acetyl acetone as a tracer and measuring the concentration by an ultra-violet absorptiometer (Lidwell and Lovelock, 1946). There was no great difference in the die-away attributable to the hexylresorcinol in the two rooms with the different concentrations (Table V), the value being about six an hour.

TABLE V.—*Die-away Rates of Streptococci from "Spraying Spit" in Rooms with Increased Hexylresorcinol Concentrations*

	Hexylresorcinol Concentration (μg./cu. ft.)			
	0	0	1·3	4·3
Ventilation rate (air changes per hr.) ..	About 5	3·2	2·6	5·0
Die-away rates (per hr.) (mean of two estimates except where *, when only one was available)				
Overall:				
Total streptococci	10·8*	7·6	13·1	14·5
Str. salivarius	8·8	9·2*	17·0	13·5
Estimated, due to settling alone:				
Total streptococci	About 6	4·4		
Str. salivarius	About 4	6·0		
Estimated as due to hexylresorcinol:				
Total streptococci			5·5	4·5
Str. salivarius			9·4	3·5

To convert μg./cu. ft./ to μg./m.³, multiply by 35·3.

We had the impression that throat irritation was detectable when the concentration of hexylresorcinol rose appreciably above 1 μg. per cu. ft. (35 μg. per m.³), as it did in all the treated rooms in which these tests were carried out; at the highest levels of concentration reached, around 4 μg. per cu. ft. (140 μg. per m.³), throat irritation was pronounced.

Discussion

Methods for the estimation of the attack rate for "common colds" have been discussed previously (Lidwell and Sommerville, 1951; Reid *et al.*, 1953); we feel strongly that absence rates are very little guide to the true level of morbidity. Nevertheless they are an important criterion in any trial of prophylactic measures, since absence from work is one of the consequences of respiratory tract illness that we wish to prevent.

In the trial reported here, hexylresorcinol was vaporized at the rate recommended, from past experience, by the manufacturers of the apparatus used. The concentration found in the air was less than 1 μg. per cu. ft. (35 μg. per m.³) and was apparently inadequate to reduce the bacterial content of the office air. From limited tests it appeared, also, that an increase in the rate of hexylresorcinol vaporization sufficient to produce any notable reduction in the bacterial count would have exceeded the level that produces irritation of the throat.

There was no evidence of any effect on the attack rate for the common cold and other similar affections, nor on the absence rate. We have no explanation for the beneficial effect reported by Dickson from vaporization by the same apparatus at about the same rate, but Dickson's paper does not give enough detail of his results to enable precise comparison with our experience to be made.

In any tests such as this, it is possible to attribute failure to the fact that most of the colds are caught outside the treated environment. We propose to analyse our results for evidence on this aspect at a later date. Meanwhile we conclude that vaporization of hexylresorcinol to give a concentration of about 0.5 μg. per cu. ft. (17.5 μg. per m.³) in the office in which our subjects spent about 40 hours a week had no effect on their experience of colds.

Summary

Hexylresorcinol was vaporized by heat at the rate of about 0.125 g. an hour into three office rooms, each of 26,000 cu. ft. (736 m.³) capacity, and each having 40–45 staff. Five similar control rooms, with the same numbers of staff, were also observed. Three of these rooms had dummy vaporizers.

The number of colds suffered by members of the staff was recorded in the treated and untreated rooms over a period of 38 weeks in the winter of 1952–3 by a nurse, who interviewed each member once a week.

The hexylresorcinol had no detectable effect on the bacterial content of the air, on the number of colds recorded by the staff, or on the number of days of sick-absence.

A short test made subsequently suggested that no great effect on the bacterial content of the air could be obtained without risk of respiratory tract irritation from the hexylresorcinol.

We are grateful to the Ministry of Pensions and National Insurance for the facilities provided, and particularly to the staff of the offices who collaborated in obtaining the records; and to members of the Establishments Department and the staff representatives for their help in organizing the study. We are also indebted to the Medical Department of the Ministry for their interest and advice. We also wish to thank Mrs. E. Hodgson, who collected the records, and the staff of Shepherd's Aerosols Ltd. for the adjustment of the vaporizers. The work was carried out as part of a wider study sponsored by the Air Hygiene Committee of the Medical Research Council.

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PROTHROMBIN AND HAEMORRHAGE

BY

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The clotting defect which may lead to haemorrhage in coumarin anticoagulant overdosage and in such pathological conditions as obstructive jaundice and hepatic cirrhosis has generally been described as hypoprothrombinaemia, and the method in general use for detecting and measuring this defect has been the one-stage accelerated clotting-time ("prothrombin time") test of Quick (Quick *et al.*, 1935). For long it was assumed that this test did in fact measure prothrombin—hence the term "hypoprothrombinaemia" to describe the clotting defect revealed by it. It is now recognized that this test is a far more sensitive index of deficiency of the prothrombin conversion accelerators—factor V (Owren, 1947; plasma ac-globulin, Ware *et al.*, 1947) and factor VII (Koller *et al.*, 1951; cothromboplastin, Mann, 1949; serum prothrombin conversion accelerator, Alexander *et al.*, 1949; convertin, Owren, 1951)—than of prothrombin itself, which can best be measured by the two-stage area method of Biggs and Douglas (1953). In fact, severe prothrombin deficiency as such (below 10% of normal) will produce only a slight prolongation of the one-stage

clotting-time (Biggs and Douglas, 1953), and the alteration in this test brought about by coumarin drugs is due to inhibition of factor VII (Douglas, 1952; Hunter and Tudhope, 1953; Walker and Hunter, 1954). The alteration in prothrombin itself brought about by coumarin treatment is very variable and, with therapeutic doses, usually insignificant. Similarly in liver disease, a prolonged one-stage clotting-time can usually be shown to be due to moderate factor VII deficiency (Hunter and Walker, 1954).

The bleeding which occurs with coumarin overdosage is generally associated with a very prolonged one-stage clotting ("prothrombin") time, and hence might be assumed to be due to factor VII deficiency. That the cause is not as simple as this is obvious from the fact that there is no strict correlation between the results of the one-stage test and the tendency to bleed: factor VII depression, measured by this test, may be extreme in the absence of haemorrhage, while bleeding may at times occur when the one-stage test is within or only slightly beyond the therapeutic range. This has been stressed by other workers (Hogben and Allen, 1950). The exact cause of haemorrhage is in fact unknown.

This communication describes four patients, who bled while under treatment with coumarin anticoagulants, and in whom the haemorrhage was associated with very low levels of prothrombin as such, measured by the two-stage test, rather than with unduly low levels of factor VII. Two cases of haemorrhage in liver disease are also described, both showing a severe prothrombin deficiency unrevealed by the one-stage test, which showed only slight prolongation demonstrably due to reduction of factor VII.

Case Reports

Case 1.—A man aged 45 was taking 150 mg. of ethyl biscoumacetate ("tromexan"), twice daily as an out-patient, following in-patient treatment for myocardial infarction. The one-stage test one week before bleeding started gave results within the therapeutic range. On the day following the onset of massive haematuria his one-stage test showed a clotting-time of 40 seconds (control 12 seconds), and his prothrombin was 5% of normal. On the following day bleeding continued, although his one-stage test was now only 19 seconds (control 12 seconds). His prothrombin was still only 15% of normal. On the fourth day from the onset bleeding was slight and finally ceased; his one-stage test was now 16 seconds and his prothrombin had risen to 34% of normal. Recovery was spontaneous, no vitamin K being given.

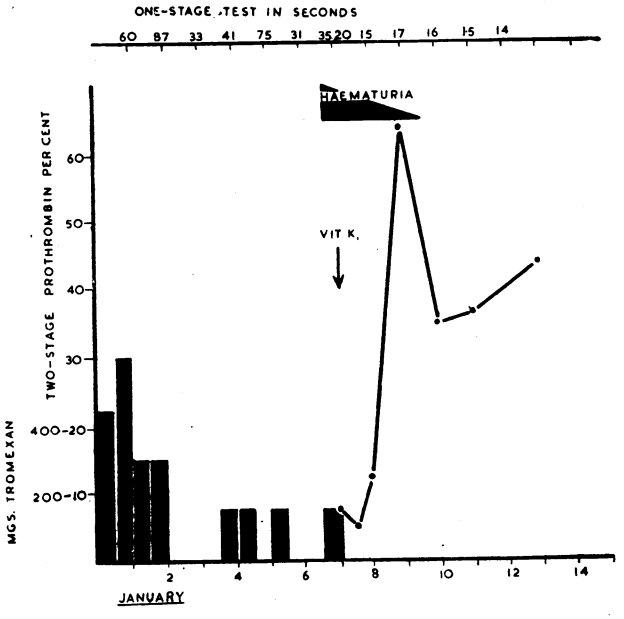

Chart showing effect of ethyl biscoumacetate in Case 2.

Case 2.—A male in-patient aged 70, with deep calf-vein thrombosis, was very sensitive to ethyl biscoumacetate, and on the third day of treatment his one-stage test reached 87 seconds (initially normal). On the sixth day it was 75 seconds, but on neither of these days did bleeding occur. On the seventh day his one-stage test was 31 seconds (control 13 seconds). On the eighth day, when his one-stage test was 35 seconds, he had heavy haematuria, and the two-stage area test showed prothrombin only 8% of normal. He was given 20 mg. of vitamin K_1 emulsion by mouth; but response to this was not immediate, and on the ninth day, although the one-stage test had fallen to 20 seconds (control 12 seconds), bleeding continued and his prothrombin was only 12% of normal. On the twelfth day it was 64% of normal and bleeding gradually stopped (see Chart).

Case 3.—A man aged 48 was taking 150 mg. of ethyl biscoumacetate daily at home following in-patient treatment for myocardial infarction. On two consecutive days he took 150 mg. of dicoumarol supplied by his pharmacist in mistake for ethyl biscoumacetate. This was followed by melaena, haematuria, and widespread ecchymoses, which were still present on his admission to hospital one week later. On the day of admission he was given 50 mg. of water-soluble vitamin K analogue ("synkavit") intramuscularly, and six hours later his one-stage test was 56 seconds (control 14 seconds). He had virtually no prothrombin—less than 1% of normal—and his whole-blood clotting-time was 15 minutes (control 5 minutes). Six hours after the administration of 20 mg. of vitamin K_1 emulsion by mouth his one-stage test was 29 seconds (control 14 seconds), but prothrombin was still absent. On the following day heavy haematuria recurred, when his one-stage test was 18 seconds (control 12 seconds). No further bleeding occurred, and on his fourth day in hospital his one-stage test was 14 seconds and his prothrombin 39% of normal.

Case 4.—A woman aged 80 was given phenylindanedione for coronary artery disease, and was maintained on a dose of only 25 mg. daily. On the ninth day of treatment profuse rectal and vaginal haemorrhage occurred, at a time when her one-stage test was 38 seconds (control 12 seconds). Prothrombin was less than 5% of normal.

Case 5.—A man aged 52, with severe alcoholic cirrhosis, had numerous large ecchymoses on trunk and limbs. His one-stage test varied from 17 to 19 seconds (control 11 to 12 seconds), and was corrected by the addition to his plasma of a 10% concentration of a factor VII preparation. His prothrombin varied from 10 to 20% of normal.

Case 6.—A woman aged 56 had severe obstructive jaundice due to secondary carcinoma, and widespread ecchymoses and skin haemorrhages. Her one-stage test was 20 seconds (control 12 seconds), and was partially corrected by the addition of a 10% concentration of a factor VII preparation. Her prothrombin was 6% of normal.

Discussion

In both groups, coumarin-treated and liver disease, the haemorrhage was associated with true prothrombin deficiency. In two of the four anticoagulant cases, the one-stage clotting-time at the onset was also markedly abnormal, and could be taken as a warning of a tendency to bleed. Even in these, however, bleeding continued when this test had returned to the therapeutic range. In the other anticoagulant cases (Nos. 2 and 4), bleeding started at a time when the Quick test was not alarmingly prolonged.

It is usual for very low levels of factor VII to be reached in coumarin-treated patients before gross deficiency in prothrombin itself occurs, so that for practical purposes the

one-stage test of Quick remains a satisfactory method of control in the great majority of cases on coumarin therapy. It is well to bear in mind, however, that occasionally such severe prothrombin deficiency may exist, together with bleeding or the imminent danger of it, when the Quick test, measuring as it does factor VII and not prothrombin, is reassuringly near or even within the therapeutic range.

In the cases of liver disease described here the situation is different. Neither of them showed more than slight prolongation of the clotting-time in the one-stage test, and on the classical interpretation of this test the hypoprothrombinaemia would be slight. Yet these patients showed haemorrhage and true prothrombin levels in the region of 10%. In such cases the Quick test may give a quite misleading indication of the tendency to bleed, showing as it does evidence only of moderate factor VII depression and no indication of the severe hypoprothrombinaemia.

In neither of these two groups can it be assumed that this deficiency in prothrombin is the necessary or only cause of the haemorrhage, but in these cases it is the one constant and common factor, suggesting a possible aetiological relationship. It should be stated, however, that other patients have been studied in whom the prothrombin measured by the two-stage area method was below 10% of normal and yet no bleeding occurred, so that other factors are probably concerned in the onset of haemorrhage.

It is common practice to measure the effect of vitamin K preparations by the changes in the one-stage Quick test. Cases 2 and 3 illustrate how fallacious this may be. The efficacy of vitamin K_1 in stopping bleeding is probably more closely related to its effect on prothrombin than on the one-stage test (factor VII).

Summary

Four cases of haemorrhage due to coumarin anticoagulants, one due to hepatocellular disease, and one to obstructive jaundice are described.

In all four coumarin-treated patients the haemorrhage was associated with very low prothrombin levels rather than with undue prolongation of the clotting-time in the one-stage test of Quick.

Neither of the patients with hepatic disease had more than moderate prolongation of the one-stage clotting-time, and this was due to factor VII deficiency. Both had very low levels of prothrombin.

The Quick test is not a good measure of hypoprothrombinaemia, which, however, may play an important part in the initiation of haemorrhage in coumarin overdosage and liver disease.

We are indebted to Professor Ian G. W. Hill and Dr. O. T. Brown for allowing us to study Cases 3 and 4, and Case 2 respectively. Vitamin K_1 emulsion was supplied by Roche Products Ltd.

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RECURRENT RENAL STONE*

BY

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Stone in the kidney has a high recurrence rate after operation. Table I shows the incidence of recurrence on the operated side in various series, following the operations of pyelolithotomy, nephrolithotomy, and ureterolithotomy (the recurrence in that case being in the kidney and not in the ureter). The figures shown in the table under my name include cases operated on by various Leeds surgeons which were followed up from two to twenty years, the recurrence being confirmed by radiography. It has unfortunately been impossible to obtain an accurate follow-up in more than a small proportion of the total cases treated. Table II shows the incidence of contralateral recurrence after operations for renal stone.

TABLE I.—*Recurrence of Renal Stone after Operation in Various Series*

	Pyelolithotomy			Nephrolithotomy			Ureterolithotomy		
	Total	Recur.	%	Total	Recur.	%	Total	Recur.	%
Cabot and Crabtree (1915) ..	33	17	51	30	17	56			
Barney (1922a, 1922b)	—	—	32·8	—	—	52·9			
Braasch and Foulds (1923)	371	44	11·85	104	25	24·0			
Brongersma *et al.* (1924) ..	38	9	23·6	62	22	35·5			
Twinem (1940) ..	102	21	20·9	100	28	28			
Sutherland (1954) ..	100	47	47	40	25	62·5	49	18	37
Pyrah	63	22	34·9	50	30	60	43	9	20·9

TABLE II.—*Contralateral Recurrence of Renal Stone after Operation in Various Series*

	Contralateral Recurrence	
	After Pyelo-, Nephro- or Ureterolithotomy	After Nephrectomy
Twinem (1937) ..		4·2%
Oppenheimer (1937) ..	15·1%	14·8%
Sutherland (1954) ..	12·3% (195 cases)	11·1% (45 cases)
Pyrah	15·4% (136 „)	15·9% (44 „)

The factors most commonly responsible for recurrent stone are, first, the small pieces of grit or tiny calculi left behind at operation; and, secondly, infection. In the remaining cases it is sometimes possible to discover a persisting cause of stone formation, which it may or may not be possible to correct, and which determines recurrence after operation; some of these causes are well understood, other less so. The factors which may lead to recurrence of calculus formation are considered below.

Extrarenal Causes

Extrarenal causes of stone formation, and hence of recurrence, are possible errors in oxalate metabolism and hyperparathyroidism.

Oxalate Metabolism.—The commonest renal stone seen in the surgical out-patient department is the calcium oxalate stone; it usually occurs in non-infected kidneys, and it not uncommonly recurs. Twinem (1937, 1940) reported recurrence in 11 out of 74 cases of proved oxalate calculi. While local renal factors may play a part, it is possible that recurrence is the result of metabolic causes. The source of the

* An abridged version of a paper read at the opening of a discussion on recurrent urinary stone at the Medical Society of London on February 8, 1954.