enterostomy, 45 patients being deprived of their ability to take a normal-size meal by partial gastrectomy as against 23 by vagotomy and gastro-enterostomy.

Ability to take a One- or Two-course Meal

Of the 100 patients under consideration, nine were found to have been deprived by vagotomy and gastro-enterostomy of their ability to take a sweet course. The distribution of these nine patients in the two groups is as follows:

Group A: of the 77 patients able to take a normal-size meal, only one did not take a sweet course.

Group B: of the 23 patients unable to take a normal-size meal, eight did not take a sweet course.

The actual figures obtained were:

Sweet Course			
Group A		Group B	
Yes	69	Yes	13
No	1	No	8
No/No	7	No/No	2

"No/No" indicates that the patient did not take a sweet course prior to the ulcer or after operation. It was found that 69 patients were taking a normal-size meal with a sweet course and eight were not taking a normal-size mixed meal or sweet course.

Evaluation.—The advantage here is overwhelmingly on the side of vagotomy and gastro-enterostomy, 35 patients being deprived by partial gastrectomy of their ability to take a sweet course as against nine similarly deprived by vagotomy and gastro-enterostomy.

Selective Impairment of Digestion

Group A

Selective Impairment of Digestion in 69 Patients Having a Normal-size Mixed Meal With a Sweet Course

Ability to Take	Yes	No	No/No	Uncertain
Milk	52	2	7	—
" puddings	63	3	2	—
Fatty foods	58	8	3	—
Eggs	59	7	3	—
Chocolates	55	5	7	—
Pastries	58	5	6	—

In addition to the above, eight patients did not drink milk and one did not take milk puddings; both could have done so had they wished.

Group B

Selective Impairment of Digestion in Eight Patients Unable to Take a Normal-size Mixed Meal or a Sweet Course

Ability to Take	Yes	No	No/No	Uncertain
Milk	3	5	—	—
" puddings	1	6	1	—
Fatty foods	1	6	—	1
Eggs	3	4	—	1
Chocolates	3	3	1	1
Pastries	2	5	1	—

The selective impairment of digestion in the 100 patients treated by partial gastrectomy and the 100 patients treated by vagotomy and gastro-enterostomy was as follows:

	No Milk	No Milk Puddings	No Fatty Foods	No Eggs
After P.G.	30	32	25	20
" vag. and P.G.E.	7	10	17	14

Evaluation.—These figures show a clearly defined advantage on the side of vagotomy and gastro-enterostomy.

Incidence of Dumping Attacks

The total number of patients with dumping was 12. In six these attacks were not related to meals. This group is constituted as follows: one patient with dumping attacks approximately once a month after exercise; one patient

with dumping attacks twice a week associated with emotion and exercise; one patient with dumping attacks occasionally after emotion; two patients with dumping attacks once a month with no ascertainable cause; one patient with three attacks of dumping in eight months with no ascertainable cause.

In the six patients in whom dumping attacks bore a definite relation to meals the record is as follows: two had dumping after hot milk, one after "horlicks"; one slightly after fatty foods; one after the midday meal irrespective of its nature; and one had two attacks a month, usually after breakfast.

Evaluation.—The incidence of dumping after vagotomy and gastro-enterostomy is less than after partial gastrectomy. The attacks are less often associated with particular foods, and there is therefore not the same necessity to restrict the diet in order to avoid the attacks.

Summary

There is no material difference in the incidence of biliary regurgitation after partial gastrectomy and that after vagotomy and gastro-enterostomy; the incidence of dumping is less after vagotomy and gastro-enterostomy; the outstanding advantage of vagotomy and gastro-enterostomy over partial gastrectomy is in the nutrition of the patient; more patients take a normal-size meal, more patients take a sweet course, fewer patients suffer from a selective impairment of digestion—and the difference in all three points is substantial.

It is a pleasure to thank the South Manchester Hospitals Management Committee for financial assistance in carrying out this work. The diagram was produced by the department of medical illustration.

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CLINICAL EVALUATION OF THREE ANTICOAGULANTS IN THROMBO- EMBOLIC DISEASE

BY

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Although anticoagulant therapy is at present widely accepted as being of value in thrombo-embolic disorders, there is less agreement on the best agent for inducing a therapeutic degree of prolongation of the one-stage prothrombin time.

The most commonly used oral anticoagulants in this country are ethyl biscoumacetate ("tromexan") and phenindione ("dindevan"), both of which rapidly produce an effect of comparatively short duration. The former is apt to produce frequent wide fluctuations in the prothrombin time, particularly during the first ten days of treatment (Barker, 1952). Toohy (1953) has reported favourably on the actions of phenindione. A third anticoagulant, cyclocoumarol ("cumopyran"), or 3,4-(2'-methyl-2'-methoxy-4'-phenyl) dihydropyranocoumarin, has become available in this country recently. It was first synthesized by Ikawa in 1942 in Link's laboratory during an investigation of substances chemi-

cally related to dicoumarol. Under the name of anticoagulant No. 63 it has been experimentally and clinically assessed in America (Battle *et al.*, 1950; Brambel *et al.*, 1950; Rotter and Meyer, 1951, 1952; Barker *et al.*, 1952), but so far no account of its effects has been published in this country.

In this paper the results obtained in treating 57 patients with cyclocoumarol, 125 with ethyl biscoumacetate, and 179 with phenindione are analysed and compared.

Methods

In general, in estimating the initial dosage, attention was paid to the age and weight of the patient and to evidence of cardiac failure and renal or hepatic disease. Any history of recent dyspepsia, especially in patients known to have been sufferers from peptic ulceration, and any source of bleeding were considered contraindications to the use of anticoagulants.

Patients given ethyl biscoumacetate or phenindione received 10,000–15,000 units of heparin intravenously every six hours for the first 24 hours of anticoagulant therapy. Because of its slower effect on the prothrombin time, those given cyclocoumarol received the same dosage of heparin six-hourly for 48 hours.

Each of the three drugs was given by mouth in divided doses at 2 p.m. and 10 p.m. An initial prothrombin time was estimated only when there was any reason to suspect that it would be abnormal. Subsequent dosage was dictated by the prothrombin time. For this purpose blood was withdrawn each day at 9 a.m. and the prothrombin time (Quick's one-stage clotting-time) was estimated, using as a source of thromboplastin a carbol-saline extract of human brain (Toohey, 1950). A control prothrombin time was done daily on a suitable subject, and all results were expressed in seconds. The control prothrombin time varied between 14 and 16 seconds. If the control prothrombin time exceeded 16 seconds it was discarded as unsuitable and a fresh control was selected. A patient's prothrombin time was regarded as being within therapeutic limits if it lay between two to three times the control value.

We decided to avoid converting the patient's prothrombin time into a percentage of normal prothrombin activity by the use of a calibration curve of the prothrombin times of serial dilutions of normal plasma. The use of such a percentage figure—the so-called "prothrombin concentration"—makes comparisons between the results from different laboratories using dissimilar sources of thromboplastin difficult and leads to the misconception that prothrombin activity is measured by the prothrombin time.

All dosage was controlled by us and by the consultant clinical biochemist. The urine of each patient receiving cyclocoumarol was examined daily for microscopic haematuria.

Results

The age, sex, and weight distributions of the three series were similar. Table I shows the diagnoses in the respective series. The initial dosages of the three substances were:

Ethyl Biscoumacetate.—The usual initial dose was 600 mg. followed eight hours later by a further 600 mg. On the second day of therapy two doses of 300 mg. were most

frequently used. The total amount given in the first 48 hours, however, varied from 300 to 2,400 mg.

Phenindione.—The most common dosage schedule was 200 mg. divided into two doses on the first day with two 50-mg. doses on the second, but again there was a wide variation in the amounts used. The sum of the doses given in the first 48 hours varies from only 125 mg. to as much as 650 mg.

Cyclocoumarol.—Two 75-mg. or two 50-mg. doses on the first day were found to be adequate for most cases. On the second day two 12.5-mg. or two 25-mg. doses were most often necessary.

Initial Response.

—The Graph shows the initial responses achieved in each of the three series. Within 48 hours of the first dose of ethyl biscoumacetate the prothrombin time of 85% of patients had reached therapeutic levels; the corresponding figure for phenindione was 76% and for cyclocoumarol only 40%.

Initial response obtained in each of the three series. The therapeutic range is between two and three times the control prothrombin time.

Daily Maintenance Dose.—The ranges of the daily maintenance doses are shown in Table II. These daily maintenance doses were calculated only for those patients who

TABLE II.—Daily Maintenance Doses

Anticoagulant	Daily Maintenance Dose in mg.	No. of Patients
Ethyl biscoumacetate	Less than 150	11
	150–300	34
	300–450	25
	450–600	16
	600–750	8
	750–900	5
	900–1,050	2
	1,050–1,200	2
	More than 1,200	1
Phenindione	Less than 25	11
	25–50	38
	50–75	56
	75–100	33
	100–125	22
	125–150	4
	175–200	1
Cyclocoumarol	300–375	2
	Less than 12.5	12
	12.5–25.0	23
	25.0–37.5	9
	37.5–50.0	1

received anticoagulants for a sufficient length of time. No close relationship was found between the daily maintenance dose of any of the drugs and the age, sex, or weight of the patients.

Time Spent within Therapeutic Limits.—After exclusion of the prothrombin times affected by the initial dosage, the number of days under treatment during which the prothrombin time was within therapeutic limits was calculated for each patient. Table III compares the three series. Although the figures shown seem to reflect a poor degree of control of the prothrombin time, it should be emphasized that, whereas in practice one is satisfied when the patient's prothrombin time is within one or two seconds of two to three times the control prothrombin time, strict interpreta-

TABLE I.—Diagnoses in the Three Series

Diagnosis	No. of Cases		
	Ethyl Biscoumacetate	Phenindione	Cyclocoumarol
Coronary artery disease ..	56	76	42
Venous thrombosis ..	53	83	11
Pulmonary embolism ..	2	10	—
Arterial ..	12	4	4
Cerebral thrombosis ..	2	5	—
Post-operative prophylaxis	—	1	—
Total ..	125	179	57

TABLE III.—Comparison of Time Spent Within Therapeutic Limits

Percentage of Days During which Prothrombin Time Lay between Therapeutic Limits	Percentage of Patients		
	Ethyl Biscoumacetate	Phenindione	Cyclocoumarol
80–100 ..	42	75	45
Over 60 ..	79	95	71

tion of the results has been employed for the purposes of comparing the three anticoagulants. To avoid any possible prejudice against cyclocoumarol caused by the increased percentage number of patients suffering from coronary artery disease in this series, the three series were re-analysed, taking from each only those patients who had coronary artery disease. Tables III and IV show that control of anticoagulant therapy was more successful with phenindione than with ethyl biscoumacetate or cyclocoumarol.

TABLE IV.—Comparison of Time Spent Within Therapeutic Limits. Patients with Coronary Artery Disease

Percentage of Days During which Prothrombin Time Lay between Therapeutic Limits	Percentage of Patients		
	Ethyl Biscoumacetate	Phenindione	Cyclocoumarol
80-100	37	61	33
Over 60	75	91	65

Duration of Effect.—Table V summarizes the duration of the effect of phenindione and cyclocoumarol in those patients whose daily prothrombin times were recorded until control level was reached. The prothrombin time of the patient is usually only a few seconds above the control prothrombin time for one to two days before the two actually

TABLE V.—Duration of Effect After Cessation of Anticoagulant

Anticoagulant	No. of Patients	Days for Prothrombin Time to Return to Control Level after Cessation of Therapy	
		Range	Mean
Cyclocoumarol	27	2-19	6
Phenindione	11	3-6	4.5

become similar, and hence the duration of significant prolongation of the prothrombin time is less than the figures shown in the table. In a series of 22 patients who had received ethyl biscoumacetate, Barker (1952) found the duration of its effect after cessation of therapy to be from two to five days, with a mean of three days. In this series no attempt was made to confirm these figures.

Deaths.—*Ethyl biscoumacetate*: 11 patients (8.8%) died during therapy, but in no case was death attributed to the drug. *Phenindione*: 12 (6.7%) died, but these deaths were unrelated to therapy. *Cyclocoumarol*: there were 10 deaths (17.5%) in this series. One patient with chronic nephritis who had developed a myocardial infarction showed skin purpura, haemoptysis, haematuria, and haematemesis when his prothrombin time was 75 seconds. Anticoagulants were discontinued and vitamin K₁ was administered. The prothrombin time fell to 21 seconds within 24 hours of receiving the vitamin K₁, but in spite of this he died five days after the appearance of the haemorrhages. It was concluded that his death was related to anticoagulant therapy.

Side-effects.—Table VI shows the incidence of haemorrhage in each of the three series. Microscopic haematuria was noted during the course of therapy in 7% of those patients who received cyclocoumarol. No close correlation existed between the prothrombin times and the appearance of red blood cells in the urine unless the haematuria became

marked. No skin rashes were noted which could be related to any of the three drugs. No gastro-intestinal symptoms of sufficient severity to warrant stopping the anticoagulants were experienced.

Effect of Vitamin K₁.—In the three series vitamin K₁ was used both intravenously and orally to reduce the prothrombin time of those patients in whom it had become unduly prolonged or who had developed haemorrhage. The dosages of vitamin K₁ were those recommended by Toohey (1954), and in this way "refractoriness" to further anticoagulant therapy was avoided. Four patients on cyclocoumarol whose prothrombin times were reduced to near control level as a result of administration of vitamin K₁ showed subsequent rises in the prothrombin times necessitating further doses of vitamin K₁. This so-called "rebound phenomenon" was not observed in three patients given vitamin K₁ after administration of phenindione or in one who received vitamin K₁ after ethyl biscoumacetate.

Discussion

Dosage

It was found difficult to assess the correct amount of anticoagulant required to bring the prothrombin time up to therapeutic levels, because of the variation in the response to each of the three anticoagulants. In those cases in which the correct initial dosage was used no close correlation could be demonstrated between the initial dosage of any of the drugs and the age, weight, or sex of the patients.

Not infrequently the initial doses prolonged the patient's prothrombin time beyond the upper limit of the therapeutic range. This occurred more commonly with ethyl biscoumacetate and cyclocoumarol than with phenindione.

Thereafter, in many patients, the maintenance dose varied little from day to day. It was noted, especially in those patients who were initially gravely ill, that, as the clinical state of the patient improved, increasing amounts of anticoagulant were required. Similarly, deterioration in the clinical condition was accompanied by a reduction in the maintenance dose. Occasionally, for no obvious reason, the prothrombin time would fluctuate unexpectedly in either direction while the patient was on a steady maintenance dose. Such fluctuations occurred more commonly when ethyl biscoumacetate or cyclocoumarol was the anticoagulant concerned.

Stats and Davison (1949) and Covert (1952) have claimed that patients with congestive cardiac failure are sensitive to oral dicoumarol. In our experience, although patients who showed signs of congestive cardiac failure were more sensitive to the initial doses of all three anticoagulants, the daily maintenance doses of such patients did not differ significantly from the maintenance doses of patients who were not in failure.

Drug Resistance and Sensitivity

The phenomena of resistance and sensitivity were experienced with all three substances. As examples of sensitivity to ethyl biscoumacetate 11 (10.6%) patients had a daily maintenance dose of less than 150 mg. Four (3.9%) patients showed resistance, having a daily maintenance dose of more than 1,000 mg.

Eleven (6.6%) patients on phenindione required a daily maintenance dose of less than 25 mg. Two (1.2%) were resistant. One of these was given 300 mg. and the other 375 mg. daily to keep the prothrombin time within the therapeutic range.

Four (8.9%) patients given cyclocoumarol had daily maintenance doses of 10 mg. or less. One patient with myocardial infarction was very sensitive. After he received two doses of 75 mg. on the first day, followed by two 12.5-mg. doses on each of the two subsequent days, his prothrombin time rose to 114 seconds on the fifth day, and, in spite of repeated 10-mg. doses of vitamin K₁ orally, remained above 30 seconds for a further 19 days, although during that period he received only two 12.5-mg. doses of

TABLE VI.—Haemorrhage During Therapy

Source of Bleeding	Ethyl Biscoumacetate	Phenindione	Cyclocoumarol
Epistaxis	2	—	—
Haemoptysis	2	3	1
Haematemesis	1	1	1
Melaena	—	2	—
Skin petechiae	1	1	—
Haematuria (macroscopic)	—	1	2
		(? renal infarct)	(1 renal infarct)
Vaginal	—	1	—
Wound haematoma	—	1	—
Rectal	—	1	—
Multiple	—	—	1
Total	6 (4.8%)	11 (6.1%)	5 (8.7%)

cyclocoumarol. The same patient received cyclocoumarol for a further myocardial infarction three months after his initial illness and showed similar sensitivity.

The two patients who were resistant to phenindione were also found to be resistant to cyclocoumarol. The first received 600 mg. of phenindione daily for two days without producing a therapeutic effect upon the prothrombin time. She was then given 200 mg. of cyclocoumarol daily for two days, but again with little appreciable effect. The second patient was given 350 mg. of phenindione daily for three days. When this failed to prolong the prothrombin time sufficiently he was given 150 mg. of cyclocoumarol without any effect on the prothrombin times of the subsequent three days. On the third day following the previous dose of cyclocoumarol a further 300 mg. was given, and this produced only a moderate increase in the prothrombin time to 32 seconds three days later. Our experience suggests that resistance to one oral anticoagulant implies resistance to another. Others have reported, however, that resistance to one anticoagulant does not of necessity mean that high doses of another will be required. Rotter and Meyer (1952) describe a patient in whom a therapeutic degree of prolongation of the prothrombin time was inadequately maintained on as much as 1,350 mg. of ethyl biscoumacetate a day. When therapy was changed to cyclocoumarol adequate therapeutic levels were produced on only 50 mg. a day.

Summary

The properties of cyclocoumarol as an anticoagulant are reviewed on the findings obtained in its use in 57 patients. The results are compared with those obtained in 125 patients given ethyl biscoumacetate and 179 given phenindione under similar conditions.

The following points of comparison are made: (1) A therapeutic degree of prolongation of the prothrombin time was effected more quickly with phenindione than with cyclocoumarol. For all practical purposes, phenindione was as rapid in its action as ethyl biscoumacetate. (2) Patients receiving cyclocoumarol and ethyl biscoumacetate showed greater and more frequent fluctuations in their prothrombin times during maintenance therapy than did those receiving phenindione. (3) The percentage incidence of haemorrhage was greatest in the cyclocoumarol series. (4) In the three series the response of the prothrombin time to vitamin K₁ was the same, but in some patients receiving the longer-acting drug cyclocoumarol the prothrombin time subsequently lengthened and necessitated repeated doses of the vitamin.

On the basis of these findings phenindione is a more satisfactory and more easily controlled anticoagulant than either ethyl biscoumacetate or cyclocoumarol.

We thank the many clinicians whose patients were treated with the above anticoagulants; Dr. J. Basil Rennie for his encouragement and assistance; and Drs. J. L. Markson and J. W. Chambers, clinical biochemists, in whose laboratory the prothrombin times were determined, for their helpful comments and advice.

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AN ASSOCIATION BETWEEN SOCIAL CIRCUMSTANCES AND APPENDICITIS IN YOUNG PEOPLE

BY

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The mortality from appendicitis is about 20% higher in men of social classes I and II (professional and managerial workers) than it is in social class V (unskilled labourers) (Registrar-General, 1954). There is also evidence that the forms of the disease severe enough to cause admission to hospital are commoner among those of higher social and economic status. Thus, Bailey (1951) showed that the proportion of undergraduates who had undergone the operation was higher in boys from the more expensive schools. Ferguson (1950a) found that, considering all the in-patient hospital treatment received by the people of Ayrshire, social classes IV and V had a disproportionately low number of admissions for appendicitis compared with the other social classes. Stewart, Webb, and Hewitt (1955) found the same trend in the proportions of men aged 30 to 44 years who had undergone the operation before being examined prior to military service in the 1939–45 war. However, they found no relationship between social class in a similar sample aged 17 to 29.

In the course of studies of the health of potential national service men, made by taking records of men examined before call-up by civilian medical boards of the Ministry of Labour and National Service, it was possible to study the frequency of the operation in different groups (Lee, 1955a, 1955b). The relevant results are given in Table I, and show that the proportion

TABLE I.—Proportion of Men who had Undergone Appendicectomy Before Their Pre-Service Medical Examination. Men Examined in 1953–4. By Type of School Attended*

Type of School:	Secondary Modern	Grammar, Independent
No. of men operated on for appendicitis ..	148	147
No. of men examined ..	4,352	2,419
Proportion operated on	3.40%	6.08%

$$\chi^2 = 8.49. \quad P < 0.01.$$

* Only data from centres in England have been used in this comparison, as the types of school in Scotland are different. The figures are reconstructed from a stratified sample—all the records of unfit men were taken, and one-quarter of the records of fit men. This selection was made in an effectively random manner. Because of the sampling procedure, the numbers in the cells of the contingency table are themselves estimates. χ^2 cannot therefore be calculated directly in the ordinary manner. The value of χ^2 quoted at the foot of the Table has been corrected by adding to the expectations in the denominators of the usual formula the variances of these estimates.

of men who had been operated on was much higher in those who had been educated at a grammar or independent school than it was among those who had been to a secondary modern or all-age school.

In these studies of men examined before national service, records were collected from a variety of centres. In view of most of the evidence given above, it was surprising to find that the proportion of men who had been operated on was much higher in a group of men drawn from Clydeside and the West of Scotland (Clydeside A in Table II) than it was in similar groups drawn from North-west London and the Home Counties. In my studies the rates found in North-west London and in the Home Counties agreed well with those found by Stewart (1955) in Southend, Northampton, and Leicester. These are also given in Table II. To check