out, has not been given in detail because the number of the severe asthmatics under treatment is not large enough for statistical evaluation. Even so, among the severe asthmatics no greater number were helped by an autogenous vaccine than by the carbol-saline. This is further evidence that, under the conditions in which the vaccine was given, any benefit obtained is apparently non-specific in effect.

The trial shows that the ordinary palliative measures, combined with the psychological support supplied by a weekly visit to and injection by the patient's own doctor, are capable of giving prolonged benefit to half the patients. It may therefore be assumed that in asthma any result that does not show a statistically significant improvement on a figure of 50% relieved does not support the value of any allegedly specific therapy.

It must, however, be pointed out that although this trial did not show any statistically significant difference between autogenous vaccine therapy and saline injections in the treatment of asthma, it does not necessarily follow that bacterial vaccines may not be of specific benefit in the treatment of asthma. No attempt was made here to compare different strengths or qualities of vaccines or the spacing of the injections, or other possible variables in vaccine therapy.

Summary

In a controlled trial in some 200 cases of intrinsic (infective) asthma, kept under observation for one year or more and given general supportive treatment, regular injections of autogenous bacterial vaccines produced no greater benefit to the patients than similar injections of carbol-saline. In both groups over 50% of the patients benefited from the treatment received.

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ANTICOAGULANT STUDIES WITH "MARCOUMAR," A NEW COUMARIN DERIVATIVE

BY

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"Marcoumar" (3-(1'-phenylpropyl)-4-hydroxycoumarin) is a synthetic anticoagulant. The initial clinical investigations with this drug have shown that it is highly active, with a prolonged anticoagulant action (Koller and Jakob, 1953). Like dicoumarol and ethyl biscoumacetate it has a greater effect on the concentration of factor VII (stable prothrombin accelerator) than on the actual prothrombin concentration of the plasma, while it exerts very little effect on the concentration of factor V (labile prothrombin accelerator) present in the plasma. Koller and Jakob considered that estimation of the "prothrombin complex" by the one-stage Quick method, using a suitable brain preparation as source of thromboplastin, was adequate for clinical control of the drug.

Marcoumar has been used widely on the Continent, and a number of workers have reported favourably on its use in the treatment of acute thrombo-embolism and in cases requiring long-term anticoagulant therapy. Control of dose was achieved with weekly or twice-weekly prothrombin-time estimations in the long-term cases (Aldehoff and Weidenbach, 1954; Matis, 1953; Deutsch *et al.*, 1954).

The following advantages have been claimed for the drug: (1) Freedom from toxic reactions. (2) A definite effect on prothrombin time within 24 hours, while a therapeutic level is obtained within 36 to 48 hours. (3) A prolonged stable action, allowing good control with a single daily dose, and a gradual return of the prothrombin time to normal once treatment is stopped. (4) Less effect on capillary fragility than certain other anticoagulant substances. This effect has been shown experimentally (Jürgens, 1953; Matis, 1953) and may be a factor in the development of haemorrhage when estimations of the prothrombin time or factor VII content are within the accepted therapeutic range.

The development of vitamin K_1 has been the most important factor allowing therapeutic use of the long-acting anticoagulants. This substance, now available in oral form, will revert a prolonged prothrombin time to a safe level within two to six hours and can be used at the first sign of haemorrhage, or prophylactically should the prothrombin concentration fall to low levels.

The purpose of this paper is to report experience with the use of marcoumar in 100 patients. Their ages ranged from 37 to 89 years.

The conditions for which patients were treated are shown in Table I.

TABLE I

	No. of Cases	Mortality
Cardiac infarction	73	13
Post-operative thrombophlebitis	10	—
Spontaneous thrombophlebitis	8	—
Retinal vein thrombosis	2	—
„ artery „	1	—
Pulmonary embolus	3	—
Recurrent cerebral thrombosis	1	—
Temporal arteritis	1	1
Rheumatic heart disease	1	—

Methods

Prothrombin times were measured by the one-stage method of Quick, using brain as a source of thromboplastin.

Prothrombin times were taken in the majority of patients before starting treatment, and this influenced the initial dose given if the prothrombin concentration was below normal. Prothrombin times were estimated each morning, except Sundays, throughout this study. In those who continued as out-patients, weekly or twice-weekly times were estimated. Careful inquiries were made for a history suggesting chronic peptic ulceration, or chronic renal or hepatic disease, but it was not found necessary to exclude any cases on these counts in the present series.

Dosage.—Marcoumar is supplied in 3-mg. tablets which are readily divided. Most patients received from 18 to 21 mg. on the first day and 9 to 12 mg. on the second day. If the initial prothrombin concentration was below 55% a smaller initial dose was given. The maintenance dose depended on the daily prothrombin time, and throughout the study the aim has been to keep the prothrombin time at two to two and a half times that of the control, which is equivalent to a prothrombin concentration of between 25 and 15%.

Heparin was given four-hourly for the first 36–48 hours in most cases until the prothrombin time was shown to be within the therapeutic range.

Results

Rapidity of Action.—The majority of patients showed a clear fall in prothrombin concentration after 12 to 16 hours and reached a therapeutic range within 36 hours. Fig. 1

illustrates the effect in a patient who was given marcoumar without heparin and shows a fall to 36% within 14 hours and to 15% 38 hours after the first dose.

Duration of Effect.—In all cases in which it has been studied the prothrombin concentration has taken a number of days to return to normal after treatment had been stopped. This has varied from 9 to 14 days (see Fig. 2).

Control Achieved.—Patients have been treated for periods ranging from several days to seven weeks. Some continued to receive the drug on a long-term basis as out-patients. In an attempt to assess the control achieved the number of days in which the prothrombin concentration was over 30% after the third day of treatment has been noted. The overall stability of the prothrombin concentration from day to day has also been taken into consideration, and undue swings, even if the prothrombin concentration remained below 30%, have been regarded unfavourably. On this basis the graphs of patients have been classified as good, fair, or poor. The control was good in 76 cases, fair in 19, and poor in 2. Three patients who died within four days have been excluded. In the whole series the prothrombin concentration exceeded 30% after the third day of treatment on 58 occasions out of a total of 1,854 days, which gives an incidence of 3%. On 20 occasions the prothrombin concentration was less than 10%, which gives an incidence of 1%. Fig. 3 is a graph representative of the "good" control group.

Maintenance Dose.—This has varied considerably from case to case and sometimes in the same case, and can be assessed in each individual only by frequent estimations of the prothrombin time in the first two weeks of treatment.

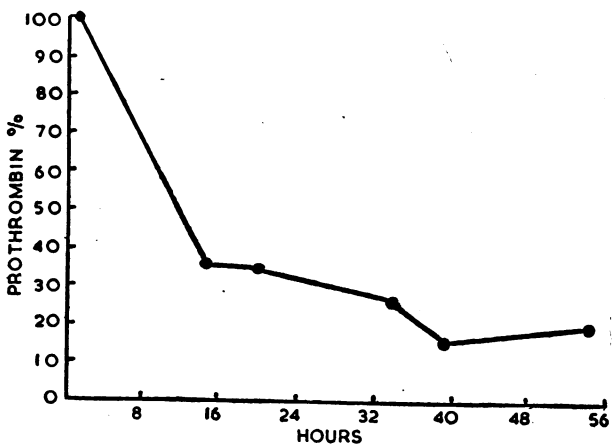

FIG. 1.—Effect of 21 mg. of marcoumar on the first day, and 9 mg. after 22 hours, in a patient with coronary insufficiency. No heparin was given.

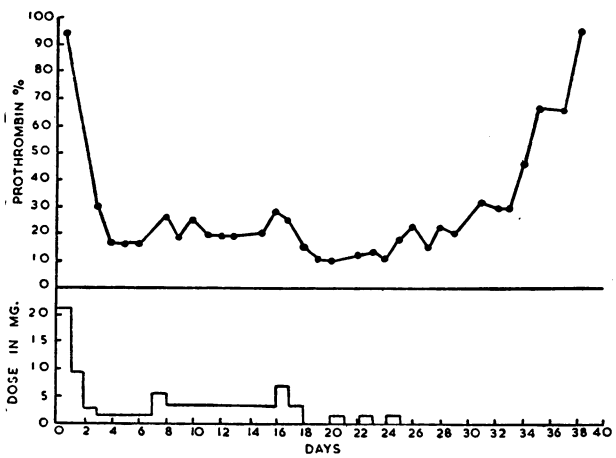

FIG. 2.—Graph of a case of cardiac infarction treated with marcoumar. The gradual return of prothrombin concentration to normal after stopping treatment is shown.

It was found that in severely ill patients a smaller initial and maintenance dose was required until clinical improvement took place, when a larger dose was often required to maintain control. Following the initial dose on the first two to three days the maintenance dose was often small, and in some cases no marcoumar was required for two to five days. The average case required 1.5–3 mg. daily to maintain control; a small number of cases needed as much as 4.5–7.5 mg., and appeared relatively resistant to the drug.

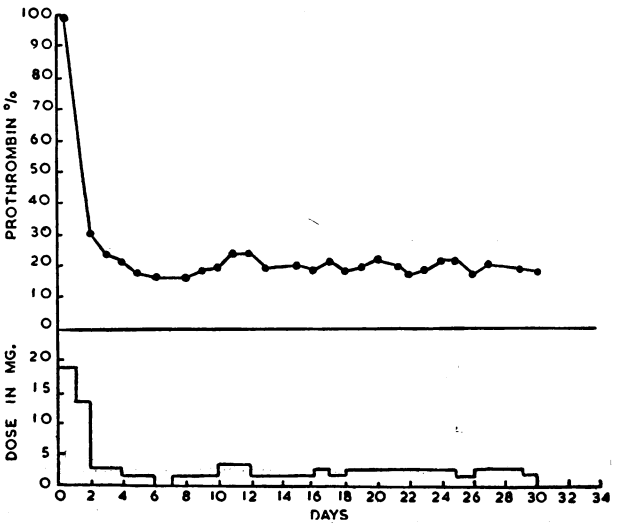

FIG. 3.—Graph of a case of cardiac infarction representative of the "good" control group.

The maintenance dose was noted to be greater in one patient during a bout of epidemic diarrhoea, when absorption may have been less adequate. In the early stages of the investigation one-quarter of a tablet (0.75 mg.) was sometimes given; it has since been found that 1.5 mg. given at less frequent intervals produced just as stable a result and avoided difficulties in dividing tablets into quarters.

Side-effects.—In one patient the drug appeared to cause some mild diarrhoea, which improved when treatment was stopped. No other side-effects were noted.

Thrombotic Complications.—Undisputed evidence of thrombo-embolus occurred in five cases. One patient with Hodgkin's disease developed an extension of a superficial thrombosis while on treatment; one patient had a cerebral embolus believed to arise from a mural thrombus, and three patients had pulmonary emboli on the second, third, and fifth day after starting treatment respectively. Three cases of cardiac infarction had an extension of their infarct and five had continued pain while on treatment. These latter were regarded as doubtful cases of further thrombosis.

Haemorrhagic Complications.—Haemorrhage occurred in 10 patients—an incidence of 10%. In only five did it cause any concern, and in one of these it may have contributed in some way to the patient's death. This patient, aged 80, had severe hypertension and temporal arteritis with coronary arteritis, and died of a massive cerebral haemorrhage. The prothrombin concentration on the day before death was 18% and control had been excellent. Anticoagulants were given in order to lessen the risk of blindness developing. Necropsy confirmed the clinical diagnosis and showed gross cerebral arteriosclerosis with an extensive cerebral haemorrhage. The hypertension and cerebral vessel changes made it unlikely that marcoumar affected the outcome in any way. Haematuria, epistaxis, and haemoptysis each occurred in different patients (Table II) and were not severe. The haemoptysis was thought to arise from ulceration of the bronchus in a patient with stenosis of the lingula lobe bronchus. One patient had a very slight bleeding per rectum from haemorrhoids. This patient had noted similar trouble before admission, and no special treatment was given, nor

were the anticoagulants stopped. In one patient a small secondary haemorrhage occurred from an operation wound on the ninth day.

TABLE II.—*Haemorrhagic Complications*

Site of Haemorrhage	Prothrombin Concentration at Time of Bleeding	K_1 Given
Epistaxis	12%	Yes
,,	16%	No
,,	17%	Yes
,,	18%	No
Haematuria	25%	No
,,	10%	Yes
Cerebral haemorrhage	18%	No
Haemoptysis	23%	Yes
Bleeding per rectum	21%	No
Haemorrhage into wound	24%	No

Discussion

The important criteria in the evaluation of any prothrombin depressant are safety, effectiveness, economy, and convenience of administration. Marcoumar would appear to fulfil these to an extent at least similar to or greater than some of its predecessors.

The important claims made for it have been supported by the present investigations. It is a potent substance which produces its effects more quickly than dicoumarol. The induction rate of marcoumar is between 24 and 48 hours, while that of dicoumarol lies between 48 and 72 hours. This rapid action gives the drug an important advantage over dicoumarol, allowing rapid restoration of the prothrombin concentration to within the therapeutic range should it show an unexpected rise during the course of treatment. Under these circumstances it is often 24 to 36 hours before a larger dose of dicoumarol exerts its effect, whereas in our experience a suitable dose of marcoumar will restore the prothrombin concentration within 12 to 18 hours and so allow smoother control.

Patients receiving the drug are readily controlled within the therapeutic range and are easily maintained within that range over a period of time. It has been found that seriously ill patients have required lower doses until their general condition improved, daily estimations of the prothrombin concentration being necessary during this phase. In some such patients initial doses of 18 and 9 mg. on the first and second days have been sufficient to maintain the prothrombin concentration at around 15–18% of normal for as long as four to six days; with clinical improvement the maintenance dose has been increased and daily doses varying from 1.5 to 3 mg. have been necessary.

The recovery period on stopping marcoumar therapy is longer than with dicoumarol, but this is not a disadvantage. If a rapid return towards normal is required for unexpected surgery, in the case of an injury, or when an unusually low prothrombin concentration and bleeding occur, then oral vitamin K_1 may be given. The development of a cheap oral K_1, which neutralizes the effect of the drug very rapidly, has removed all objections to long-acting anticoagulants and lessened very greatly the dangers of haemorrhage in response to such drugs.

Observations made during the present investigation confirmed that restoration of prothrombin concentration to a safe level occurred within four to six hours of an oral dose of 10–20 mg. of vitamin K_1.

Some evidence of haemorrhage occurred in 10 cases in the present series. In the elderly patient in whom a fatal cerebral haemorrhage occurred the necropsy showed severe cerebral atheroma and an extensive cerebral haemorrhage. Anticoagulants may not have contributed significantly to the fatal outcome in this patient, although cases of severe hypertension and arteriosclerosis may be expected to be more liable to retinal or cerebral haemorrhages when on anticoagulants, and the risks must be carefully assessed in such cases.

In only one of the remaining patients who showed evidence of haemorrhage was it found necessary to stop treatment and give vitamin K_1; this patient, who was being treated for coronary insufficiency, had small haemoptyses from a post-tuberculous bronchostenosis with ulceration, and the bleeding occurred when the prothrombin concentration was 23% of normal. In three other cases vitamin K_1 was given and treatment continued when bleeding had stopped.

The incidence of further thrombo-embolic episodes has been small in the series, clear evidence of thrombo-embolism occurring in five cases. In two of these it appeared on the second day of treatment before full control had been achieved and while the patients were on heparin in addition to marcoumar.

The indications for long-term ambulant anticoagulant therapy are well recognized in certain cases of recurrent thrombophlebitis, in thrombophlebitis migrans, and in certain cases of mitral valve disease which have suffered repeated embolic accidents; the indications in peripheral vascular disease and in coronary artery disease are less well defined, but may include some cases of recurrent cardiac infarction. The therapeutic level which should be aimed at in such ambulant patients is a matter of some debate, but probably lies between 20 and 25% of the normal prothrombin concentration. The availability of long-acting stable anticoagulant substances, whose action may be quickly reversed by vitamin K_1, has made ambulant anticoagulant therapy relatively safe for the patient and easily controlled by the physician who has good laboratory facilities available. The value of such therapy will be known only when the results of carefully controlled observations made over a considerable period of time are available.

Summary

Marcoumar (3-(1'-phenylpropyl)-4-hydroxycoumarin) has been used in the treatment of 100 patients suffering from conditions considered to require anticoagulant treatment.

It is a potent oral anticoagulant substance which reduces the prothrombin concentration to a therapeutic level within 36 to 48 hours, while some effect may be demonstrated within 12 hours of an oral dose.

The maintenance dose varies from patient to patient and at times in the same patient, and is less in severely ill persons. In the majority of subjects the maintenance dose becomes stable, and good control in out-patients has been achieved with small daily doses and prothrombin estimations every fourth to seventh day.

Marcoumar has a prolonged action and the recovery period has varied from 9 to 14 days. This recovery has been shown to be very materially accelerated by oral vitamin K_1, should it be necessary in the event of haemorrhage.

Bleeding occurred in 10 patients. One elderly patient with severe hypertension and temporal arteritis died of a cerebral haemorrhage. The bleeding in the remaining patients was mild, and vitamin K_1 was given on four occasions.

No other toxic effects were observed, and it is concluded that marcoumar is a satisfactory long-acting anticoagulant which is stable, easy to control, and suitable for both short-term and long-term anticoagulant therapy.

I wish to acknowledge the help received from the physicians and surgeons of the Wellington Hospital who have allowed me to supervise the anticoagulant control of patients under their care, and to the laboratory staff for their very careful attention to the prothrombin estimations. I am grateful to Roche Products Limited, who generously provided the "marcoumar" and vitamin K_1 ("konakion") used in this trial.

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