When in 1828 University College was opened as the beginning of a University of London, it had some difficulty in arranging its medical courses. Until 1836 the university students used to take the L.S.A. The secretary or warden of University College wrote to the Society of Apothecaries, and a special meeting of the court of examiners was held on April 14, 1829. Another meeting took place on April 28 and resolved "that a committee consisting of four members of the court be appointed for the purpose of arranging with the Council of the University of London a plan of medical study to be pursued in that institution, so that both the views of the medical professors of the University and the spirit of the regulation of this court may be fulfilled." The University welcomed the proposal, and a useful conference was held to consider the matter. Later two representatives of the Society were put on the Senate of London University.

Testimonies to the Society's Work

The great effect upon medical education produced by the painstaking work of the Society of Apothecaries was praised by all informed opinion of the time. It improved medical practice and raised the status of the practitioner; it was instrumental in causing many provincial medical schools to be founded and beneficially influenced the London medical schools. Let us listen to some of those who had been opposed to the Act of 1815, but changed their minds when they saw how it was administered. They gave evidence before the Select Committee of 1834.

Sir Henry Holford, President of the Royal College of Physicians, was quite definite and explicit in his evidence: "I was one of those that was sorry that the power was ever given out of the hands of the physician to license practitioners of that description; but since they have had it I must do the apothecaries the justice to say that they have executed that Act extremely well; and that the character of that branch of the profession has been amazingly raised since they have had that authority; I only do them justice when I state that, though I was very much against it in the first instance."

Sir David Barry testified that "the examination now given at the Apothecaries Hall is by far the best and the most likely to produce the stimulus to study and emulation among the pupils of any at present in London."

Finally, hear what the President of the Royal College of Surgeons of that time said to the Committee. "I beg to say that the Court of Examiners of the Apothecaries' Company have done their duty admirably and for the advantage of the public; and I would let no surgeon take out his diploma at the College of Surgeons till after he had been examined by the board appointed by the Society of Apothecaries."

These testimonies, given by those who were convinced against their will of the remarkable work in medical education performed by the ancient and honourable Society, are sufficient to place the role of the Society in fashioning medical practice in this country in its correct and important position.

When in 1858 was passed the Medical Act which created the General Medical Council and organized medical education on a broader basis, the Society of Apothecaries raised no objections, but helped in every possible way to bring about the change. The gracious way in which they relinquished their responsible task did them as much honour as the readiness with which they performed the difficult duty put upon them 43 years previously. Since that time they have maintained their position as a responsible qualifying body, sustained and encouraged by the records and memories leading back to the golden age when they wielded such a benevolent control over medical education in this country.

I wish to express my thanks to the Society of Apothecaries for permission to consult their records, some kept in their own building and others at the Guildhall. My gratitude is also due to Dr. H. C. Cameron, who kindly allowed me to read the proofs of his forthcoming book on the history of the Apothecaries' Society.

ANTICOAGULANT THERAPY IN CARDIAC INFARCTION

BY

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Although the efficacy of the anticoagulant drugs in reducing mortality in the few weeks immediately following cardiac infarction is now conceded by most authorities, there still exists some difference of opinion. For example, Evans (1954) has expressed the view that they have no useful place in treatment, while Russek and Zohman (1952) considered their use justified only in "poor risk" cases. Wright *et al.* (1954) in America, and Gilchrist and Tulloch (1954), in Great Britain, have been the most enthusiastic advocates of this form of therapy in all patients admitted to hospital with cardiac infarction, and they claim mortality rates of 16% (Wright *et al.*, 1954) and approximately 15% (Gilchrist and Tulloch, 1954) with therapy as compared with 23.4% and approximately 28% respectively with the conventional treatment without anticoagulants.

The subject is one of such importance that the publication of further series is still justified, and this consideration has stimulated us to analyse our figures for the period 1949-54. An opportunity was also afforded to us of analysing a series of patients treated for a few weeks with heparin intramuscularly. This form of treatment is often used for a few days after cardiac infarction, but the period of observation is usually too short to allow valid conclusions to be drawn. It was felt that the figures for the long-term heparin series might provide clearer information about a form of treatment which is expensive and, at the same time, usually causes considerable discomfort or pain to the patient.

Material

The material for this study comprised patients with recent myocardial infarction admitted to the wards of Aberdeen Royal Infirmary and Woodend Hospital during 1949-54. Electrocardiographic confirmation of the clinical diagnosis has not been regarded as essential in all cases included in the survey, since the frequency with which electrocardiograms could be obtained varied somewhat in the different wards and at different times throughout the period of the survey.

The following groups were excluded from the survey: (1) all patients who died within 24 hours of admission to hospital, because it was felt that this period was too short for effective action of the oral anticoagulants; (2) patients who had sustained the infarction more than 48 hours before admission to hospital, as judged by the history; (3) patients whose period of observation in hospital was less than three weeks; and (4) patients under 40 and over 70 years, since the numbers of these younger and more elderly patients were small.

The cases are divided into three groups, as follows.

Group I consists of patients admitted to one of the wards of Aberdeen Royal Infirmary who, in addition to conventional treatment, had anticoagulant therapy with ethyl biscoumacetate ("tromexan") for a minimum of three weeks and an average duration of four weeks. This treatment has been used routinely in this ward in patients with cardiac infarction except for the very small number with an

obvious contraindication—for example, haemorrhagic tendencies, peptic ulceration with recent haemorrhage, renal failure, etc. In this group there are 102 patients (70 males and 32 females).

Group II comprises patients admitted to another ward of Aberdeen Royal Infirmary who were treated with heparin intramuscularly. The dosage was 12,500 units twice daily without regular control by clotting-time estimations. The duration of this treatment was usually about three weeks. This group comprises 62 patients (41 males and 21 females).

Group III consists of 150 patients (91 males and 59 females) admitted to two wards in Woodend Hospital. Anticoagulant therapy was not used in these wards during the period of the survey, and accordingly these patients constitute the control group.

The group into which each patient was placed depended simply on the ward to which he was admitted, which in turn depended solely on which day of the week he was admitted to hospital. It is therefore considered that the groups are comparable in all respects except for a higher average age in the control group. To overcome this discrepancy the results have been analysed separately for the three decades, 40-49, 50-59, and 60-69 years. In none of the wards included in the survey was the interest of the staff predominantly in cardiovascular diseases. It was felt that inclusion of wards with a preponderance of patients with heart disease might to some extent influence the type of patient admitted. Accordingly these wards have not been included in the survey.

Duration of Observation

All patients who were not observed in hospital for a minimum of three weeks have been excluded from the survey unless death occurred during this period. The average duration of observation in Group I was 39.5 days, in Group II 33 days, and in Group III 39.5 days. It is important to note that the average period of observation in Groups I and III was exactly the same. The shorter period in the heparin group gives a slight weighting in favour of a reduced mortality and incidence of thrombo-embolic complications in this group.

Results

Table I shows the results in Group I. Of the 102 patients in this group, only 8 (7.8%) died whilst under observation,

TABLE I.—Patients Treated with Ethyl Biscoumacetate (Group I)

	Age in Years			Total
	40-49	50-59	60-69	
Uncomplicated	19	33	27	79 (77.5%)
Thrombo-embolic complications ..	3	9	3	15 (14.7%)
Deaths	1	4	3	8 (7.8%)
Total	23	46	33	102

TABLE II.—Patients Treated with Heparin (Group II)

	Age in Years			Total
	40-49	50-59	60-69	
Uncomplicated	15	13	14	42 (67.7%)
Thrombo-embolic complications ..	1	0	4	5 (8.1%)
Deaths	1	4	10	15 (24.2%)
Total	17	17	28	62

TABLE III.—Control Group (Group III)

	Age in Years			Total
	40-49	50-59	60-69	
Uncomplicated	14	24	45	83 (55.3%)
Thrombo-embolic complications ..	3	9	10	22 (14.7%)
Deaths	5	6	34	45 (30.0%)
Total	22	39	89	150

and 15 (14.7%) developed a thrombo-embolic complication with survival. Thus 79 (77.5%) had an uncomplicated course while under observation. Tables II and III give the figures for the heparin and the control groups respectively. From Table III it can be seen that the mortality rate shows a tendency to increase with age. The mortality rates for the three groups are presented together in Table IV: this shows that the mortality rate in patients treated with ethyl biscoumacetate is much less than that in the control group.

TABLE IV.—Deaths

Group		Age in Years			Total
		40-49	50-59	60-69	
I	No. Deaths	23 1 (4.3%)	46 4 (8.7%)	33 3 (9.1%)	102 8 (7.8%)
II	No. Deaths	17 1 (5.9%)	17 4 (23.5%)	28 10 (35.7%)	62 15 (24.2%)
III	No. Deaths	22 5 (22.7%)	39 6 (15.4%)	89 34 (38.2%)	150 45 (30%)

This is true of each decade, and is particularly striking in the 60-69 group, in which the mortality rate has been reduced from 38% (89 patients with 34 deaths) to 9% (33 patients with 3 deaths). The total mortality rate in the heparin-treated group is slightly less than in the control group, but the rate is markedly less only in the 40-49 decade, and it is greater in the 50-59 decade than in the control group.

Incidence of Thrombo-embolism

The object of anticoagulant therapy is, theoretically, to reduce the frequency of recurrence or extension of the cardiac infarction and other thrombo-embolic complications. Even if this form of treatment were completely successful in this respect there would still remain a significant mortality after cardiac infarction from such causes as shock, cardiac failure, rupture of the heart, and intercurrent disease. Accordingly the efficacy of ethyl biscoumacetate and heparin has been assessed by comparing the figures for (a) all thrombo-embolic complications, and (b) fatal thrombo-embolism, including extension or recurrence of cardiac infarction, in the three groups. The results are presented in Table V and represented diagrammatically in Fig. 1. It is clearly seen that the incidence of thrombo-embolism in the ethyl biscoumacetate group is much less than in the controls, and the frequency of death from such an occurrence is much reduced in each decade. In other words, a patient treated with ethyl biscoumacetate is less likely to develop further thrombo-embolism after cardiac infarction, and, if he does, his chances of dying as a result of it are very much reduced.

FIG. 1.—Incidence of thrombo-embolic complications. T = Group I; H = Group II; C = Group III.

TABLE V.—Incidence of Thrombo-embolic Complications (T.E.C.)

Group		Age in Years			Total
		40-49	50-59	60-69	
I	No. of patients	23	46	33	102
	Total T.E.C.	4 (17.4%)	11 (23.1%)	6 (18.2%)	21 (20.6%)
	Fatal T.E.C.	1 (4.3%)	2 (4.3%)	3 (9.1%)	6 (5.9%)
II	No. of patients	17	17	28	62
	Total T.E.C.	2 (11.8%)	4 (23.5%)	12 (42.9%)	18 (29.0%)
	Fatal T.E.C.	1 (5.9%)	4 (23.5%)	8 (28.6%)	13 (21.0%)
III	No. of patients	22	39	89	150
	Total T.E.C.	6 (27.3%)	14 (35.9%)	34 (38.2%)	54 (36.0%)
	Fatal T.E.C.	3 (13.6%)	5 (12.8%)	24 (27.0%)	32 (21.3%)

The figures for the heparin series are more difficult to assess. In the 40-49 decade the incidence of thrombo-embolism is less than in the ethyl biscoumacetate and control groups; in the 50-59 decade all the patients who developed thrombo-embolism died as a result; and in the 60-69 decade the incidence of thrombo-embolism and the deaths from this cause are slightly higher than in the controls and much higher than in the ethyl biscoumacetate group. The numbers are perhaps too small to allow definite conclusions to be drawn, but it would appear that heparin, as used in this series, did not reduce significantly the incidence of thrombo-embolic complications or of deaths resulting from them.

Causes of Death

A brief account of the causes of death in the three groups is of interest.

In the ethyl biscoumacetate group, six of the eight patients who died had an extension or a recurrence of cardiac infarction. There were no instances of peripheral thrombo-embolism. The remaining two patients in this group died following a ruptured heart muscle; both were in the 50-59 age group. Neither had had a previous episode of myocardial infarction so far as could be ascertained from the history and from the necropsy findings. One had a rupture of the right ventricle with haemopericardium, and the other ruptured the papillary muscle of the mitral valve, with resultant massive pulmonary oedema.

Of the patients treated with heparin, 15 died—11 as a result of a further myocardial infarction, 2 from cerebral embolism, 1 developed intractable cardiac failure, and 1 died in uraemia.

In the control group there were 45 deaths: 24 patients died as a result of another myocardial infarction; 8 deaths were due to peripheral thrombo-embolic complications; 8 died in cardiac failure, 4 in peripheral failure, and 1 during an Adams-Stokes attack.

All the deaths occurred within six weeks of the onset of the illness, the majority of them in the first week. The time incidence of these occurrences is shown graphically in Fig. 2, where the number of deaths in each week is expressed as a percentage of the total in each group. This shows that the number of deaths falls rapidly week by week, and after the fourth week death occurred only in the control group, when there were three deaths due to recurrence of myocardial infarction.

FIG. 2.—Deaths per week as a percentage of total group.

Control of Ethyl Biscoumacetate Therapy

During most of the five-year period the dosage of ethyl biscoumacetate was governed by the results of the one-stage "prothrombin time," using Russell viper venom (Fullerton, 1940). For part of the time the venom-and-lecithin method (Witts and Hobson, 1940) and human brain extract were used as well. It is not our purpose at present to consider the comparative merits of these different tests, but attention should be drawn to the satisfactory results obtained by the venom method in our hands, although this test was introduced before the advent of anticoagulant therapy. The mortality rate in the ethyl biscoumacetate series is less than in any other published series of comparable size, so that the venom method can be accepted as giving a good indication of effective therapeutic dosage of that drug.

Of the 102 patients who received a full course (not less than three weeks) of ethyl biscoumacetate, only four developed microscopic haematuria. In these, anticoagulant therapy was continued in reduced dosage for one to two days

and then in full dosage for the remainder of the course without further haemorrhagic manifestations. In addition, five patients had more severe bleeding, necessitating withdrawal of the anticoagulant before the end of the course. Of these, three had macroscopic haematuria for two to three days, and one had rectal haemorrhage, the significance of which was doubtful, since he suffered from haemorrhoids. The fifth had severe haematemesis, and this was the only case in which blood transfusion and vitamin K₁ had to be used. There was no previous history of peptic ulceration, and a later barium-meal examination showed no gastro-intestinal lesion. This incidence of haemorrhagic complications compares favourably with that given for most series in which brain extract was used.

Accordingly, on grounds both of efficacy and of safety, the venom method has been found satisfactory, and we feel that many of the objections raised to it have been due to a failure to appreciate that lipaemia and slight haemolysis result in a shortening of the one-stage "prothrombin time" (Fullerton and Anastasopoulos, 1949). We are of the opinion that the very low mortality rate in the ethyl biscoumacetate series and the reliability of the venom method have been due mainly to the fact that all the blood samples were collected, the "prothrombin times" were done, and the dosage of ethyl biscoumacetate was decided upon by one individual. At the same time we do not wish to contend that brain extract does not have advantages as compared with venom, and it is quite clear that these advantages are definite if "prothrombin times" are estimated on blood samples withdrawn and handled without due care.

Early Deaths

All patients who died within 24 hours of admission to hospital were classified as "early deaths" and excluded from this survey. During the years 1949-54 there were 38 such deaths in the wards contributing to this study. The age distribution was as follows: 40-49 years, 4 cases; 50-59, 13 cases; and 60-69, 21 cases. Unfortunately necropsies were obtained in relatively few, but the most common cause of death appeared to be recurrence or extension of the original infarction. In an attempt to reduce this number of early deaths each patient is now treated initially with heparin as well as with oral anticoagulants. The first dose of heparin is 200 mg. intravenously. The clotting-time (Lee and White, 1913) is estimated at five-hour intervals. If it exceeds 20 minutes, heparin is withheld and the clotting-time repeated after a further two hours. If the clotting-time is 15-20 seconds, 150 mg. of heparin is injected intravenously; if it is less than 15 seconds, 200 mg. is given. The heparin treatment is continued for at least 24 hours.

Summary

Anticoagulant therapy with ethyl biscoumacetate greatly reduced the incidence of thrombo-embolic complications and the mortality rate in a series of 102 cases of cardiac infarction.

Prolonged treatment with intramuscular heparin was without notable effect in 62 cases.

In view of the large number of deaths occurring early after an episode of cardiac infarction, large doses of heparin should be given for at least 24 hours as well as oral anticoagulants.

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