between income and haemoglobin level, but this might be explained by the higher-paid workers being older and leading a more sedentary life than the lower-paid ones.

There was no evidence of a difference between the haemoglobin of married and that of unmarried men. Employed married women, on the other hand, had a higher mean level than spinsters in all three groups, D, E, and F, the differences being 0.65, 2.5 and 3.0%, respectively. These differences were found to be independent of income.

In 187 of the housewives the effect of parity could be investigated. Over the range 0-3 children no change in level was found, but the level for mothers of four or more children was well below that of the rest (Table II).

TABLE II.—*Haemoglobin Levels of Housewives According to Parity*

No. of Pregnancies	No. in Sample	Mean Hb % Haldane
0	14	90.2
1	62	91.4
2	64	90.8
3	31	91.7
4 and over	16	86.2

In the study of Magee and Milligan (1951) the haemoglobin of women who had borne three or more children and who were either pregnant or within 65 weeks after labour was lower than in comparable women who had had a smaller number of children. In the present survey all pregnant and nursing women were excluded, and it may be that this effect of repeated pregnancies disappears gradually.

Summary

Haemoglobin levels were determined in 245 adult men and 266 adult women employed in clerical and industrial work, on 214 non-pregnant and non-nursing housewives under 60 years living in and around London, and on 1,628 boys aged 6, 10, and 14 years living in two Lancashire towns (I and K), one Surrey town (J), and one Gloucestershire town (L). The mean findings are set out in Table I.

So far as they are comparable with the M.R.C. survey of 1943 the present findings are about the same or on a slightly higher level. Of the 214 housewives 5.6% had values less than 72.3% (Haldane). Medical reasons for the low levels were elicited by questioning.

Male clerical workers had higher values than male manual workers, a difference attributable to the more active lives of the latter. In some of the groups of men and women a direct relationship between income and haemoglobin level was observed; this difference may have been due to a more leisurely life in the higher income groups.

The haemoglobin level of boys of town I was lower than that of the boys of any of the other towns, and that of grammar and public school boys in town L was slightly higher than for modern school boys in the same city. The reasons for these differences in boys living in different parts of England and in different surroundings are being further investigated.

ADDENDUM.—Since writing the above, the doctors of women with Hb below 80% have tried the effects of iron therapy, in almost every case with satisfactory results. The proportion (8.9%) of women with Hb below 80% in this unselected sample and their ready response to iron medication suggests that the work of the general practitioner would be facilitated by routine Hb determinations in women patients. The colour of the mucous membranes, as reported elsewhere (Adcock *et al.*, 1949) may fail as an index of Hb level, but the Tallqvist method provides a

simple and inexpensive means of ascertaining the Hb level with sufficient accuracy for practical purposes. This method was found by Macfarlane *et al.* (1948) to compare surprisingly well with other more complicated procedures.

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EFFECT OF VITAMIN-K PREPARATIONS ON HYPOPROTHROMBINAEMIA INDUCED BY DICOUMAROL AND TROMEXAN

BY

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The administration of dicoumarol (3,3'-methylene-bis-(4-hydroxycoumarin)) or "tromexan" (bis-3,3'-(4-oxycoumarinyl)-ethyl acetate) in the treatment of thromboembolic states may lead to severe or even fatal haemorrhage. Although careful control of treatment by repeated estimation of the blood prothrombin levels reduces this risk, a reliable and convenient antidote against such potent therapeutic substances would be of great value. Both dicoumarol and tromexan are anti-coagulants by virtue of their causing hypoprothrombinaemia, and the two measures recommended to reverse this effect are the administration of preparations possessing vitamin-K activity and the transfusion of blood. There is no doubt that the latter treatment gives immediate and significant results, but for it to be most effective the blood must be in sufficient quantity. It is not always easy to meet this requirement, and reliance may be placed on the use of vitamin-K preparations such as are commercially available.

There is a measure of belief, based on experimental observations carried out during the past ten years, that these vitamin-K preparations are capable of reversing dicoumarol-induced hypoprothrombinaemia. From the available evidence at hand there can be no doubt that substances with vitamin-K activity do possess such powers, but there is still much confusion regarding the practical value of the various preparations which are available for this purpose.

It is hoped that the experiments described below will provide more conclusive evidence concerning the action and therapeutic value of these preparations.

Material and Methods

Either dicoumarol or tromexan was administered in therapeutic doses to patients in whom there was no obvious potential source of haemorrhage or evidence of hepatic, alimentary, or renal dysfunction. A test dose of the anticoagulant drug was given, and the effect on the prothrombin levels was observed at least daily. When the prothrombin levels had returned to normal, and had remained normal for two to three days, the same dose of the same drug was repeated, and a selected dose of a vitamin-K preparation was given. Plasma prothrombin levels continued to be estimated at least daily. In a few instances the technique was varied in respect of time of administration and of the number of the doses of vitamin K. The variations are indicated with the results in Table II.

The hypoprothrombinaemia expected from the anticoagulant therapy was not usually beyond customary therapeutic levels, as it was not considered necessary or justifiable to induce dangerous depletion of the plasma prothrombin.

TABLE I.—Details of the Vitamin-K Preparations Tested

Substance	Other Designation	Route of Administration	Dosage
2-methyl-3-phytyl-1:4-naphthoquinone	Vitamin K ₁	Intravenously	200–340 mg. single doses
2-methyl-1:4-naphthoquinone	"Prokayvit" (B.D.H.); menaphthone; menadione	Intramuscularly	15–30 mg. in 2–3 days
2-methyl-1:4-naphthohydroquinone diacetate	Acetomenaphthone; oral prokayvit (B.D.H.)	Orally	90 mg. in 3 days
2-methyl-1:4-naphthohydroquinone carboxymethoxine	"Kapilon" (Glaxo)	Intramuscularly	60 mg. in 3 days
2-methyl-1:4-naphthohydroquinone diphosphate	"Synkavit" (Roche)	Intravenously	300–1,600 mg. in 3–4 days
Dipotassium 2-methyl-1:4-naphthylene bisulphate	Water-soluble K analogue (Boots)	"	200 mg i.v. single dose

Vitamin-K Preparations.—The vitamin-K substances which were tested, and their routes of administration, are shown in Table I. With the exception of vitamin K₁ these preparations are readily available commercially, and the doses of those which were given parenterally were limited

only by the occurrence of untoward reactions. In the case of vitamin K₁, which is fat-soluble and which was received as an oily concentrate, a preparation suitable for intravenous administration was made as described by Davidson and MacDonald (1943). The oily fluid was dissolved in absolute alcohol (200 mg. K₁ in 4 ml. alcohol), and the solution was then added to 5% glucose (200–400 mg. K₁ in 500 ml.). The preparation was then autoclaved. Suspension of the vitamin in the glucose solution was assisted by injecting the alcoholic solution forcibly through a long fine needle into the centre of the bottle of glucose solution, but in spite of this the preparation tended to be unstable and had to be used almost at once. This preparation of vitamin K₁ was administered by intravenous infusion over a period of half to five hours without delay, otherwise the vitamin K₁ tended to settle out and adhere to the glass, with consequent loss of potency. No untoward reaction of any kind was encountered.

Estimation of Plasma Prothrombin.—Plasma prothrombin was estimated by the one-stage method of Quick. The same batch of rabbit-brain thromboplastin was used in each case, for the control and the test periods. The estimations were carried out on 100% and on 12.5% plasma. Only the figures obtained with 100% plasma are recorded here.

Results

The results of the various therapeutic trials of the vitamin-K analogues against the hypoprothrombinaemic effect of dicoumarol and tromexan are presented in Table II. In the case of vitamin K₁ the results of single tests are tabulated. In the case of the other preparations the average results from groups of patients are recorded: a more detailed analysis of these results is given below.

Vitamin K₁

Vitamin K₁ was tested against a single dose of tromexan in three patients. In the first case (Table II) 900 mg. of tromexan resulted in a prothrombin time approximately four times normal. The same dose of tromexan was given on the first day of the test period, and on the following day, when the prothrombin time had begun to rise, 200 mg. of vitamin K₁ was given intravenously. Within twenty-four hours the prothrombin time was 19 seconds, as compared with 60 seconds at this stage in the control period. In Case 2, 200 mg. of vitamin K₁ given at the same time as 900 mg. of tromexan appeared to act as a complete antidote. In Case 3

TABLE II.—Effect of Dicoumarol and Tromexan on Plasma Prothrombin Time and the Modification of this Effect by Vitamin-K Analogues.

	Days of Control and Test Period					Remarks
	1	2	3	4	5	
		sec.	sec.	sec.	sec.	
Case 1	16 (T)	32	60	25	—	Control. T=900 mg. tromexan. K=200 mg. vitamin K ₁ i.v.
.. 2	15 (T)	28 (K)	19	16	—	Control. T=900 mg. tromexan. K=200 mg. vitamin K ₁ i.v.
.. 3	20 (T)	30	22	18	—	Control. T=900 mg. tromexan. K=340 mg. vitamin K ₁ i.v.
.. 4	19 (TK)	18	20	20	—	Control. D=400 mg. dicoumarol. K=200 mg. vitamin K ₁ i.v.
.. 5	17 (T)	36	26	—	—	Control. D=400 mg. dicoumarol. K=300 mg. vitamin K ₁ i.v.
.. 6	21 (TK)	20	19 (T)	38	—	Control. D=400 mg. dicoumarol. K=300 mg. vitamin K ₁ i.v.
.. 7	17 (D)	19	28	33	25	Control. T=600+300 mg. tromexan. K=300 mg. vitamin K ₁ i.v.
.. 8	20 (D)	22	28 (K)	19	19	T=600+300 mg. tromexan. K=300 mg. vitamin K ₁ i.v.
.. 9	19 (D)	19	28	33	25	T=Maintenance 300 mg. tromexan/day. K=300 mg. vitamin K ₁ i.v.
.. 10	16 (DK)	19	22	19	19	Control T=900 mg. tromexan M=10 mg. menaphthone i.m.
.. 11	17 (T)	22 (T)	40 (K)	12	—	Control T=900 mg. tromexan. AM=300 mg. acetomenaphthone
.. 12	—	75 (T)	75 (TK)	to 21 in 6 hours	—	Control D=200 mg. dicoumarol. AM=30 mg. acetomenaphthone
Group 8 (5 cases)	16 (T)	25	28	—	—	Control T=900 mg. tromexan. K=20 mg. kapilon i.m.
Group 9 (5 cases)	16 (TM)	21 (M)	23	—	—	Control D=200–400 mg. dicoumarol. K=20 mg. kapilon i.m.
Group 10 (2 cases)	16 (T)	24	28	21	—	Control T=600 mg. tromexan. S=100 mg. synkavit i.v.
Group 11 (5 cases)	18 (TAM)	26 (AM)	21 (AM)	16	—	Control D=200 mg. dicoumarol. S=100 mg. synkavit i.v.
Group 12 (3 cases)	16 (D)	20	22	21	—	Control T=1,200 mg. tromexan. S=400 mg. synkavit i.v.
Group 13 (6 cases)	18 (DAM)	22 (AM)	22 (AM)	21	—	Control T=1,200 mg. tromexan. B=200 mg. water-soluble analogue (Boots)
Group 14 (5 cases)	16 (T)	25	22	18	—	
Group 15 (1 case)	18 (TK)	22 (K)	22 (K)	18	—	
Group 16 (1 case)	15 (D)	19	26	29	—	
	16 (DK)	24	22	20	—	
	15 (T)	24	28	12	—	
	16 (TS)	24 (S)	20 (S)	11	—	
	15 (D)	20	28	25	—	
	15 (DS)	16 (S)	28 (S)	20	—	
	18	18 (T)	31	23	18	
	18 (S)	18 (TS)	29 (S)	22 (S)	19	
	16 (T)	42	34	17	—	
	17 (TB)	40	29	18	—	

the effect of 900 mg. of tromexan was likewise blocked by simultaneous administration of 340 mg. of vitamin K₁. As an additional check on the method of testing, this patient was given a further dose of tromexan without vitamin K₁. Hypoprothrombinaemia resulted.

Vitamin K₁ was tested against a single dose of dicoumarol in two patients. In the first of these (Case 4) the administration of 200 mg. of vitamin K₁ on the third day of the test period was followed by return of the prothrombin time to pre-treatment levels within twenty-four hours. In Case 5 the simultaneous administration of 300 mg. of vitamin K₁ was almost completely effective in blocking the action of 400 mg. of dicoumarol.

As a further test of the action of vitamin K₁ (Case 6) 900 mg. of tromexan was given over two days. On the third day, when the prothrombin time was 40 seconds, 200 mg. of vitamin K₁ was given intravenously. The prothrombin time fell to 30 seconds in two hours, and to normal within twenty-four hours. Case 7 illustrates the effect of 300 mg. of vitamin K₁ on a persistently high prothrombin time (75 seconds) occurring in a patient who was given 300 mg. of tromexan daily for several weeks for therapeutic purposes. In spite of the administration of the usual daily dose of tromexan, vitamin K₁ produced a rapid fall in the prothrombin time to 21 seconds within six hours.

From these investigations it is evident that when 200–340 mg. of vitamin K₁ was given at the same time as a reasonable therapeutic dose of tromexan or dicoumarol the action of the anticoagulant drug on the plasma prothrombin levels was completely, or almost completely, inhibited. When the vitamin was given at any time after hypoprothrombinaemia had been induced, the prothrombin levels were restored to normal in 24 hours. Furthermore, significant reduction of the prothrombin time occurred within an even shorter period, and safe values were achieved within six to nine hours even when previously the hypoprothrombinaemia had been more severe than is usually considered necessary for therapeutic purposes.

Menaphthone and Acetomenaphthone

The average results of the intramuscular administration of menaphthone (Group 8, Table II) suggest that this substance had an incomplete inhibitory effect on mild hypoprothrombinaemia induced by tromexan. In this group the individual test results and the control results were practically identical.

Acetomenaphthone was given orally to seven patients, to five who had received tromexan, and to two who had received dicoumarol. The average figures for those given tromexan (Group 9) suggest that the response to the anticoagulant was modified slightly by the acetomenaphthone. The individual results indicated that the effect of this vitamin-K analogue was slight and inconstant. Acetomenaphthone was tested against dicoumarol in two patients (Group 10). In each the test curve and the control curve were identical. Although larger doses of menaphthone and acetomenaphthone might well have been given by mouth, it was felt that oral treatment was unsuited to this purpose and no further observations were made with acetomenaphthone. Dosage of menaphthone was limited by pain which followed the intramuscular injection.

Kapilon, Synkavit, and Water-soluble K Analogue (Boots)

Kapilon was tested against tromexan in five patients (Group 11, Table II). In no case could it be said that kapilon given intramuscularly in doses of 20 mg. daily for the first three days significantly affected the response to tromexan. Kapilon was tested against dicoumarol, which was given in doses of 300 mg. During the test period kapilon was given in doses of 20 mg. on the first and third days. In all three patients slight but significant modification of the prothrombin response occurred. In no case, however, did the prothrombin time return to normal within three days of administration of the first dose of kapilon.

Synkavit, given intravenously in doses of 100 mg., was tested against tromexan in six patients (Group 13). In five of these the control and the test curves were practically identical. In the sixth case of this group slight modification of the response occurred during the test period. Synkavit was tested against doses of dicoumarol, which produced prothrombin times of 30–40 seconds, in five patients (Group 14). Each patient was given 100 mg. of synkavit daily for the first three days of the test period, and in no case was there any demonstrable effect on the prothrombin-time curve. As an additional test of the action of synkavit, even larger doses were given (400 mg. intravenously), beginning on the day before the administration of tromexan (Group 15) and continuing for a further three days. No modification of the action of the tromexan was demonstrated: the control curve and the test curve were identical.

Water-soluble K analogue (Boots) was tested against tromexan in one patient. Given intravenously in a dose of 200 mg. it slightly modified the effect of the anticoagulant (Group 16) but failed to reduce the prothrombin time to normal within 24 hours.

The various water-soluble vitamin-K analogues have thus been shown to be relatively inactive against the hypoprothrombinaemic effect of tromexan and dicoumarol. Although in some instances—notably the tests of kapilon against dicoumarol—an effect was demonstrated, this effect was insufficient to prevent a fall in plasma prothrombin concentrations as a result of the administration of a single relatively small dose of the anticoagulant. That the lack of effect is not merely a matter of dosage of the vitamin-K analogue is indicated by the complete failure of 1,600 mg. of synkavit given over a period of four days to modify the normal therapeutic effect of a single dose of tromexan.

Discussion

Among all the vitamin-K analogues tested against dicoumarol and tromexan in this investigation the only substance which was uniformly significantly active was vitamin K₁. This material was given intravenously in doses of 200–340 mg., and it was almost invariably completely effective in blocking or in reversing the action of the anticoagulant under the circumstances of the test. The other substances tested did occasionally modify the effect of the anticoagulant, but the effect was inconstant and slight. Comparable doses were not always given, but, from the practical point of view, oral administration of vitamin K is unlikely to be satisfactory as an emergency treatment, and, given by other routes, the doses of menaphthone and synkavit were limited by local or general reactions.

In the present investigation no attempt was made to give doses of anticoagulants which would result in dangerously low prothrombin levels. It might therefore be considered that the tests do not give information directly applicable to the treatment of the hypoprothrombinaemic emergency. On the other hand, this would merely point to some doubt about the value of vitamin K₁ under more exacting conditions, and the immediate result of administering it to a patient with a prothrombin time (100% plasma) about four times normal (Case 7, Table II) without stopping the tromexan administration is good evidence of the potency of this substance even in very adverse conditions. As regards the other analogues, the relatively small dosage of the anticoagulant employed serves to emphasize the inefficiency of these vitamin-K preparations.

During the past 10 years considerable interest has been shown in the effect of vitamin-K analogues on dicoumarol-induced hypoprothrombinaemia, and numerous experiments have been carried out both in animals and in the human subject. It cannot be said, however, that there is general agreement about either the relative effects of the various vitamin-K preparations or the form of vitamin-K activity which is most suitable for the treatment of hypoprothrombinaemic bleeding occurring as the result of the administration of dicoumarol or tromexan.

This lack of agreement has probably been due to two variable factors. In some experimental trials water-soluble vitamin-K preparations were regarded as effective when the anticoagulant was given in minimum active quantities. There is good evidence that this is so (Shapiro *et al.*, 1943), but little that they are effective against therapeutic doses of dicoumarol. The second variable factor has been the expected response to administration of vitamin K. Many writers have considered adequate a response demonstrable in the course of days and have been content to advise the use of the water-soluble preparations. Our own findings on the inadequacy of these preparations and the greater reliability of vitamin K₁, together with evidence presented by others on the use of vitamin K₁ or its oxide, seem to justify the conclusion that there are only two known effective means of treating hypoprothrombinaemia induced by dicoumarol or tromexan. These are by transfusion of blood or by administration of vitamin K₁ or its oxide.

In view of the fact that transfusion, to be effective, involves the use of blood or of frozen fresh plasma from possibly more than a single donor, and that thereby delay may often occur in beginning adequate treatment, there is some justification for regarding a suitable preparation of vitamin K₁ or its oxide as an essential material in any department in which treatment by dicoumarol or tromexan is being carried out. Neither vitamin K₁ nor its oxide is available commercially, but it could doubtless be made so, and, as has been shown (Shoshkes *et al.*, 1950), a convenient, effective, and stable emulsion can be prepared for intravenous use. No reliance should be placed on the use of larger doses of the synthetic water-soluble vitamin-K analogues. The action of vitamin-K preparations against the hypoprothrombinaemic effect of dicoumarol or tromexan is not simply a matter of dosage. There is a difference in the action of water-soluble and oil-soluble preparations which has not so far been explained except that it has been related to the presence of the "phytyl" group in the molecule of vitamin K₁ (Miller *et al.*, 1950).

Summary and Conclusions

The effect of certain substances with vitamin-K activity in modifying the action of dicoumarol and tromexan has been investigated in the human subject. The vitamin-K preparations employed were vitamin K₁, menaphthone, acetomenaphthone, kapilon, synkavit, and water-soluble K analogue (Boots).

Apart from vitamin K₁, these substances have been shown to possess a minor and inconstant ability to modify the action of these anticoagulants. Vitamin K₁, on the other hand, is a reliable and efficient antidote, and is capable of completely blocking the action of therapeutic doses of dicoumarol and tromexan, and capable of restoring to safe levels within a few hours excessive hypoprothrombinaemia due to these drugs.

Since these differences between the vitamin-K preparations are not merely a question of dosage, of all the substances tested here only vitamin K₁ can be regarded as a reliable antidote for a hypoprothrombinaemic emergency.

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ACQUIRED SENSITIVITY TO PARA-AMINOSALICYLIC ACID

BY

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Since the widespread use of *para*-aminosalicylic acid (P.A.S.), either by itself or in conjunction with streptomycin, in the treatment of pulmonary tuberculosis, reactions have occurred which indicate that it is possible to distinguish two groups of cases.

First there are those patients with a natural intolerance to P.A.S. who develop gastro-intestinal symptoms during the first few days of treatment. As reported by Lehmann (1947) nausea is the symptom most frequently encountered, and may be accompanied by vomiting and diarrhoea in cases which exhibit a greater intolerance to the drug. Nagley and Logg (1949) pointed out that these effects are often due to impurities in the preparation of the drug and are seldom so severe as to cause abandonment of P.A.S. therapy.

Secondly, there are a few patients who develop an acquired allergic sensitivity to P.A.S. In these cases the onset of symptoms is characteristically sudden and usually occurs between two and four weeks after the beginning of treatment. Drug fever, with a rise of body temperature to 100–103° F. (37.8–39.4° C.), and symptoms of a marked constitutional disturbance are the usual features of this type of reaction and are commonly accompanied by a pruritic skin eruption as reported by Kierland and Carr (1949). Other toxic effects which have been recorded include renal damage (Nagley and Logg, 1949), hepatitis and enlargement of lymphatic nodes (Cuthbert, 1950), and lowering of the serum potassium (Cayley, 1950).

Case Report

The following case of an unusually severe sensitivity reaction to P.A.S. recently occurred at the Brompton Hospital.

A draughtsman aged 29 was admitted with the following history. He had developed pulmonary tuberculosis involving the right lung in 1944, for which he was treated by rest for 10 months at the Royal National Sanatorium, Ventnor. During this time a right artificial pneumothorax was induced, but this was abandoned after two months owing to the formation of an effusion. He subsequently returned to work and remained well until January, 1951, when, following a febrile coryza, he had a sudden haemoptysis of about 1 oz. (28 ml.).

Treatment consisted of rest in bed at home, and in March he began treatment with P.A.S., 18 g. daily by mouth. Three weeks later he had an evening rise of temperature, followed in two days by nausea, vomiting, and headache, and four days later by a morbilliform rash and pyrexia rising to 104° F. (40° C.). P.A.S. was discontinued, and the pyrexia and rash subsided on treatment with mepyramine hydrogen maleate ("anthisan").

One week later, while still receiving mepyramine, 100 mg. thrice daily, he was given two 3-g. doses of P.A.S., and within six hours the temperature rose to 102° F. (38.9° C.) and the rash returned. Despite discontinuation of P.A.S. the pyrexia and rash persisted, and five days later there was tender enlargement of the cervical, axillary, post-occipital, inguinal, and epitrochlear lymphatic nodes accompanied by sore throat, epigastric pain, and tenderness. The following