aggressive treatment of the disorder over the years is a most important factor in their prevention or postponement. I believe that to obtain good control diabetic diets should not usually contain much more than 200 g. of carbohydrate; that patients should be initially trained in the hard school of food-weighing, for it is only in that way that they learn to appreciate quantities; and that they should report regularly to a diabetic clinic to be assessed as regards symptoms, weight, glycosuria, and occasionally blood-sugar concentration, and, depending on the findings, to have their insulin dosage and diet suitably altered, for it is most exceptional to encounter a well-controlled diabetic who has been made entirely responsible for his own treatment.

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SULPHONAMIDE PROPHYLAXIS IN CHRONIC BRONCHITIS

A CLINICAL TRIAL

BY

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AND

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A clinical trial was carried out to determine whether the continuous administration of small doses of one of the sulphonamide drugs through the winter months would reduce the frequency and severity of the attacks of "winter bronchitis" which are common in cases of pneumoconiosis, emphysema, and "chronic bronchitis." The seriousness of the problem in general practice has been emphasized by Pemberton (1949) and Fry (1953, 1954), while Goodman *et al.* (1953) have stressed its importance as a cause of morbidity and mortality in the country. Energetic treatment by means of penicillin and streptomycin (Mulder *et al.*, 1952) is usually effective in an established attack, but if prophylaxis were possible much disability might be prevented and economy of hospital facilities achieved.

Plan of Investigation

Strict criteria for the suitability of a subject for inclusion in the trial were laid down initially. Subjects were included only if they gave a clear-cut history of having had an attack of increased cough and purulent sputum, necessitating their going to bed or being off work for more than one day, in each of the two previous winters. Those with conditions such as rheumatic or hypertensive heart disease, cor pul-

monale, rheumatoid arthritis, or pulmonary tuberculosis, which might lead to periods of illness unassociated with bronchitis, were excluded. A medical and industrial history was taken from each subject, followed by a clinical examination and a chest radiograph. The appearance of the sputum was noted, but no bacteriological examinations were made.

Methods of Assessment.—Previous experience suggested that all attacks of "bronchitis" were not similar and that a satisfactory classification and method of assessment would not be easy. This difficulty has been noted by Lister (1949), Oswald *et al.* (1953), and Fry (1954). We paid particular attention to the subject's history of the types of attack experienced, which were classified as follows:

Type A1.—A typical unmodified attack of winter bronchitis as severe as any previous one, with increased cough and purulent sputum causing the subject to stay off work and usually retire to bed.

Type A2.—A less severe variant of A1, the subject not having to stay off work, there being less cough, and the sputum being less in both amount and purulence.

Type B.—An attack of tightness of the chest or bronchial spasm without any change in cough or sputum.

Type C.—A typical "head cold" or influenza without involvement of the lower respiratory tract.

It was decided that the attacks should be assessed by one person, and, although some difficulty in classification was occasionally encountered, on the whole the system worked well.

The investigation took place in two stages, while the subjects fell into three separate groups.

Stage I

Group 1.—In the winter of 1951–2 35 subjects were selected from men with pneumoconiosis (simple or complicated) who had attended the Pneumoconiosis Research Unit and from men with emphysema and "chronic bronchitis" who were under the care of general practitioners near Llandough Hospital. It had been hoped that a much larger number of suitable subjects would be found: the trial was begun in November, and extra subjects were included, as they became available, until the beginning of January, when it was decided that further additions should cease. As they were selected, subjects were allocated to either a "treated" or a "control" group on a random basis in such a way that neither they nor the medical assessor knew to which group they had been assigned.

The treated group were given one tablet of sulphadimidine (0.5 g.) three times a day (on waking, at mid-day, and before retiring), and the control group an indistinguishable but inert tablet at the same times. The purpose of the trial was explained to each subject's own doctor in a letter, and each subject was issued with one week's supply of tablets at a time, with written instructions on when to take them; it was explained that they must report any sore throat or skin rash. The majority of subjects started taking the tablets in November, and the remainder had begun by the beginning of January; all stopped at the end of April. Information on the date and duration of any illness or absence from work was obtained weekly, and a clinical examination was carried out monthly. Frequent interviewing is considered very important, as people with chronic cough and sputum often have difficulty in establishing the precise date of onset of an attack of bronchitis.

When the results of this first small experiment had been evaluated it was found that differences suggestive of a beneficial effect of the drug had occurred. It was therefore decided to start a subsequent trial rather earlier in the autumn and increase the number of subjects. Accordingly, Stage II of the trial was planned for the winter of 1952–3, this time using two groups of subjects chosen in exactly the same way.

Stage II

Group 2.—This group comprised 30 men from a factory in a South Wales valley employing a large proportion of ex-coal-miners with pneumoconiosis.

Group 3.—This group comprised 32 subjects (27 men and 5 women) from an out-patient clinic in Stoke-on-Trent. A few had "chronic bronchitis," but the majority were ex-pottery-workers with pneumoconiosis.

Again much smaller numbers of suitable subjects had been found than was hoped for, but, provided that differences of a magnitude similar to or greater than those in Stage I occurred again between treated and control groups, the numbers were sufficient to establish significance. Accordingly the second stage was continued, methods of administration of the tablets and assessment of attacks being the same as in Stage I.

Results of Trial (Both Stages)

In group 1, eight patients stopped taking the tablets, two of them had definite sulphonamide sensitivity in the form of a skin rash. In group 2 there were four lapses, and in group 3 two lapses. The various reasons for ceasing to take the tablets are given in Table I.

The age distribution of the various groups of subjects remaining in the trial is given in Table II. It will be seen that the groups were all very similar in age, and that the random allocation into treated and control subjects was fairly successful in making the groups comparable, although the treated group contained rather more older subjects.

TABLE I.—Lapses—All Groups

Reason for Stopping Tablets	Treated Group. No. of Patients	Control Group. No. of Patients
Skin rash—i.e., definite sulphonamide sensitivity	2	0
Non-attendance	0	2
Giddiness	1	0
Headache, nausea, and vomiting	1	0
Worsening of respiratory symptoms	3	4
Died of other causes	1	0
Total	8	6

TABLE II.—Age Distribution of Subjects in Trial

		Date of Birth					All Ages
		1870—	1880—	1890—	1900—	1910—20	
Group 1	Control	—	2	8	3	1	14
	Treated	—	3	5	5	—	13
	Total	—	5	13	8	1	27
Group 2	Control	—	—	5	7	—	12
	Treated	—	1	4	8	1	14
	Total	—	1	9	15	1	26
Group 3	Control	—	5	9	1	—	15
	Treated	1	6	6	2	—	15
	Total	1	11	15	3	—	30
All groups	Control	—	7	22	11	1	41
	Treated	1	10	15	15	1	42
	Total	1	17	37	26	2	83

TABLE III.—Distribution of Subjects with A1 Attacks

		No. of Subjects		Total
		Attacked	Not Attacked	
Group 1	Control	7	7	14
	Treated	2	11	13
	Total	9	18	27
Group 2	Control	4	8	12
	Treated	4	10	14
	Total	8	18	26
Group 3	Control	3	12	15
	Treated	6	9	15
	Total	9	21	30
All groups	Control	14	27	41
	Treated	12	30	42
	Total	26	57	83

The analysis was confined to attacks classified as A1 or A2. Table III shows the distribution of subjects who had A1 attacks, in the three groups separately and in combination. Only in group 1, as has been mentioned above, was there any suggestion that the treated subjects did better than the controls ($0.10 > P > 0.05$). The proportions attacked, in the combined data (34% of controls, 29% of treated) did not differ significantly ($0.8 > P > 0.7$), and a χ^2 test, applied to see if the three groups differed significantly between themselves in the proportions of treated and controls attacked, also gave a negative answer ($0.10 > P > 0.05$). When A1 and A2 attacks are considered together, all suggestion of an effect of treatment is lacking. Table IV shows the distribution of subjects who had A1 or A2 attacks. Significance tests are clearly not required.

TABLE IV.—Distribution of Subjects Having A1 or A2 Attacks

		No. of Subjects		Total
		Attacked	Not Attacked	
Group 1	Control	9	5	14
	Treated	8	5	13
	Total	17	10	27
Group 2	Control	9	3	12
	Treated	8	6	14
	Total	17	9	26
Group 3	Control	6	9	15
	Treated	9	6	15
	Total	15	15	30
All groups	Control	24	17	41
	Treated	25	17	42
	Total	49	34	83

So far only the numbers of subjects attacked have been compared. It is possible, however, that treatment might reduce the frequency of attacks in the same subject. Only three subjects had as many as two A1 attacks—two of these being in the group 1 control group, one in the group 2 treated group. In consequence, in group 1 the average number of A1 attacks per man differs almost significantly ($0.10 > P > 0.05$) between the treated (0.15 attacks per man) and control groups (0.64 attacks per man). When all the groups are combined the overall difference is not remarkable. Table V shows the distribution of attacks per sub-

TABLE V.—Distribution of A1 Attacks

No. of Attacks	No. of Subjects		Total
	Controls	Treated	
0	27	30	57
1	12	11	23
2	2	1	3
Total	16	13	29
Average no. per man	0.39	0.31	0.35

ject. There were 29 attacks in all, 16 among the controls, 13 among the treated. Twenty-three subjects had one attack each (12 controls and 11 treated), and, as has been said, two controls and one treated subject had two attacks each. The average number of attacks per man was 0.39 for the controls, 0.31 for the treated, and this difference is not statistically significant ($0.5 > P > 0.4$). When A2 attacks are included the distributions are even more alike (Table VI). Three subjects in each group had three attacks; six controls and four treated had two attacks; 15 controls and 18 treated had one attack. The average number of attacks per subject was 0.88 for the controls, 0.83 for the treated.

It might be thought that the subjects were insufficiently alike in their tendency to have attacks for these averages to have much meaning. The results do not confirm this criticism, however. If the risk is the same for each subject, the numbers having no attacks, one attack, two attacks,

etc., should be predictable from the terms of a Poisson series. Table VI shows the expected numbers if each man has in fact an equal risk of attack. Clearly, the agreement is quite close, and there is little suggestion that unusually resistant or susceptible subjects were included in the trial.

TABLE VI.—Distribution of A1 or A2 Attacks

No. of Attacks	Controls	Treated	Total	Expected
0	17	17	34	35.0
1	15	18	33	30.2
2	6	4	10	12.9
3	3	3	6	3.7
4 or more	—	—	—	1.0
Total	36	35	71	71.1
Average no. per man	0.88	0.83	0.86	0.86

The number of subjects fulfilling the criteria laid down for inclusion in the trial was much smaller than expected. In consequence the trial was an insensitive one, and quite large real effects for sulphonamide are compatible with the negative results obtained. For example, the proportion of all subjects having an A1 attack was 31.3% (26 out of 83). Attacks occurred in 28.6% of the treated subjects and in 34.1% of the controls, a difference of 5.5% in favour of sulphonamide. If the overall attack rate is taken as fixed, the observed results for the treated group are not less probable than 0.05 if their true attack rate was as little as 19% or as much as 40.5%. That is to say, any true attack rates giving sets of results lying between the two extremes shown in Table VII cannot be ruled out on present evidence. More generally, without fixing the overall attack rate, various combinations of attack rates in the separate groups can be shown to be possible without conflicting with the present results,

TABLE VII.—Extreme Results Compatible with Observed Figures

		A1 Attacks	None	Total
Favourable to treatment	Controls	18 (43.9%)	23	41
	Treated	8 (19.0%)	34	42
	Total	26 (31.3%)	57	83
Unfavourable to treatment	Controls	9 (22.0%)	32	41
	Treated	17 (40.5%)	25	42
	Total	26 (31.3%)	57	83

Chart showing range of effects of sulphonamide. The closed curve shows the zone within which any combination of attack rates is not too improbable ($P > 0.05$) in view of the observed result.

provided that the resultant point on the graph lies within the closed curve shown in the Chart. For example, equal attack rates ranging from 24 to 40% are possible; if the rates for the control group lie between 34 and 45% the rates for the treated group can be half as great, while it is in no wise possible for the treated group attack rates to be twice as great as the control group rates. The Chart illustrates the very large range of different effects of sulphonamide which are compatible with the observed results, or, in other words, the great insensitivity of a small trial of this kind.

Discussion

The continuous administration of small doses of one of the sulphonamide drugs has been employed in the prophylaxis of rheumatic fever and meningococcal infections. One of these drugs (usually sulphadiazine) has been used as a prophylactic against respiratory infections, and favourable results were reported by Watson *et al.* (1943), Hodges (1944), Coburn (1944, 1945), and Billow and Albin (1946). These authors give accounts of controlled trials in the American Services during the 1939-45 war, but it should be remembered that the subjects were practically all young healthy recruits, and that the organism responsible for the acute respiratory illnesses was usually the streptococcus. Subsequently doubt was cast upon the advisability of "mass chemoprophylaxis," as increasing numbers of sulphonamide-resistant streptococci were found in cases both in the Services and in the general population (Epidemiology Unit Number 22, 1945; Delamater *et al.*, 1946; Wilson, 1946; Roberg, 1946; Damrosch, 1946; Johnson and Hartman, 1947). These authors thought that sulphonamide prophylaxis was ineffective and possibly dangerous. Kuh and Collen (1949) found that penicillin was ineffective prophylactically, but Gezon *et al.* (1953) carried out an investigation comparing oral penicillin, sulphonamides in small doses, and aspirin for the prophylaxis of respiratory infections, and reported favourable results in the penicillin and sulphonamide groups. The latter authors stressed the difficulty of diagnosis of acute respiratory infections and found that streptococci were responsible for only a third of their cases, the remainder being caused by other bacteria and viruses. In this country, Joules (1953) has advocated the use of 1 g. of sulphonamide daily in chronic bronchitis.

Many investigations of the bacteriology of the sputum in bronchitis have been made, but it is difficult as yet to assess the significance of the findings. It appears that pneumococci and *Haemophilus influenzae* (Stuart-Harris *et al.*, 1953; May, 1953a) are frequently present, and that other organisms such as *Streptococcus viridans* and *Neisseria catarrhalis* are probably non-pathogenic. The precise role of viruses has yet to be established, but it is suggested by Stuart-Harris *et al.* (1953) that they may play a part in the acute exacerbations.

According to May (1953a) there is a significant association between purulent sputum and the presence of potential pathogens, especially pneumococci and *H. influenzae*. He also found that suitable chemotherapy could render purulent sputum mucoid in character, but that a return of purulent sputum was common on cessation of therapy. Furthermore, it was found that patients expectorating mucoid sputum only did not benefit from chemotherapy, and, in some, the change from purulent to mucoid sputum resulted in an increased viscosity of the sputum with consequent difficulty in expectoration (May, 1953b). Elmes *et al.* (1953) investigated the effect of various antibiotics on the sputum in chronic bronchitis, and came to the conclusion that none of the drugs at present available was suitable for the prophylaxis of acute exacerbations.

So far as our trial is concerned there are several possible reasons why sulphonamide was not found to be effective as a prophylactic agent. Its true effect may lie within the zone of uncertainty in the Chart, so that it is too small to be established by a trial of this size. The classification of the attacks may have been erroneous, or the subjects not really true "chronic bronchitics." The majority of subjects in this

trial had industrial lung disease, and it is possible that such subjects may be less likely to respond to prophylactic chemotherapy than those who have not been exposed to a dust hazard. One of the sulphonamide series may not, in fact, have been the best drug to choose: the administration of drugs (such as penicillin) by injection was thought to be impracticable with working subjects, while the possible undesirable side-effects of chloramphenicol (Franklin and Garrod, 1953) and aureomycin—apart from the expense of these two drugs—would hardly justify their use over prolonged periods for prophylaxis, although good results have been claimed recently for the continuous administration of aureomycin in preventing acute respiratory infections in patients with congestive cardiac failure (McVay *et al.*, 1953). The dosage of sulphonamide may have been inadequate to establish a sufficiently high blood level, and the production of sulphonamide-resistant organisms may have been stimulated, but larger doses would probably have produced toxic effects.

In conclusion it may be said that at present there is no evidence that a suitable drug for the prophylaxis of the acute exacerbations of chronic bronchitis exists, but that if and when such evidence became available, as a result of a controlled trial, much disability might be prevented. In seeking such a drug much help would be obtained if more were known about the epidemiology, clinical types, bacteriology, and pathology of chronic bronchitis.

Summary

The acute exacerbations of "winter bronchitis" that occur in pneumoconiosis, emphysema, and "chronic bronchitis" are a serious problem.

A controlled clinical trial is described in which subjects with various forms of chronic bronchitis were studied in three centres during the winters of 1951–2 and 1952–3. In all, 83 subjects were included. Of these, 42 were given 0.5 g. of sulphadimidine three times a day during the winter months and 41 were given inert tablets in the same way.

A clinical assessment of the subjects was made at monthly intervals. Acute exacerbations of respiratory symptoms were classified as follows: (1) an acute "unmodified" attack of bronchitis; (2) a modified and less severe attack of bronchitis; (3) an attack of bronchial spasm; and (4) a head cold or "influenza."

No evidence was found that sulphonamide was effective in preventing the acute exacerbations of "winter bronchitis," but the trial was relatively insensitive.

We acknowledge our indebtedness to Dr. C. M. Fletcher (previously director of this unit), at whose instigation the trial was planned; to Dr. J. C. Gilson (director) for his advice and criticism; to our colleagues in the unit, especially Dr. I. Davies and Dr. M. C. S. Kennedy (M.R.C. Silicosis Treatment Centre, Stoke-on-Trent), who helped in the running of the trial; also to the general practitioners who referred patients. We are grateful to the Imperial Chemical (Pharmaceuticals) Ltd. for the supply of the tablets used, and to the Austin Motor-Car Company for facilities afforded.

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ACUTE APPENDICITIS IN CHILDHOOD

BY

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A review of a personal series of 118 cases of acute appendicitis treated in conjunction with the children's department of the Royal Victoria Infirmary has led to the appreciation of certain aspects of this disease which it is felt are not widely known. Any factor which may lead to the delay in admission of over 24 hours is worthy of close study. In 63 children peritonitis was already present, a figure which cannot be viewed with any complacency. Comment on some of the difficulties of diagnosis in this disease has been made recently (*British Medical Journal*, 1953).

Pathology

Study of the pathological lesion of the appendix in 101 cases in which this was recorded shows that an obstructive element occurred in 74. This obstruction was produced by faecaliths (32), kinking (20), and stricture (10). In 12 cases obstruction was reported, but the exact nature of this was not stated. One case of acute appendicitis was a complication of a carcinoid of the appendix which had caused some occlusion of the lumen. The high incidence of a degree of obstruction to the lumen of the appendix is to be noted, and is contrary to the experience of Bunton (1953). In many cases in which occlusion of the lumen was present it was noted that the infective process tended to stop at this point, only the distal portion of the appendix being involved in the disease process. It would therefore seem that the acute infection starts within the lumen of the appendix, and subsequently, either by tension or by spread into the walls, produces perforation. Perforation often occurs at the site where a faecalith is impacted; a faecalith causing this complication, and measuring 2 cm. in length, is shown in Fig. 1. A faecalith may be present in very young children, as was shown by one child aged 18 months.

FIG. 1.—Faecalith associated with acute appendicitis in a child of 9 years, producing obstruction of the lumen and perforation at the point of impaction.

Catarrhal or intramural appendicitis occurred in 26 cases. In this type of lesion the infection would appear to start in the wall, as commented upon by Bunton, and subsequently spread throughout the length of the appendix and sometimes on to the caecal wall. There is, however, in this series, insufficient evidence to suggest that it is possible to make a clinical differentiation of one type of appendicular lesion from another. The omentum was found limiting the spread of the infection in only 18 cases. Another variable factor in acute appendicitis is the infecting organism and its toxicity. While *Bact. coli* is undoubtedly present in most