it was shown on two occasions that even the increased dosage of phthalylsulphathiazole did not control infection in nurseries infected with a sensitive strain.

During the course of this trial it became clear that the occurrence of secondary infection could be largely predicted from the proportion of children infected at the beginning of the incident.

In Table V the nurseries in both treated and control groups are divided on the basis of the extent of their infection at the beginning of the incident. When the initial

TABLE V.—Incidence of Secondary Infection in Nurseries Compared with Initial Infection

Series	Initial Infection in More than One-sixth Total Children			Initial Infection in Less than One-sixth Total Children		
	No. of Incidents	Initial Infection	Secondary Infection	No. of Incidents	Initial Infection	Secondary Infection
Treated	5	79/215 (37%)	21/130 (16%)	8	23/274 (8.4%)	3/281 (1.1%)
Control	4	53/169 (31%)	20/104 (19%)	10	32/414 (7.7%)	5/367 (1.4%)
Total	9	132/384 (34%)	41/234 (17.5%)	18	55/688 (8%)	8/648 (1.2%)

infection was in more than one-sixth of the child population ("high-infection" group), secondary infection occurred in all the incidents in the control and treated groups (the figure of one-sixth was chosen by inspecting the original data—in fact, no nurseries had an initial infection between one-fifth and one-seventh); when the initial infection was limited to less than one-sixth of the children ("low-infection" group), secondary infection was uncommon. It will be seen that these two types of incident were not distributed equally in the two series: the control series had one fewer of the "high-infection" group and two more of the "low-infection" group than the treated series. The rate of secondary infection in the treated series is lower absolutely and in proportion to the initial infection compared with the control series. The difference between the treated and the control series is, however, small compared with the difference between the "high-infection" and "low-infection" groups.

Discussion

The effect of prophylaxis with phthalylsulphathiazole in these day nurseries was very small. This finding does not appear to be due to the occurrence of sulphonamide-resistant strains: the choice of sulphonamide and the dosage, while possibly open to question, was made because it seemed that a wide safety margin was necessary in administering drugs to children in these particular circumstances.

It was found that on two-thirds of the occasions when *Sh. sonnei* was introduced into these nurseries the infection did not spread widely. It will be seen from Table V that in the 18 "low-infection" incidents only 63 persons were infected, an average of less than four per nursery. The close watch for diarrhoea and other suspicious symptoms necessitated by a trial of this kind may have contributed to the unexpectedly large number of low-infection incidents.

The different incidence of secondary infection in the "high-infection" and "low-infection" groups is remarkable and may go some way to explain how such divergent views of the value of sulphonamide prophylaxis have arisen. Thus, of the six day-nursery outbreaks described by Ross (1954) only one would fall into our "low-infection" group, and this was the only outbreak in which he found sulphonamide prophylaxis to appear to be of any value.

It is not possible to say what factors were responsible for "high-infection" and "low-infection" incidents. While it is possible that the former were caused by strains of *Sh. sonnei* with a higher infectivity and were able to spread more rapidly in a day nursery, it seems more likely that, when a high rate of infection was revealed at the beginning of an incident, the infection had been spreading in the nursery unnoticed for some time.

Summary

A controlled trial of prophylaxis of Sonne dysentery in day nurseries using phthalylsulphathiazole has been carried out. The effect of this sulphonamide in preventing secondary infection in the nursery was negligible.

We wish to acknowledge the generous gift of phthalylsulphathiazole used in some nurseries by Messrs. May and Baker Ltd., and the valuable co-operation of the medical and nursing staffs of many day nurseries.

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AUTOGENOUS BACTERIAL VACCINES IN TREATMENT OF ASTHMA

BY

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Bacterial vaccines have been used for many years in the treatment of the infective type of asthma. Different procedures are adopted by different workers. Vaughan and Black (1948) use skin-testing with the vaccine to decide on the dose, Cooke (1947) uses an autogenous vaccine but does not recommend skin tests with it, while Rackemann (1950) believes that the effect of vaccine is non-specific. Yet the general opinion seems to be that in suitable cases, particularly of the infective type of asthma, definite help is obtained from bacterial vaccine therapy.

The trial to be described was undertaken to decide whether an autogenous bacterial vaccine that has been used for a number of years in the asthma clinics at this hospital and elsewhere gives specific help. In attempting a controlled trial of vaccines in asthma we realize that results would be difficult to assess and could easily be misleading in a condition so susceptible to psychological influences. This problem has been discussed by Gadum (1954) for drug trials in headache such as those carried out by Jellinek (1946), who found that no significant results could be obtained on unselected groups, but that if all those patients who were relieved by blank tablets were excluded a trial could be arranged using the remainder. Such a solution to the problem is impossible among allergic patients, since all of them are to some extent influenced by psychological factors. Even in the case of hay-fever, one of the most clear-cut allergic conditions, 20% of the patients reported improvement on blank tablets in controlled trials of antihistaminics (Frankland and Gorrill, 1953).

It was therefore decided to continue all patients on the treatment that had previously given them the best relief, to advise all of them on diet and environment in the light of skin tests and case histories, and to arrange where necessary for suitable breathing exercises. Thus the pattern of the Medical Research Council chemotherapeutic trials was followed in that the best available

standard methods were given to both groups supplemented either with vaccine or with a control fluid administered in the same way (see Hill, 1951).

Selection of Patients

Only patients with bronchial asthma of an intrinsic type (Rackemann, 1947) were included in the trial, but grossly emphysematous patients as well as those with predominantly psychogenic and premenstrual asthma were excluded. The patients were selected by two doctors, who continued to review their own cases. Post-nasal swabs or sputum were examined by one bacteriologist (W. H. H.), who prepared a suitable vaccine for each patient. When taken into the trial the patient was given a card with a serial number. All the vaccines with the numbered cards were passed to the statistician (R. H. G.), who placed patients in either the vaccine or the control groups by the use of random number tables. Patients in the control group were issued with carbol-saline instead of the prepared autogenous vaccine. The patients were allowed to have the vaccine changed as often as it was thought necessary, so long as the vaccine passed through statistical control. Not until the completion of the trial and the patient had been fully assessed was it possible for either of the doctors reviewing their patients to know whether the patient had received vaccine or carbol-saline.

Vaccine Treatment

Weekly injections were given, starting with 0.1 ml., and increasing by this amount to 0.5 ml. until first review. The patient then either continued on a maintenance dose, which was often given less frequently than once a week, or the patient had another post-nasal swab or sputum specimen taken and a new vaccine was prepared. The organisms that were considered significant were *Streptococcus viridans* or a non-haemolytic streptococcus when in almost pure culture, any pneumococcus, or *Haemophilus influenzae*, or Friedländer's bacillus. Often there were several types of organism in one vaccine. The equivalent of 0.3 ml. per ml. of a stock vaccine containing per ml. Pneumococcus (mixed types) 50 millions, Friedländer's bacillus 25 millions, Staphylococcus (mixed types) 200 millions, *Bacillus septus* 25 millions, *H. influenzae* 50 millions, Streptococcus 10 millions, and *Micrococcus catarrhalis* 25 millions was added to all autogenous vaccines. The strength of the vaccine was such that it contained 10 million per ml. of each of the autogenous strains.

Method of Assessment

The patients were advised to return for review every fourth month for one year. Table VI shows the numbers returning for 4, 3, 2, or 1 review. The following points were considered: the weight change, the consumption of drugs, the frequency and severity of attacks, the days in hospital, in bed, off work or off school, the general change in incapacity, and the patient's as well as the doctor's opinion as to the general condition following treatment. A system of scoring was used (see Numerical Key), and the final figure from the key gave the final overall result. Although some standard skin tests were performed on all patients and their size was compared each time the patient came up for review, these findings will not be considered in this paper.

Numbers in Trial

The trial was designed to take up to 200 patients for each observer. As only 100 patients were used the control and test groups are of unequal size.

One observer (H.) took 102 patients into the trial and 7 were discarded. The reasons for discarding were: 3 disappeared and could not be traced, 2 died before the trial ended, one developed carcinoma of the lung, and the remaining patient developed pulmonary tuberculosis. Of the 95 patients remaining, 52 were allocated to vaccine treatment and 43 to the control group. Unfortunately, 6 of the

Numerical Key for Asthma Survey

	Definition	Score
Original condition and Final condition	Severe continuous	1
	Continuous	2
	Intermittent severe	3
	" mild	4
	Nil	5
Natural progress of disease	Deteriorating	A
	Constant	B
	Improving	C
Consumption of drugs	Heavy continuous	1
	Regular	2
	Occasional	3
	Nil	4
Weight change	Unintentional loss over 5% ..	-2
	" " " 2½% ..	-1
	No change, ±2½%	0
	Slight gain, 2½%	+1
	Definite gain, 5%	+2
	Patients deliberately reducing mark	*
Incapacity	Increased greatly	-4
	" slightly	-2
	No change	0
	Decreased	+2
	Greatly decreased	+4
Patients' and doctors' opinions	Much worse	-4
	Worse	-2
	No change	0
	Doubtful improvement	+1
	Definite improvement	+2
	Well	+4
Vaccine administration	Continued	A
	Given up	B
	Not given	C

patients were not given any injections by their doctor, so that in this series 50 received vaccine and 39 the control fluid.

The other observer (F.) started with 100 patients, and two were discarded, as they could not be traced at the end of the trial. In this series 52 were allocated to vaccine and 46 to the control. However, 3 were not given the injections, and so the numbers are reduced to 50 in the vaccine and 45 in the control group.

Results

Tables I-V show the distribution of the patients in regard to a number of characters on entry into the trial. While there are differences between the age and marital status of the two main groups, it will be seen that within a group the vaccine and control subgroups are comparable. Table I shows the distribution of all patients who were in the trial at its completion. Tables II-IX show only those who received injections—that is, they exclude the nine patients who did not receive either vaccine or control.

In assessing the results of treatment the grand total of the various factors taken into account has been used (see Table VII). It will be seen that while there is a difference

TABLE I.—Distribution of Age, Sex, and Marital Status

Age in Years	H.		F.	
	Female	Male	Female	Male
0-9 ..	0	0	3	8
10-19 ..	6	5	6	16
20-29 ..	14	13	9	4
30-39 ..	13	9	8	0
40-49 ..	11	7	15	3
50-59 ..	8	7	12	6
60+ ..	1	1	3	5

Marital Status			
	H.	F.	
Married ..	66	49	
Single ..	28	49	
Widow ..	1	0	
	95	98	

between the two series the vaccine and control groups are similar. The grading of the results is naturally arbitrary, but the results may be grouped as: less than -2 = poor, -2 to +2 = no change, +3 and above = improvement. The data in Table VII have been grouped according to this classification. It will be seen that 54% and 62% (average

TABLE II.—*Duration of Asthma in Years, with 0-9 Group Further Subdivided*

Years	H.		F.	
	Vaccine	Control	Vaccine	Control
0-3	10	6	13	9
4-6	6	8	5	7
7-9	11	5	11	6
0-9	27	19	29	22
10-19	15	10	11	13
20-29	5	8	5	7
30-39	1	2	3	2
40+	2	0	2	1
All ages	50	39	50	45

TABLE III.—*Original Condition. See Numerical Key for Coding*

	H.		F.	
	Vaccine	Control	Vaccine	Control
Severe continuous (1)	1	0	2	3
Continuous (2)	12	13	21	15
Intermittent severe (3)	23	19	16	21
" mild (4)	14	7	11	6
	50	39	50	45

TABLE IV.—*Drug Consumption at Start of Trial*

	H.		F.	
	Vaccine	Control	Vaccine	Control
Heavy continuous (1)	6	5	4	6
Regular (2)	28	24	29	23
Occasional (3)	9	5	15	15
Nil (4)	7	5	2	1
	50	39	50	45

TABLE V.—*Natural Progress of the Disease*

	H.		F.	
	Vaccine	Control	Vaccine	Control
Deteriorating, A	20	13	17	17
Constant, B	30	26	33	28
Improving, C	0	0	0	0
	50	39	50	45

TABLE VI.—*Follow-up*

No. of Times Seen	H.		F.	
	Vaccine	Control	Vaccine	Control
4	35	29	47	43
3	12	8	3	2
2	3	2	0	0
1	50	39	50	45

TABLE VII.—*Results of Treatment*

Score	H.		F.	
	Vaccine	Control	Vaccine	Control
-11	0	2	5	1
-7-10	1	1	3	1
-3-6	5	2	4	8
-2	13	13	11	12
+2				
+3+6	10	8	9	1
+7+10	16	9	15	14
+11	5	4	3	8
	50	39	50	45

TABLE VIII.—*Comparison of Patients Who Completed (A) With Those Who Defaulted from (B), the Vaccine Course*

Score	H.				F.			
	Vaccine		Control		Vaccine		Control	
	A	B	A	B	A	B	A	B
Less than -3	1	4	2	3	7	5	4	6
-3	11	3	11	4	10	2	12	1
+3	25	6	16	3	23	3	20	2
More than +3	37	13	29	10	40	10	36	9

TABLE IX.—*Results of Treatment by Duration of Disease*

Duration in Years	H.				F.			
	Vaccine		Control		Vaccine		Control	
	0-9	10+	0-9	10+	0-9	10+	0-9	10+
Score less than -3	3	2	3	2	5	7	4	6
-3	8	6	6	9	9	3	5	8
+3	16	15	10	9	16	10	13	9

58%) improved on the vaccine, while 51% and 54% (average 52.5%) improved on the saline injections.

In an attempt to determine any factors that might influence the results, those who stopped having injections (Group B) were compared with those who took the full course (Group A) (Table VIII). The grouping has been widened to allow for the smaller numbers. It will be seen that, comparing A and B in each subgroup, the patients who gave up vaccine injections fared worse than those who took the whole course. It would be interesting to know if there is any character which allows recognition of a "B" patient before treatment is begun. Despite extensive analysis no positive results in this direction were obtained, and the tables concerning these are therefore omitted.

The relationship of duration of asthma to the final grading was also investigated, and is shown in Table IX, where it will be noted that the duration of the disease had surprisingly little effect on the results.

Finally, there is the small group of patients who failed to receive any injections whatever. Their scores were: (H.), -4, -3, 0, +1, +4, +10; (F.), 0, +5, +8; that is, using our original standard 2 gave poor result, 3 were unchanged, and 4 were improved.

Discussion

This trial was devised to see whether an autogenous bacterial vaccine, as usually given to the intrinsic type of asthma as specific prophylactic therapy, produced any greater benefit to the patient than carbol-saline injections. The selection of the patients might well have been biased in some way, though it was hoped that this factor would be offset by the division of the trial under two doctors, one of whom believed that a bacterial vaccine helped specifically, while the other considered that any improvement was quite incidental to vaccine therapy. The number of injections of the vaccine used by the two doctors, and its strength, differed to some extent, so that each saline control group as well as the total in each group served as a control for any difference in the details of vaccine therapy. Although the results have been given separately in the tables, the pooled results can be considered together. It will be seen that 58% showed improvement on the bacterial vaccine, while 52% showed improvement on the carbol-saline.

Conybeare and Knott (1936) noted, in their series of asthmatic patients treated with bacterial vaccines, that if many of the patients were mild asthmatics, particularly of a short duration, any kind of treatment tended to show a high percentage of improvement. They suggested that the lack of preliminary grading in severity of asthma had led to the great variation in the reported results from the use of vaccines. In this trial, grading of asthma, although carried

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 K₁ 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