the photographs of Cases 1 and 2, before and after treatment, shows that, for one observer at least, gross facial changes produced by myxoedema can be overlooked. This was probably due to the fact that when the patients were first seen there was no standard of appearance against which to make comparison.

The voices of all these patients had changed as a result of disease, but again there was no pre-existing normal standard. The fact that the voice rather than the facial change was appreciated in these cases suggests that the voice change in myxoedema may be pathognomonic, as suggested by Means (1937). It would therefore seem to be a most important clinical sign. The most characteristic changes are an impression of dysarthria, slurring together of groups of words, and what I have called clotting of the voice. No amount of verbal description can adequately demonstrate these changes, but once they are appreciated they are readily recognized. Serial voice recordings, in my opinion, can take their place beside serial B.M.R.s and photographs as diagnostic aids in doubtful cases of myxoedema, as they have done in the five cases I have discussed.

Summary

Five cases of myxoedema in people over the age of 60 are described. In these cases recognition of the characteristic change in the voice led to the diagnosis. The importance of the voice changes in myxoedema in the elderly is stressed and an attempt is made to describe them.

It is a pleasure to record the help I have received in the preparation of this paper from Dr. Ian Goldberg, assistant pathologist to Oldham General Hospital; Mr. Peter A. D. McCarthy, department of phonetics, Leeds University; Mr. C. Richardson, department of photography, Oldham Royal Infirmary; and Miss Joyce Wynne, my secretary. The radio-iodine uptake tests were performed at the Christie Hospital and Holt Radium Institute, Manchester. The Hospital Management Committee have generously provided a tape recorder, which has enabled these voices to be studied.

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NICOUMALONE: A NEW ANTICOAGULANT

BY

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Dicoumarol was introduced in 1943 for the treatment of thrombosis, and in the ensuing years this form of therapy has become firmly established. The action of dicoumarol was slow and prolonged, and the search was continued for drugs which were more rapidly metabolized. The latest addition to this ever-lengthening list is nicoumalone ("sinthrome"), and an attempt is here made to evaluate its worth.

It is to be noted that initial and maintenance doses of nicoumalone used in this series are much lower than those recommended by American authors (Table I).

TABLE I

Author	No. of Patients	Method	Therapeutic Level	Dose of Nicoumalone	
				Initial	Maintenance
Walker (1955)	20	Quick's one-stage method	10-30% prothrombin activity	16-24 mg.	2-4 mg.
Long <i>et al.</i> (1956)	92	" "	" "	16-40 "	2-10 " (av. 5 mg.)
Neill <i>et al.</i> (1957)	156	Link and Schapiro's modification of Quick's one-stage	15-20% activity	28 "	5-9 mg.
Pratt (1956)	116	" "	Prothrombin time of 25-32 secs. 40% of normal	12-32 "	4-12 "
Johnson <i>et al.</i> (1957)	50	Bedside method of Howell		20-28 "	2-6 "

These have ranged up to 40 mg. for the loading dose and from 2 to 12 mg. a day for maintenance. Their patients may have been kept nearer the limit of safety than our own patients. Nevertheless, I am of the opinion that a loading dose of over 20 mg. is unnecessary and may be dangerous. The drug is dispensed in 4-mg. tablets. This is not convenient, since 2-mg. and 3-mg. doses are often required.

Material and Methods

In the period August, 1957, to September, 1958, inclusive, 269 patients received this drug. These comprise 155 cases of coronary thrombosis, 107 cases of venous thrombosis, and 7 cases of arterial occlusion. As a routine, patients with coronary thrombosis were started on heparin and oral anticoagulant therapy simultaneously, the administration of heparin being terminated after 36 hours. The dose of oral anticoagulant was controlled by "prothrombin" estimations, using Quick's one-stage technique. Unless the case presented some special difficulty, these tests were done three times a week, the week-end doses being based on the Friday's results. Where the patient's reaction to the drug was abnormal (more or less sensitive) more frequent controls were made. Results were recorded as "percentage prothrombin activity," the figures being obtained by reference to a "prothrombin" dilution curve. The dose of the drug was prescribed by a member of the laboratory staff with ample experience of this form of therapy.

For comparison, a study was made of the records of 117 patients who received "indema" (phenindione) and

242 patients who were treated with "dindevan" (phenindione). In all these cases essentially the same procedure as detailed above, was followed.

Results

Induction Therapy.—Early results indicated that a dose of 12 mg. on the first day and of 6–8 mg. on the second day were sufficient to depress the "prothrombin" to the desired level—20% activity (prothrombin time 39 seconds, compared with a control time of 13 seconds).

Maintenance Therapy.—The dose varied slightly from case to case, but was most often in the region of 2 to 3 mg. a day, given as a single evening dose. In more sensitive patients the occasional omission of a dose sufficed, and did not result in wide fluctuations of the "prothrombin" level.

Recovery Phase.—In patients receiving maintenance therapy of 2–4 mg. a day, withdrawal of the drug resulted in a return to normal in 36 to 48 hours. In very sensitive patients this period might be longer, while in a few less-sensitive cases the return occupied no more than 24 hours.

Evaluation of the Drug

An attempt was made to compare the three drugs mentioned by studying the constancy of the "prothrombin" levels obtained during the period of maintenance therapy. To do this the results of all tests on patients receiving these drugs (excluding the period of induction and the last test) were collected and grouped as shown in Table II. The number in each group (columns e to o) was calculated as a percentage of the total number of tests in that particular series (column p), and these percentages were used to construct the frequency curve shown in the Graph.

The study includes 1,284 tests (column p) on 269 patients who received nicoumalone. Of these, 893 tests (69.8%) fall within the range 15–35% activity. Only 13 results (1%) occur in the less than 10% range, and 85 tests (6.6%) gave readings above 60%. Compared with this are 984 tests on 117 patients who received indema. Of these, 487 tests (49.3%) were within the range 15–35%, 15 (1.5%) were below 10%, and 175 (18%) were above 60%. There are also recorded 1,344 tests on 242 patients who received dindevan. Of these, 806 tests (60.1%) were within the 15–35% range, 16 (1.2%) were below 10%, and 111 (8.3%) were above 60%.

These figures are better appreciated when presented as a frequency curve (see Graph). The highest peak of

incidence of tests within the range 15–35% occurs among those patients receiving nicoumalone, and the incidence of tests in the (undesirable) extreme ranges are also lowest in this group of patients.

Frequency curves with the three drugs.

Discussion

Since the introduction of dicoumarol in 1943 much effort has been directed towards producing an anti-coagulant which approaches perfection. Such an ideal drug (1) should be rapid in action, but not dangerously so; (2) should be non-toxic and well tolerated; and (3) its action should be maintained for 24 hours, but not much longer: this will permit adequate control to be achieved on a single daily dose, and will reduce to a minimum any cumulative tendency, allowing normal values to be reached rapidly should the drug be withdrawn. Upon this activity-time relationship will turn the effectiveness of an anticoagulant in clinical practice, enabling the physician to maintain a stable "prothrombin" level with minimal fluctuation, thereby reducing the incidence of progressive thrombosis and of spontaneous haemorrhage.

Reports of the use of nicoumalone have appeared from America (Pratt, 1956; Long *et al.*, 1956; Johnson *et al.*, 1957; Neill *et al.*, 1957) and Europe (Scardigli and Guidi, 1955; Moeschlin and Schorno, 1955;

TABLE II.—Distribution of Tests Grouped in Relation to "Prothrombin" Levels

Year	Drug	No. of Cases	No. of Patient-days	"Prothrombin" Levels—No. of Tests									Total No. of Tests
				< 10%	10%–	15%–	20%–	30%–	35%–	40%–	50%–	60%+	
(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(k)	(l)	(m)	(n)	(o)	(p)
1958	Nicoumalone	182	2,373	7	21	52	320	176	56	52	18	41	743
1957	"	87	1,448	6	18	44	210	91	59	44	25	44	541
	Total	269	3,821	13	39	96	530	267	115	96	43	85	1,284
				(1.0)	(3.0)	(7.5)	(41.3)	(21.0)	(9.0)	(7.5)	(3.4)	(6.6)	(100.3)
1957	Indema	117	1,638	15	66	77	260	150	87	92	62	175	984
				(1.5)	(6.7)	(7.8)	(26.3)	(15.2)	(8.8)	(9.4)	(6.3)	(18.0)	(100.0)
1957	Dindevan	51	773	3	7	27	90	51	31	30	14	11	263
1956	"	191	3,092	13	37	91	371	177	130	117	45	100	1,081
	Total	242	3,865	16	44	118	461	227	161	147	59	111	1,344
				(1.2)	(3.3)	(8.8)	(34.3)	(17.0)	(11.9)	(10.9)	(4.4)	(8.3)	(100.1)

The figures in italics represent percentages.

Montigel and Pulver, 1955). It is a coumarin derivative with the following formula:

Nicoumalone: 3-[α-(4'-nitrophenyl)-β-acetyethyl]-4-hydroxy-coumarin.

Like other derivatives of coumarin its main action is to depress factor VII, and later, and to a less extent, prothrombin, though after several weeks of treatment both substances are equally affected (Moeschlin and Schorno, 1955).

It is not cumulative, and rapidly disappears from the body, being excreted unaltered in the urine.

It is of low toxicity in animals (Pratt, 1956), the mouse LD₅₀ being 1,470 mg./kg. body weight compared with 270 mg./kg. in the case of dicoumarol. It is practically tasteless and is well tolerated by patients.

In this study no attempt has been made to assess the drug on purely clinical grounds—that is, incidence of deaths among patients with coronary artery disease, or the frequency of spontaneous haemorrhage. This omission has been allowed for two reasons. Firstly, because such statistics are often difficult to interpret and may be misleading (Honey and Truelove, 1957). Secondly, because it seems a reasonable deduction that the clinical results are but a reflection of the stability, or otherwise, of the "prothrombin" level during anti-coagulant therapy. The patient with the "straight line graph" is less likely to suffer the hazards of extending thrombosis or dangerous haemorrhage than his less fortunate neighbour whose tests indicate widely fluctuating "prothrombin" levels from day to day.

Only two cases of severe spontaneous haemorrhage have occurred in this series of patients receiving nicoumalone. In one instance the patient exhibited abnormal sensitivity to the drug, a "prothrombin" activity of less than 10% being recorded after the patient had received a total of only 12 mg. in 48 hours. In the second instance melaena occurred in a patient with a history of probable gastric ulcer. In this case also the "prothrombin" activity was less than 10%.

The results recorded in Table II and in the Graph indicate that a high degree of stability of the "prothrombin" level may be anticipated with the use of nicoumalone. This is likely to be accompanied by an improved prognosis among patients with thrombo-embolic phenomena.

Conclusion and Summary

Nicoumalone, a new coumarin derivative, represents a step forward in the search for the ideal anticoagulant.

The stability of the "prothrombin" levels of 269 patients receiving nicoumalone is compared with the same in 117 patients receiving indema and 242 patients receiving dindevan. In this series the results with nicoumalone are superior to those obtained with the other two drugs.

The properties of this new anticoagulant are briefly reviewed.

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MASS RADIOGRAPHY AND CANCER OF THE LUNG

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During 1955, the last year for which national figures have been published, mass radiography units in England and Wales detected 1,482 cases of cancer of the lung and mediastinum (Ministry of Health, 1957a). National morbidity figures for new cases of cancer of the lung are not available, but the 17,272 deaths from cancer of the lung during that year (Ministry of Health, 1956) suggest that at present mass radiography does not find more than 10% of all new cases of cancer of the lung in England and Wales. It must be added that of the above figures almost half were not detected by conventional routine mass radiography, but at sessions for symptomatic cases referred by general practitioners, a type of service now widely employed by many units. The organization and deployment of the mass radiography units in the Birmingham Region have recently been described by one of us (McDowell, 1958).

The small contribution of the service to the finding of a highly fatal disease, such as carcinoma of the lung, is thought by many to be a major challenge. From the public health viewpoint the problem is, of course, entirely different from that of tuberculosis; the community derives no epidemiological benefit from finding cases of cancer whether they are curable or not, and the results are purely personal. Nevertheless, if it could be shown that mass radiography improves the prognosis for this disease by "early diagnosis" it could be argued that the present mass radiography policy needs revising and that an intensive national campaign for periodical chest x-ray examination of persons in the critical age groups is called for.

In the United States some workers believe mass radiography to be an effective method for finding cases with good chances of operability and survival (Overholt and