreary, and it might be dangerous. We have always been told that our souls are the best part of us. And yet your best chemists have searched every corner of us, and have found no chemical trace of soul. Could it not be that soul is of different and non-chemical stuff, that if you used other long-tried non-chemical methods of search, at once and everywhere, within our bodies and without, you would find soul?"

Conclusion

To sum up: Harvey's discovery of the circulation of the blood was the beginning of a new chapter in physiology. It may be compared to the appearance of the punctum saliens in the 4-day-old chick; "like a spark darting from a cloud" (his own words), it was the first sign of new life in European physiology, and was followed in a kind of epigenesis by a succession of other discoveries. Much of what he wished to do he left undone; but his unfinished work has been brought to fulfilment by others, and the verities of physiology are now no more in their chaos.

As to his teaching on the soul, both his particular doctrine of the soul and the blood, and his general statement of the soul in man and in animals, and the Soul of the Universe—all this has been rejected by modern biology. But biology has not said its last word, and is struggling even now to find its own metaphysic on the question of cause. Meantime Harvey's general statement on the soul is worth setting alongside those of other great minds in ancient times. *The Book of Wisdom*: "The Spirit of the Lord hath filled the whole earth." Aristotle: "All things are full of Soul." Virgil: "All things are full of Jove." Last, Harvey, speaking as a biologist: "For, as the same intelligence or spirit which incessantly actuates the mighty mass of the Universe . . . so also is there a *vis enthea*, a divine principle, inherent in our common poultry."

At the third annual general meeting of the British Rheumatic Association held on September 28 it was reported that the association is now established as a national organization and a registered charity. It maintains helpful connexions with the Ministry of Health and regional hospital boards. As the result of these, spa treatment can now be authorized under the National Health Service by a consultant in rheumatism, and those who can find their own accommodation can be treated as out-patients in any hospital rheumatic unit, subject to the recommendation of their own doctor and a recognized consultant. To meet the difficulties of rheumatics in finding accommodation close to centres where they can get urgently needed treatment, the association has promoted the formation of a housing society with charitable status under the title of B.R.A. Homes Limited to provide accommodation on a voluntary basis. Another of its activities is to provide flatlets for the old and disabled rheumatics within a certain income group. This will make it possible to combine geriatric with rheumatic treatment, which recent experience shows can relieve pressure on hospital beds.

ANTICOAGULANTS IN TREATMENT OF CORONARY THROMBOSIS

BY

JOHN A. TULLOCH, *M.C.*, M.D., M.R.C.P.Ed.*

Registrar, Department of Cardiology, Royal Infirmary, Edinburgh

AND

A. RAE GILCHRIST, M.D., F.R.C.P., F.R.C.P.Ed.

Physician, Royal Infirmary, Edinburgh; Reader in Clinical Cardiology, Edinburgh University

Adequate care for the patient suffering from acute coronary occlusion is one of the most urgent problems in present-day therapeutics. A disease which statistics prove to be on the increase, which is afflicting younger lives (Ryle and Russell, 1949), and which after 25 years' study can still be shown to have a mortality rate of 40% among hospital patients within the first six weeks, is a challenge that for too long has been neglected.

Myocardial infarction, the result of coronary artery occlusion, now constitutes a large part of cardiological practice. The exact incidence of the condition throughout the general population is difficult to assess. All grades of severity are encountered, from the most severe cases dying immediately or within a few minutes or hours from the onset, to the very mild which experience little upset and have no ensuing disability. It is therefore the moderately severe or the complicated cases which provide the greater part of hospital experience. Statistics gathered from the hospitals cannot be applied to the population as a whole, but in this disease they certainly indicate the course followed by the moderately severe case treated, as we believe, under the best available conditions.

A study of the literature indicates that the immediate mortality following myocardial infarction varies widely in different centres and perhaps in different hospitals in the same city. In Table I the mortality rate ranges from the

TABLE I.—*Showing how the Mortality Rate Varies in Different Series of Patients in the First Few Weeks After the Acute Occlusion*

Author	No. of Cases	Mortality %	Remarks
Levine and Brown (1928) ..	145	53	
Conner and Holt (1930) ..	284	16	First attacks only
Harrington and Wright (1933) ..	148	54	
Master *et al.* (1936)	267	17	
" " (1937)	140	21	
Bland and White (1941) ..	200	19	4-weeks period
Levine and Rosenbaum (1941) ..	208	33	
Woods and Barnes (1941) ..	128	47	
Newman (1946)	50	78	Young adults
Katz and Mintz (1947) ..	572	22	
Yater *et al.* (1948)	866	52	Young adults; 4-weeks period
Wright *et al.* (1948)	368	24	

78% of Newman (1946) to the 16% of Conner and Holt (1930). Our current Edinburgh experience has been assessed from two series of hospital patients, the first being composed of 100 consecutive cases of coronary thrombosis observed during the period 1939–46, before the introduction of anticoagulants; their mortality rate was 43%. A second series of 84 consecutive patients, forming the present control group and observed concurrently with a similar number receiving anticoagulants, had a mortality rate of 41%. Through the courtesy of physicians elsewhere in

*Work done during the tenure of a Grocers' Company Research Scholarship, 1947–9.

this country—Dr. Boyd Campbell, Dr. J. H. Wright, and Professor Crighton Bramwell in personal communications—we are able to report hitherto unpublished mortality rates for hospital-treated cases of coronary thrombosis in Belfast, Glasgow, and Manchester. The findings, presented in Table II, indicate that, in the absence of any specific

TABLE II.—*Presenting Recent Experience of Mortality Rates After Coronary Thrombosis at Four Centres in this Country. Anticoagulants were Not Employed in the Treatment of These Patients. The Figures Indicate that Among Hospital-treated Patients 33% is an Average Mortality Rate During the First Six Weeks*

Locality	No. of Patients	No. of Deaths	Mortality %
Belfast (Boyd Campbell)	169	50	30
Glasgow (Wright, J. H.)	100	25	25
Manchester (Bramwell, C.)	50	13	26
Edinburgh: This series (*a*)	100	43	43
„ „ (*b*)	84	34	41
Total	503	165	33

therapeutic measures, coronary thrombosis has a mortality rate in the neighbourhood of 33% among hospital patients in this country.

Embolic and thrombotic episodes, which may handicap a convalescent patient or prove immediately fatal, are common after myocardial infarction. Such episodes comprise: (1) the sudden occlusion of a systemic artery; (2) the development of a fresh myocardial infarct or the spread of the occlusive process to adjoining branches of the affected artery, and hence an extension of the original damage; (3) peripheral phlebothrombosis; notably in the calf veins; and (4) pulmonary infarction. In recent years a much higher clinical incidence for thrombo-embolic phenomena after coronary occlusion has been recorded, suggesting that in earlier reports minor episodes had been overlooked. This is demonstrated in Table III. Mural thrombus formation

TABLE III.—*Showing that the Frequency with Which Thrombo-embolic Incidents after Coronary Thrombosis are Recognized has Apparently Increased in Recent Years*

	Authors	No. of Cases	No. with Thrombo-embolic Episodes
A. Early series	Gordinier (1924)	13	3
	Anderson (1928)	9	1
	Parkinson and Bedford (1928)	100	8
	Levine and Brown (1928)	145	17
	Conner and Holt (1930)	287	42
	Hyman and Parsonnet (1931)	51	17
	Howard (1934)	165	17
	Blumer (1937)	175	27
	Master *et al.* (1939)	500	29
		1,445	161 = 11·1%
B. Recent series	Nay and Barnes (1945)	100	37
	Peters *et al.* (1946)	60	10
	Glueck *et al.* (1948)	44	27
	Greisman and Marcus (1948)	100	21
	Wright *et al.* (1948)	368	92
		672	187 = 27·8%

on the endocardial surface of the infarcted area of the ventricle is present in 44% of necropsy cases, but all peripheral arterial occlusions are not necessarily embolic in origin (Hellerstein and Martin, 1947). It is during the first three weeks after the acute occlusion that thrombo-embolic incidents are most apt to occur (Nay and Barnes, 1945), and it is during this same period that an upset in the control of intravascular blood-clotting has been demonstrated (Ogura *et al.*, 1946). Using the Waugh–Ruddick (1944) heparin-retarded clotting test, Ogura and his colleagues observed the development of an enhanced clotting tendency in 75% of cases of recent myocardial infarction. An increased coagulability of the blood appeared during the first week, reached a maximum towards the end of the second week, and disappeared during the third week. Our own experience has been that there is considerable individual variation in the time of onset, duration, and degree of this change.

In the treatment of myocardial infarction the possibility of controlling this enhanced clotting tendency and preventing thrombo-embolic complications appeared attractive. The introduction of the anticoagulant dicoumarol made this supposition a practical measure. The earliest reports on anticoagulant therapy by Wright (1946) and Peters *et al.* (1946) indicated that not only was the incidence of thrombo-embolic complications greatly lessened, but the immediate mortality rate was strikingly reduced. With the accumulation of further reports in the American literature, supplemented by the large-scale investigation at 16 leading hospital centres sponsored by the American Heart Association, the evidence is overwhelmingly in favour of this method of treatment. Table IV, constructed from American statistics, suggests that anticoagulants are capable of reducing the mortality rate by one-half.

TABLE IV.—*Constructed from Reports in Recent American Literature. Contrasts Mortality Rates in Cases Treated With and Without Anticoagulants. The Mortality Rate is Apparently Halved by the Use of these Drugs*

Author	Anticoagulant Cases		Control Cases	
	Total	Deaths	Total	Deaths
Wright (1946)	76	15	—	—
*Peters *et al.* (1946)	50	2	60	13
Nichol (1947)	68	11	—	—
Parker and Barker (1947)	50	5	—	—
*Greisman and Marcus (1948)	75	7	100	35
Glueck *et al.* (1948)	44	9	44	20
Reich and Eisenmenger (1948)	30	4	—	—
*McCall (1948)	71	9	—	—
Wright *et al.* (1948)	432	65	368	88
Hilton *et al.* (1949)	38	5	76	18
Loewe and Eiber (1949)	20	1	—	—
	954	133	648	174
Mortality rate	13·8%		26·8%	

* Cases dying within 48 hours of admission are not included.

Whether all cases derive equal benefit has not been adequately investigated. Wright *et al.* (1948) indicated that males aged 60 years and over showed greatest improvement, and Greisman and Marcus (1948) in a small series reported a greater improvement among males than among females. The present investigation, now to be reported, was begun in 1947 with the object of assessing the value of anticoagulant therapy in myocardial infarction and of determining, if possible, the type of case most likely to benefit from this form of treatment.

Material

During the past three years 154 cases of myocardial infarction have been observed and treated. These comprise two series of cases: one series, consisting of 84 cases, was treated by conventional conservative measures and constitutes the "control" series; the second series, consisting of 70 cases, received anticoagulant therapy during the first three weeks after admission in addition to the standard forms of treatment, and constitutes the "treated" series. All cases were unselected, their inclusion in one or other series being determined by the day of their admission to hospital. All cases admitted to one medical block were treated conservatively, whereas all cases admitted to a second block received anticoagulants—unless some contraindication to their use existed. Both series comprise, therefore, the

everyday emergency admissions to a medical ward. No case was admitted specifically for anticoagulant therapy. All cases admitted and dying within six hours of admission have been excluded from both series, as insufficient time had elapsed for any benefit to result from the treatment given.

Diagnosis was based on the history and the usual signs, supported by positive electrocardiograms in 134 of 136 patients thus examined, and by the course of the illness. Cases in which a doubt existed regarding the presence of a recent myocardial infarct have been rigorously excluded from the series under review.

Treatment

The routine treatment adopted for all cases consisted in rest in bed for five to six weeks, morphine for relief of pain, sedation with phenobarbitone, low calorie intake, graduated exercises from the fourth week, and treatment of complications as and when they arose. The "treated" series received in addition heparin and dicoumarol (64 cases) or dicoumarol alone (6 cases). Heparin was given by the interrupted intravenous injection method, the interval between injections being 8 hours in 62 cases and 6 hours in two cases, the later two cases having both experienced thrombo-embolic complications before their admission to the ward. Except in the first few cases, each injection consisted of 10,000 units of heparin. Adequacy of dosage was assessed by estimation of the clotting time one hour after the injection, using the Lee–White (1913) method. A time of 20 minutes, three or four times the normal value, was regarded as satisfactory. The injections of heparin were stopped as soon as a therapeutic reduction in prothrombin content had been achieved with dicoumarol. The object in using the latter drug was to obtain a prothrombin content less than 30% of normal (Allen, 1947). This level was seldom attained before the fourth or fifth day of treatment. Dicoumarol was therefore started on the day of admission, the dose being 300 mg. on the first day, 200 mg. on the second day, and 100–200 mg. on the third day. All subsequent doses of dicoumarol were determined in relation to the daily estimation of the prothrombin time. The Fullerton (1940) modification of the Quick method, using venom as the source of thrombokinase, was the technique employed. It was appreciated that at low concentrations of prothrombin this method is less sensitive than the original Quick method in detecting minor variations in prothrombin content, but the same technique was used throughout this series.

The daily dose of dicoumarol was regulated approximately by the following guide: using a control prothrombin time of 19 seconds, 100–200 mg. of dicoumarol was given if the patient's prothrombin time was under 28 seconds, but if the prothrombin time was over 28 seconds a dose of 0–100 mg. was given. In regulating the dicoumarol dosage, Wright (1950) commends the Sterling Nichol formula whereby the ideal prothrombin therapeutic level is maintained between two and two-and-a-half times the control prothrombin-time for that day in the laboratory (Nichol and Borg, 1950). It is important to note that, unfortunately, there is no clinical guide to the regulation of dosage with this drug. Individuals vary greatly in their susceptibility to it, and the appropriate dose on any one day can be ordered only when the laboratory has reported on the prothrombin-time existing on that date. Patients given dicoumarol without laboratory control may bleed heavily. Even 150 mg. daily may lead to serious haemorrhage in a short period of time.

A minimum period of three weeks of dicoumarol therapy was decided upon for three reasons: (1) the great majority of thrombo-embolic phenomena occur during that period; (2) the clotting tendency previously mentioned tends to disappear towards the end of the third week; and (3) the effect of dicoumarol persists for several days after administration of the drug has ceased.

In this series the total dicoumarol dosage in the three weeks of treatment ranged from 1,100 mg. to 4,200 mg., the majority of cases receiving 2,000 to 3,000 mg. Haemorrhagic complications were treated by stopping the drug, and, if severe, by administration of vitamin K, 50 mg. intravenously as a single dose, with 100 to 150 mg. daily by mouth.

Comparison of Two Groups

Before drawing any conclusions regarding the efficacy of anticoagulant therapy it is necessary to compare the two series of cases in respect of similarity in important details. The immediate prognosis in myocardial infarction depends on a number of factors, which should be equally distributed between the two groups. Both series have therefore been analysed in respect of (1) age, (2) sex, (3) pre-existing hypertension, (4) pre-existing angina pectoris, (5) number of previous myocardial infarcts, (6) obesity, (7) myocardial state prior to the infarct, (8) duration from onset of symptoms to admission to hospital, (9) degree of shock at the onset, (10) incidence of heart failure, thrombo-embolic phenomena, and arrhythmias after the infarct, and (11) mortality rate within the first six weeks after the infarct.

Details of the age and sex incidence are given in Table V.

TABLE V.—*Presenting Details of the Age and Sex Incidence of the 154 Cases of Coronary Thrombosis Comprising the Present Series. The "Control" Series Consisted of 84 Patients and the "Treated" of 70 Patients Receiving Anticoagulants*

Age	Male				Female			
	Total		Died in Ward		Total		Died in Ward	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated
35– ..	1	1	1	—	—	—	—	—
40– ..	—	2	—	—	—	—	—	—
45– ..	9	4	1	—	1	—	—	—
50– ..	5	11	1	1	1	2	—	2
55– ..	8	8	2	1	6	1	4	—
60– ..	15	13	4	3	8	10	5	2
65– ..	9	3	3	1	7	9	4	5
70– ..	6	4	5	1	4	2	1	—
75+ ..	1	—	1	—	3	—	2	—
Total	54	46	18	7	30	24	16	9

In the control series the males averaged 60 and the females 64 years of age, while in the treated series the males averaged 57 and the females 64 years. So far as sex and age distributions are concerned, it appears that the two samples —control and treated—are sufficiently homogeneous to warrant comparison. As shown in Table VI, the incidence of hypertension and previous angina pectoris did not differ widely in the two groups, though the incidence of obesity

TABLE VI.—*Showing that the Incidence of Hypertension and Previous Angina Pectoris did Not Differ Widely Between the Two Groups, Though the Incidence of Obesity was Almost Twice as Great in the "Treated" Series*

	Male		Female	
	Control	Treated	Control	Treated
Previous hypertension	33 (61%)	24 (52%)	16 (53%)	19 (79%)
Previous angina ..	16 (30%)	20 (43%)	14 (47%)	15 (62%)
Obesity	12 (22%)	19 (41%)	12 (40%)	18 (75%)

TABLE VII.—*Showing that Multiple Attacks of Coronary Thrombosis had been More Commonly Experienced in Those Receiving Anticoagulants*

	Male				Female			
	Total		Died in Ward		Total		Died in Ward	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated
First..	48	32	16	3	27	16	14	7
Second	6	10	2	3	2	3	1	1
Third	—	3	—	—	1	3	1	1
Fourth	—	1	—	1	—	1	—	—
Fifth..	—	—	—	—	—	1	—	—

was almost twice as common in the treated series. Table VII demonstrates that multiple attacks of coronary thrombosis had been more commonly experienced in the treated series. One remarkable woman among those receiving anticoagulants had survived five myocardial infarcts.

In all cases in which a satisfactory history was obtained an attempt was made to gauge the state of the myocardium before the onset of the acute coronary occlusion. In some patients the attack was preceded for months or years by definite angina of effort; others had had no exertional pain but were restricted by dyspnoea; others again admitted to no cardiac symptoms previous to the occlusion. By applying the standards of functional capacity adopted by the New York Heart Association (1939) we placed our patients in the following broad categories:

Grade I patients are symptom-free, ordinary physical activity causing no discomfort.

Grade II A patients experience a slight-to-moderate limitation of physical activity. Walking on the flat out of doors at an average pace constantly reproduces ischaemic pain or dyspnoea after a few hundred yards.

Grade II B patients have a moderate-to-great limitation of activity. Less than ordinary activity causes discomfort. In this group we include those people who experience angina on light household activity or walking 20 to 50 yards out of doors, and those who have recurrent spontaneous attacks at rest, perhaps awakening them from sleep.

Grade III patients are those unable to carry on any physical activity without discomfort. As a rule they are confined to bed, congestive failure in some form being already present.

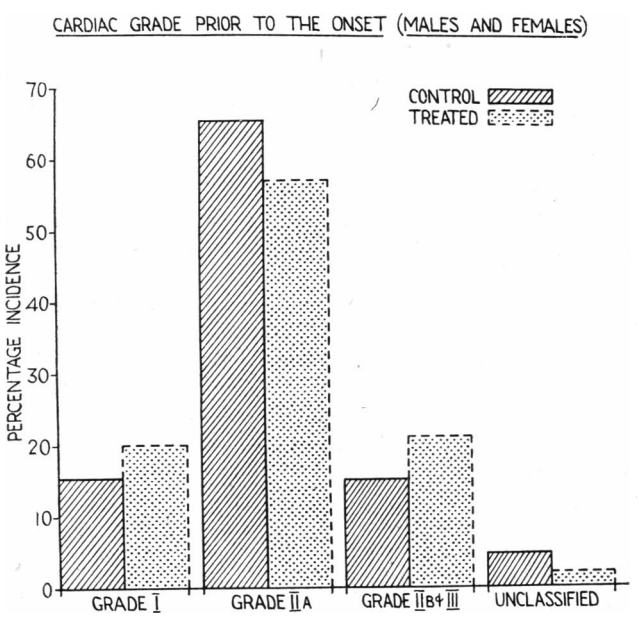

FIG. 1.—Incidence of various grades of functional capacity of the heart existing in the two series of cases of coronary thrombosis, previous to the onset of the acute occlusion. There is little difference between the "control" and the "treated" cases.

In applying this rough-and-ready measure of cardiac efficiency, we regarded symptoms developing comparatively suddenly during the two weeks immediately preceding the infarction as premonitory in nature and have not taken them into account in assessing the cardiac grade. The incidence of the various grades, which are evenly distributed between the two series, is shown in Fig. 1. Only in the treated series were there patients actually in congestive heart failure prior to the infarct.

For statistical purposes it is difficult to grade cases of myocardial infarction according to their severity. Clinically, the actual size of the infarct cannot be determined with much precision, nor does its extent determine the degree of shock. In an admittedly arbitrary fashion, the grade of shock, expressed according to clinical experience as severe, moderate, and mild or absent, may be taken as a measure of the severity of the illness. In a number of patients admitted some days after the onset the degree of shock could not be estimated, but Fig. 2 shows that the

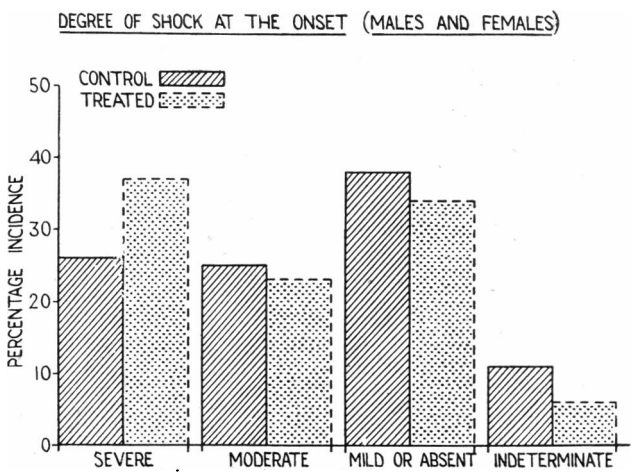

FIG. 2.—When the degree of shock is taken as a rough-and-ready measure of the severity of the attack of coronary thrombosis, the three grades—severe, moderate, and mild—were fairly evenly distributed between the two groups of patients.

three grades were fairly evenly distributed between the two series, with a preponderance of more severe cases in the treated group.

Finally, in the estimation of comparative mortality rates a further and commonly neglected factor has to be taken into consideration. A moment's reflection indicates that the mortality rate in a hospital series of cases of coronary thrombosis will be all the less the greater the delay in securing admission. It is known that the mortality rate in coronary thrombosis is highest in the first few days, and therefore the longer patients are excluded from the hospital the lower will be the death rate for the series, the more severe cases dying before admission. When the duration of illness before admission to hospital is compared, the two series—control and treated—are strikingly similar, 32% of the former and 34% of the latter arriving in hospital within 24 hours of the onset of the coronary occlusion (Fig. 3). Our two groups bear a close resemblance in this respect.

We may therefore conclude that the two samples—control and treated—in respect of sex and age distribution, pre-existing state of the heart muscle, severity of the acute attack, and duration of the illness before hospital treatment, are sufficiently homogeneous to warrant comparison.

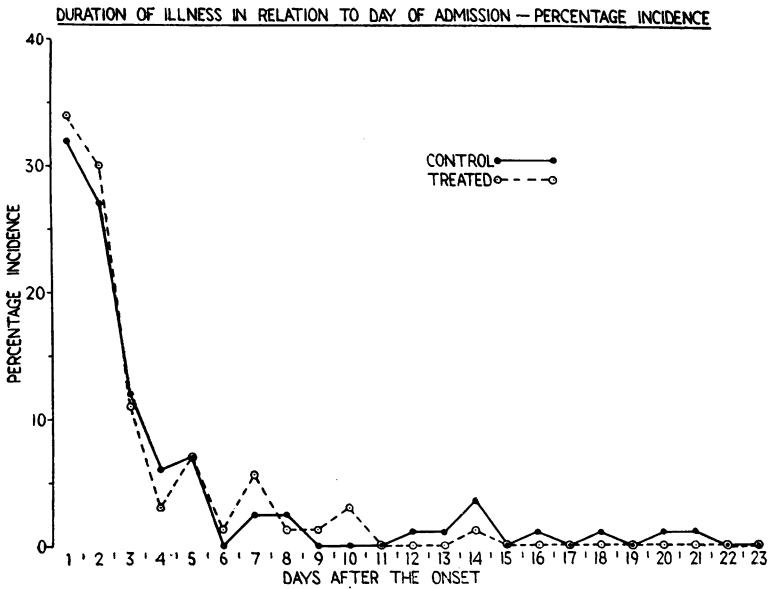

FIG. 3.—The duration of the illness as measured from the time of onset until admission to the ward is strikingly similar in the two groups, 32% of the "controls" and 34% of the "treated" arriving in hospital within the first 24 hours.

Results of Anticoagulant Therapy

In as severe an illness as coronary thrombosis it is natural to assess the results of treatment on the basis of (1) mortality rates and (2) incidence of thrombo-embolic complications.

Our experience is that 34 of the control group of 84 persons died within six weeks of the onset, giving a mortality of 40.5%. This contrasts with the 16 deaths among 70 persons in the treated series, with a mortality rate of 22.8%. It would appear that by efficient anticoagulant therapy during the first three weeks after the myocardial infarct the mortality rate in the first six weeks may be almost halved. Our experience confirms the American conclusions to which reference has already been made.

When the sexes are considered separately it is apparent that the males show a greater improvement than do the females. The reduction in male mortality rate is of statistical significance, the degree of probability (P) being less than 0.05. In the control group of males the death rate was 33.3%—18 deaths among 54 men. In the treated group, composed of 46 males, 7 died, giving a mortality rate of 15.2% (Fig. 4). This is a striking difference, and, being of statistical significance, we conclude that in males, during the first six weeks after a myocardial infarct, the death rate can be reduced by half. Analysis of the figures for females does not allow similar deductions, largely owing to the smaller number of cases observed. In the control series 16 of the 30 females died, giving a mortality rate of 53.3%; whereas 9 deaths occurred among the 24 females in the treated series, the mortality rate being 37.5%. Such a difference is not of statistical significance.

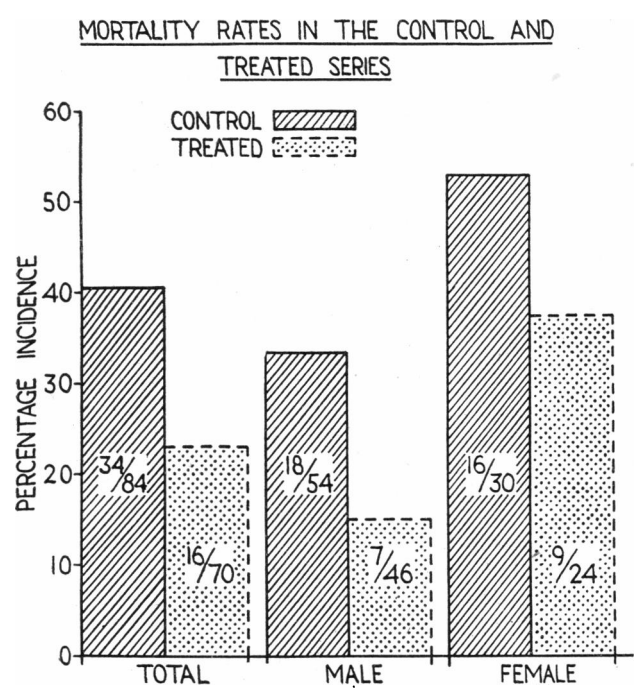

FIG. 4.—Efficient anticoagulant therapy reduces the total mortality rate by half. The difference is statistically significant among men. The smaller experience, based on 30 "control" and 24 "treated" females, does not justify similar conclusions among women.

In estimating the prognosis after myocardial infarction, one factor of great importance is the state of the heart muscle at the time when the acute coronary occlusion was sustained. By using the method of functional grading to which reference has already been made, it becomes apparent that those patients referred for treatment in the hospital who have been in Grade I immediately prior to their coronary occlusion seldom die, provided they survive the immediate effects of the occlusion long enough to be admitted to the ward. In contrast to this, patients in cardiac Grade II B when the infarct is sustained seldom recover. Grade III cases, already seriously handicapped, never recover. Fortunately, the majority of victims fall into the Grade II A capacity, and it is in this grade that every aspect of the case must be carefully considered.

Our patients classified as Grade II A prior to the infarct total 55 in the control group and 40 in the treated group, including 38 and 23 males respectively. The most striking difference is observed in the mortality of these Grade II A males. Among the control group the mortality was 31.6%, whereas among the treated males 1 of 23 died —a mortality of 4.4%. This improvement is of statistical significance, P being almost 0.01. We make no claim for any betterment in the other groups, male or female, but we suggest that when a larger series of some hundred cases is presented for statistical analysis it would be advantageous to have these patients assessed in regard to their functional capacity before the myocardial infarct was sustained. We have proof that it is possible to influence the course of events favourably in regard to males classified in Grade II A. Our figures do not suggest that one particular age group in either sex derives greater benefit than any other age group.

As a further test of the efficacy of anticoagulant therapy, the incidence of thrombo-embolic episodes in the two groups has been analysed (Fig. 5). No fewer than 24 patients (28.6%) in the control series developed thrombo-embolic complications of one kind or another while under observation, and 13 of these died. Ten deaths were the outcome of the thrombo-embolic complication, while in three cases death was unrelated to the complication. On the other hand, 9 (13%) of the 70 patients in the treated group developed thrombo-embolic complications, and of these 4 died. No death followed immediately on any such

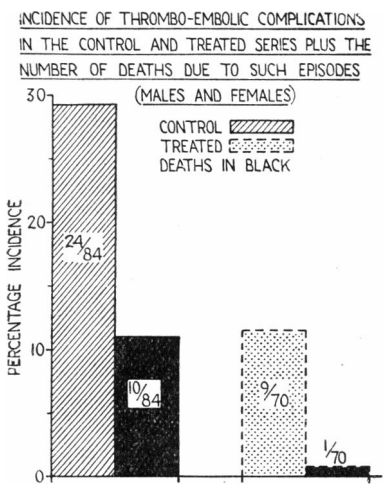

FIG. 5.—The incidence of thrombo-embolic complications was reduced from 28.6% in the "controls" to 13% in the anticoagulant "treated" group. In the "control" group 10 deaths were attributable to these complications, in contrast with one death in the "treated" series.

complication, but in one patient death was related to an embolic incident. The incidence of complications was 13% in the treated group—less than half that observed amongst the controls. Taking the incidence of complications separately between males and females, no significant reduction is observed statistically. However, as the data show no significant difference in the incidence of complications as between males and females, they may reasonably be taken together as one group, and if this is done there is then a significant difference in the incidence of complications between the treated and control groups (P being 0.01). We can therefore confirm the observation of Wright *et al.* (1948) that the incidence of thrombo-embolic complications in myocardial infarction can be reduced by half by the proper use of anticoagulants.

Marple and Wright (1948) have drawn attention to the possible relationship of a lapse in dicoumarol therapy to the occurrence of thrombo-embolic episodes. In this series seven patients sustained thrombo-embolic complications during the first four to five days of treatment, either while heparin was being given or during the 24 hours after the heparin had been stopped. The two episodes occurring at a later date developed in adequately treated males.

Other Complications

Other complications of significance occurring during the period of treatment in hospital were the development of heart failure and the occurrence of arrhythmias. Heart failure developed in 23 cases in each series—an incidence of 27% in the control series and 33% in the treated series. In the control series 17 of the 23 patients died—a death rate of 74%, but in the treated series only 13 died—a death rate of 56.5%. Arrhythmias occurred in seven cases of each series; four deaths occurred in the control group and five in the treated series.

The causes of death in the two series are listed in Table VIII. It will be seen that in the control series death resulted from a variety of causes, while in the treated series the great majority of patients died in heart failure. One patient in each series died suddenly from rupture of the infarcted area. Our necropsy experience in both series is small and unsuited for statistical analysis. In the control series 12 cases came to necropsy. Six showed mural thrombus formation; of these, four had had thrombo-embolic complications. In the treated group there were nine post-mortem examinations. Mural thrombus was found in the ventricles in two patients and thrombo-embolic phenomena were limited to one of these—the first female to be treated—in whom the anticoagulant therapy then employed would now be regarded as inadequate.

TABLE VIII.—*Causes of Death in the Two Series of Patients*

	Control	Treated
Heart failure	7	8
Persistent shock	2	—
Recurrence of myocardial infarct	5	—
Cerebral embolus	3	1
Sudden death	10	7
Coma	1	—
Death within 24 hours of onset	6	—

General Considerations

All the reports in the literature substantiate the claim that anticoagulants are at the present day a remedy of outstanding value in the treatment of coronary thrombosis. By their proper use the death rate and the incidence of thrombo-embolic complications can each be reduced by half—a very substantial contribution to the treatment of this serious disease.

Unfortunately, with the anticoagulants at present available, it is a tedious and difficult form of therapy, depending upon laboratory facilities, a reliable technique, and trustworthy technicians in whose hands is the life of the patient. More laboratory assistants require to be trained for this work so that this particular treatment can be made available to larger sections of the community, even outside the walls of the hospital. Until a domiciliary service can be arranged, the only alternative is to refer such cases of coronary occlusion as are fit to be moved, to those institutions where appropriate laboratory facilities exist for the control of anticoagulant therapy. The practitioner can always begin treatment with heparin in the patient's home, but at present the coumarol compounds cannot be used without daily estimations of prothrombin time. The mortality rate for coronary thrombosis throughout the general population will fall when a larger number of hospital beds are made available for its treatment and when a domiciliary laboratory service provides the practitioner with technical help, without which this particular treatment cannot be undertaken.

No doubt the use of anticoagulants may be simplified in the future. At the present time they are difficult to handle. A painless, inexpensive, slow-acting but reliable substitute for intravenous heparin would be a great advantage. We have been disappointed in depot-heparin and heparin-retard, partly on account of the intense and persistent local pain after the intramuscular injection and partly on account of irregular absorption. "Heparin-Evans" (25,000 units per ml.) has proved more satisfactory when given at eight-hour intervals intramuscularly in doses of 20,000 units. This amount will usually maintain a clotting time in excess of 20 minutes throughout an eight-hour period. We have no personal experience of new synthetic heparin-like substances, such as "paritol," which have the virtue of cheapness and are now under clinical trial (Sorenson *et al.*, 1949). "Tromexan" (Burt, Wright, and Kubik, 1949) possesses certain advantages over dicoumarol in that it comes into action more quickly and is less cumulative. The oral dose being larger, it can be more easily adjusted from day to day. It should be given in divided amounts at 6-hour to 12-hour intervals according to the morning prothrombin-time.

Finally, it is worth emphasizing that there are definite contraindications to dicoumarol and tromexan. In view of the risk of serious haemorrhage, they should not be used in the presence of hepatic or renal disease, or the severer anaemias, pregnancy, or vitamin deficiencies. Any ulcerated surface, particularly of mucous membranes, such as a peptic ulcer or a diverticulitis, may bleed profusely when these drugs are used.

Conclusions

Anticoagulant therapy, suitably controlled by specialized techniques, reduces by one-half the mortality rate during the first six weeks after myocardial infarction. Our experience is that it appears to benefit males to a greater extent than females, particularly men whose myocardial efficiency was only slightly impaired before the acute damage was sustained.

Thrombo-embolic complications are reduced by half, and, when they do occur, fatalities are lessened.

Anticoagulant therapy cannot succeed in the absence of strict attention to the established methods of treatment. It does not shorten the stay in bed.

It should be considered for every sufferer from myocardial infarction. This implies an extension of laboratory facilities for the regulation of treatment and a greater number of hospital beds set aside for this purpose. A scheme for domiciliary laboratory control is desirable if the practitioner is to continue to care for these patients.

For the purposes of this investigation Professor Stanley Davidson, Dr. W. D. D. Small, and Dr. W. A. Alexander have kindly given us access to patients suffering from coronary thrombosis under their immediate charge in the Royal Infirmary. We are also indebted to Mr. George Waugh, F.F.A., of the Scottish Statistical Research Bureau, for help in the statistical analysis of our findings.

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CAPILLARY RESISTANCE AND ADRENOCORTICAL ACTIVITY

BY

H. N. ROBSON, M.B., M.R.C.P.Ed.

AND

J. J. R. DUTHIE, M.B., F.R.C.P.Ed.

(From the Department of Medicine, University of Edinburgh; Rheumatic Unit, Northern General Hospital; and the Eastern General Hospital, Edinburgh)

The starting-point of the present investigation was the observation that the resistance of skin capillaries to rupture by negative pressure rises sharply after many types of surgical operation (Scarborough, 1944). It was decided to study the effects on capillary resistance of other types of tissue damage. The variety of such types of damage which produced increased capillary resistance led to the possibility that this rise might be produced by any form of non-specific stress. Positive results were obtained after the application of various forms of stress. Interest was then stimulated by recent work on the physiology of the pituitary – adrenal axis, and it seemed possible that all the conditions which had been investigated were such as would lead to activation of this axis through the release of endogenous adrenaline or through some other pathway as yet unknown. This paper describes the investigations outlined above, leading to the study of the effects of the injection of adrenocorticotrophic hormone (A.C.T.H.) on capillary resistance.

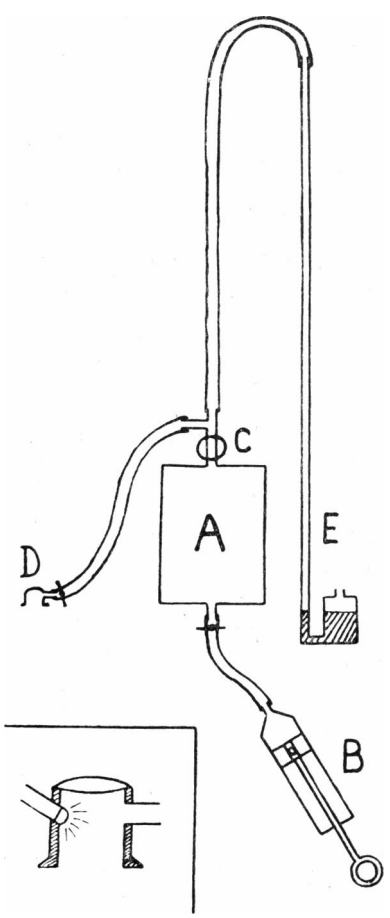

FIG. 1.—Diagram of apparatus used.

Methods

Capillary resistance has been measured throughout these studies by a negative pressure method. The apparatus (Fig. 1) was the same as that used by