A marked antagonistic effect of the vitamin K₁ on the hypoprothrombinaemia caused by these drugs is shown.

Patients with low prothrombin activities, when given vitamin K₁ emulsion, showed modification of the prothrombin level while maintained on regular dosage of either ethyl biscoumacetate or phenylindanedione.

The application of these effects to the management of anticoagulant therapy is discussed. It is emphasized that small doses of vitamin K₁ of the order of 10–15 mg., when used in this particular form, should normally be employed if states which are refractory to the action of these anticoagulant drugs are to be avoided.

The fact that vitamin K₁ is now generally available makes it safer to use dicoumarol-group drugs or phenylindanedione in obtaining therapeutic levels of hypoprothrombinaemia.

Thanks are due to those students and members of the Medical School staff who volunteered as subjects for the experiments, and to Roche Products Ltd. for supplies of the vitamin K₁ solution used.

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TRIAL OF HEXYLRESORCINOL AS AIR DISINFECTANT FOR PREVENTION OF COLDS IN OFFICE WORKERS

BY

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Hexylresorcinol was recommended for use as an air disinfectant by Twort and Baker (1942). Bourdillon *et al.* (1948), in their comparative study of a variety of possible disinfectant agents, showed that as little as 2 µg. per cu. ft. (about 70 µg. per m.³) was needed to produce a killing rate of 10 an hour against natural salivary bacteria sprayed from the mouth; but they could not obtain a killing rate of 30 an hour with any attainable concentration. The only field investigation reported appears to be that of Dickson (1953), who dispersed hexylresorcinol from "aerovap" vaporizers in a number of government offices in Dublin, and recorded a decrease in the amount of sick-absence among the staff in the treated rooms.

During the winter of 1951–2 we made some preliminary observations on the incidence of colds among the staff of the central offices of the then Ministry of National In-

surance in Newcastle-upon-Tyne, using the personal-interview method of enumerating colds described by Reid, Williams, and Hirsch (1953). Since the attack rates recorded in six separate rooms, each with about 45 staff, were very similar, the situation seemed suitable for a test of the value of hexylresorcinol for the reduction of the incidence of colds. This paper reports our failure to achieve any reduction in a carefully controlled trial carried out in the winter of 1952–3.

Material and Methods

Population Studied.—The investigation was made in eight rooms, each of about 26,000 cu. ft. (736 m.³) capacity, and each having 40–45 staff. They were particularly suitable for a controlled study, since the rooms were identical in size and shape, and very similar in the layout of furniture and fittings. The staff in each room were very similarly distributed in respect of age, sex, and status. In two groups of five and three rooms, the work done was identical. The observations made during 1951–2 had shown that the attack rates for colds in each of six rooms (similar to and including some of those observed in the present work) did not differ greatly, the room attack rates varying from 4.5 to 6.2 per 100 person-weeks of exposure.

Recording of Illness.—As in the study reported by Reid *et al.* (1953), a nurse visited each member of the staff once a week and inquired for a history of any upper respiratory illness occurring during the past week. The great majority of the incidents recorded were typical common colds, with no symptoms of fever and no aches or pains. The symptoms for each incident were recorded, and we can distinguish a group of influenza-like illnesses; there was, however, no epidemic of virus influenza recognized in Newcastle during the winter of 1952–3. For the purpose of analysis we have not regarded any cold as a new cold if it occurred in the week immediately succeeding a week in which another new cold was recorded.

Installation of Vaporizers.—Four "aerovap" vaporizers, each designed to yield 30 mg. of hexylresorcinol an hour, were installed in each of six rooms. These vaporizers were simple electrically heated pots which maintain the hexylresorcinol at a temperature of about 116° C. Distribution of the vapour around the room was dependent on natural air currents. During the period September 8, 1952, to January 22, 1953, hexylresorcinol was put into the vaporizers in three of the rooms, A, B, and C. Three other rooms, D, E, and F, had vaporizers running but containing only an inert material. Two further rooms, G and H, had no vaporizers. On January 22 the hexylresorcinol was transferred to the vaporizers in rooms D, E, and F without informing either the occupants of the rooms or the nurse who recorded the colds. Rooms A, B, and C then had the inert material.

Relative Humidity.—The relative humidity in the offices was recorded twice weekly; it varied between 50 and 60% throughout the investigation except for a short period in March and April, 1953, when it fell to 40–50%.

Air Sampling.—On four occasions during the winter, samples were collected from the air for bacteriological analysis with a slit-sampler modified from those described by Bourdillon *et al.* (1948). Two different counts of airborne bacteria are recorded in the tables. The "general count" is the number of particles carrying viable bacteria that grow on serum agar incubated at 37° C. for 18–20 hours. The count of "mouth streptococci" was obtained by method C of Williams and Hirsch (1950), and is an estimate of the number of streptococci thought to be derived directly or indirectly from the mouths of the occupants of the room. The *Str. salivarius* count is another measure of mouth pollution of the air. Air samples for estimation of hexylresorcinol content were taken on one occasion, the air being bubbled through phosphate buffer, which was subsequently reacted with diazotized sulphanilic acid.

Results

Incidence of Colds.—There was no detectable difference between the incidence of colds in the treated and control rooms (Table I). There was reasonable consistency in the

TABLE I.—Incidence of Colds Per 100 Person-weeks at Risk

	Rooms Treated with Hexylresorcinol			Rooms with Dummy Vaporizers			Untreated Control Rooms	
	A	B	C	D	E	F	G	H
Sept. 8, 1952–Jan. 22, 1953								
No. of person-weeks ..	966	1,096	947	978	720	959	882	1,187
Colds	9.2	8.2	8.6	7.8	7.1	8.0	8.0	7.9
	D	E	F	A	B	C	G	H
Jan. 22–May 12, 1953								
No. of person-weeks ..	789	993	765	761	900	771	683	768
Colds	4.5	4.1	2.9	3.6	5.7	3.1	3.8	3.5
Whole period								
No. of person-weeks ..	5,556			5,089			3,520	
Colds	6.1			5.7			5.8	
Colds which were febrile or resembled influenza	0.4			0.4			0.3	
Absences	0.9			0.6			0.8	
Days' absence from work	5.7			3.9			2.8	

attack rates within each group during each of the two periods; and in the summation of the two periods the staff in the rooms treated with hexylresorcinol actually had a slightly higher attack rate than those in the control rooms. The attack rate in the two rooms without vaporizers was very similar to that in the rooms with vaporizers, showing that the presence of vaporizers had no psychological effect on the number of colds reported. The week-to-week incidence of colds is shown in the Chart; there was some suggestion that the treated group had a higher rate during the first autumn epidemic than the controls, but the difference was not great. Absence from work due to respiratory disease was not very common, and the duration of absence was, as might be expected, very variable. There was, however, no indication of any reduction in absence rates (Table I) among the staff of the treated rooms; nor was the duration of absence shorter (Table II).

Weekly attack rate for colds in the treated and control offices.

TABLE II.—Duration of Absences from Work for Respiratory Tract Diseases

No. of Days' Absence	No. of Persons Absent in		
	Rooms Treated with Hexylresorcinol	Rooms with Dummy Vaporizers	Untreated Control Rooms
1–3	28	15	18
4–7	9	5	7
8–42	14	8	2
Total days lost	318	198	97
No. of absences	51	28	27
Mean duration of absence	6.2	7.1	3.6

Bacterial Counts.—The vaporization failed to produce any reduction in the number of bacteria in the air of the rooms (Table III). Although the number of occasions on which the samples were taken was small, a total of 16 cu. ft. (0.45 m.³) of air was examined for the general count and about 300 cu. ft. (8.5 m.³) for the streptococcal count in each of the eight offices on each of the four separate occasions spread over the winter and spring. It seems certain that the results give a reasonably fair picture of the bacterial count in the air.

TABLE III.—Median* Bacterial Content of the Office Air (Colonies per cu. ft.)

	Rooms Treated with Hexylresorcinol	Rooms with Dummy Vaporizers	Untreated Control Rooms
General bacterial flora ..	39.7	38.8	46.9
Total mouth streptococci	0.10	0.10	0.13
<i>Str. salivarius</i>	0.025	0.025	0.023

To convert cu. ft. to m.³, multiply by 35.3
* The medians were derived after transforming the counts to log₁₀ (count +1) to allow for the logarithmic frequency distribution and the presence of some zero entries.

Air Sampling for Hexylresorcinol.—Air samples taken in October, 1952, showed barely detectable amounts of hexylresorcinol present in the air, probably not exceeding 0.5 µg. per cu. ft. (17.6 µg. per m.³). The amount of the substance vaporized from the pots over the whole period of the trial was determined from the weight loss, and averaged 0.125 g. per room per hour. This approximates to the expected yield of the vaporizers.

Short-term Test of Higher Hexylresorcinol Concentrations

When it became clear that the amount of hexylresorcinol vaporized from the four standard vaporizers in each room was inadequate to affect the bacterial count, a short-term experiment was carried out in July, 1953, to determine the effect of a higher concentration of the bactericide. One room was equipped with vaporizers giving 12.5 µg./cu. ft./hr. (440 µg./m.³/hr.) (compared with the estimated 4.8 µg./cu. ft./hr. (170 µg./m.³/hr.) for the standard installation employed during the winter), and two with vaporizers giving respectively 29.7 µg. and 21.9 µg./cu. ft./hr. (1,048 and 773 µg./m.³/hr.). These increased quantities were generated for three days, and then, on two successive days with the vaporizers still running, air samples were collected for bacterial counts (Table IV). The count in the room with

TABLE IV.—Bacterial Counts in the Air of Rooms with Increased Hexylresorcinol Concentration

Hexylresorcinol		No. of Samples*	Mean Bacterial Counts (Colonies per cu. ft.)		
Rate of Vaporization µg./cu. ft./hr.	Concentration µg./cu. ft.		General Flora	Total Mouth Streptococci	<i>Str. salivarius</i>
0	0	8	56.9	0.090	0.0091
12.5	1.15	2	84.0	0.0980	0.0100
25.8	3.83	4	22.0	0.053	0.0025

To convert µg./cu. ft./hr. to µg./m.³/hr., multiply by 35.3.
* In the control rooms the samples were of 30 cu. ft. for the general count and 600 cu. ft. for the streptococcal counts; the volumes in the hexylresorcinol rooms were 5 and 100 cu. ft. respectively.

the lower hexylresorcinol content did not differ greatly from that in the controls. The count in the presence of the higher concentration was substantially reduced, but we had evidence that this, at least in part, resulted from killing of bacteria on the culture plate after collection, due to absorption of hexylresorcinol from the air into the medium during sampling.

As a further test, sprays of mouth streptococci in saliva were generated in each of four rooms by "spraying spits" (Bourdillon *et al.*, 1948), and the rate of die-away was observed with slit-sampler and settling-plate counts. The ventilation rates were also determined simultaneously, using

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 ($\mu\text{g./cu. ft.}$)			
	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
<i>Str. salivarius</i>	8.8	9.2*	17.0	13.5
Estimated, due to settling alone:				
Total streptococci	About 6	4.4		
<i>Str. salivarius</i>	About 4	6.0		
Estimated as due to hexylresorcinol:				
Total streptococci			5.5	4.5
<i>Str. salivarius</i>			9.4	3.5

To convert $\mu\text{g./cu. ft.}$ to $\mu\text{g./m.}^3$, multiply by 35.3.

We had the impression that throat irritation was detectable when the concentration of hexylresorcinol rose appreciably above 1 $\mu\text{g. per cu. ft.}$ (35 $\mu\text{g. per m.}^3$), as it did in all the treated rooms in which these tests were carried out; at the highest levels of concentration reached, around 4 $\mu\text{g. per cu. ft.}$ (140 $\mu\text{g. per m.}^3$), 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 $\mu\text{g. per cu. ft.}$ (35 $\mu\text{g. per m.}^3$) 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 $\mu\text{g. per cu. ft.}$ (17.5 $\mu\text{g. per m.}^3$) 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