CLINICAL TRIAL OF METHYL CYSTEINE HYDROCHLORIDE IN CHRONIC BRONCHITIS

BY

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Many factors are responsible for the development or aggravation of bronchitis, such as climate, atmospheric impurities, infection, and heavy cigarette smoking (Oswald *et al.*, 1953; Stuart-Harris *et al.*, 1953; Palmer, 1954). Thus injury to the respiratory tract by chemical substances or viruses and bacteria appears to be responsible for the pathological changes in the bronchi at the various stages of the disease. These consist of ulceration and patchy desquamation of the ciliated epithelium of the bronchi, often with replacement by stratified epithelium, acute or chronic inflammatory change in and around the bronchioles leading to structural damage, and hypersecretion of mucus due to overactivity of mucous glands and goblet cells (Florey *et al.*, 1932; Reid, 1954). Clinically these changes are characterized by intermittent periods of cough with mucoid sputum, especially after colds, or by persistent cough with mucoid sputum. Purulence of the sputum due to infection of the bronchi by *Streptococcus pneumoniae* and *Haemophilus influenzae* also occurs (May, 1953), but this is usually intermittent, and cough and mucoid sputum are the most constant abnormalities (Oswald, 1954). As the disease advances, impairment of ventilatory function due to bronchospasm and emphysema is added to the clinical picture, giving rise to wheezing and dyspnoea.

The view has been advanced that bacteria of the bronchi and bronchioles in cases of chronic bronchitis should be regarded as bacteria in an infected wound, and that when they are eliminated by suitable chemotherapy, as shown by elimination of the organism in the sputum, expectoration should cease (Stuart-Harris *et al.*, 1953). But excess mucoid sputum persists in spite of chemotherapy (May, 1953), and the question may well be asked why this hypothetical "wound" of the lower respiratory tract fails to heal (Stuart-Harris and Hanley, 1957). A substance which aided repair and regeneration of the damaged bronchial epithelium would clearly be useful in the treatment of chronic bronchitis, and its effect might be shown by a reduction or abolition of cough and mucoid sputum.

There is much experimental evidence that sulphur-containing amino-acids accelerate the healing of experimental wounds (Williamson *et al.*, 1951; Williamson and Fromm, 1952, 1953, 1954). Animal experiments with amino-acids containing ³⁵S-labelled sulphur have shown that the metabolism of cysteine and methionine is greater in wounded than in normal animals, and that wound tissue contains a high concentration of cysteine and methionine (Williamson and Fromm, 1954, 1955).

These workers conclude that sulphur-containing amino-acids, especially cysteine, when present in the diet, appear to be unique in their ability to accelerate the rate of healing of experimental wounds.

As long ago as 1933 preparations of cysteine were shown to stimulate the healing of cutaneous ulcers in man when applied topically (Brunsting and Simonsen, 1933; Riley, 1940); but cysteine is unstable and is readily oxidized to insoluble cystine, which is inactive. These disadvantages have now been overcome, and derivatives of cysteine have been prepared which can be applied topically or given by mouth, which are stable yet freely soluble in water, and which are cheap and non-toxic. One of these substances, methyl cysteine hydrochloride ("acdrile"), has been shown to increase the sulphur content of the lungs in animals when given by mouth or intravenously (Laurre, 1960, unpublished), and it has been shown to reduce the bronchial secretion provoked by an irritant aerosol in rabbits (La Barre, 1958, unpublished). It has been used, principally in France, in the treatment of bronchitis and sinusitis when the acute symptoms have subsided. It has been given to patients by mouth and also by aerosol, and good results have been reported, with much reduction in cough and sputum (Lallement and Meng, 1955; Weiller, 1955; Klaus, 1958).

In a trial in England conducted by 40 general practitioners in cases of chronic bronchitis treated with a 21-day course of methyl cysteine hydrochloride by mouth, 138 out of 208 (66%) showed a reduction in cough and sputum, and in 35 (18%) cough and sputum were eliminated (R. Vaughan Hudson, 1960, unpublished).

Because these results seemed encouraging it was thought that a controlled trial of this substance was warranted, and a trial by the double-blind method was planned and carried out with the help of general practitioners in Aberdeen and Preston.

Method

The trial started on November 1, 1960, and ended on March 31, 1961. Bottles containing active and inert tablets of identical appearance were used, and the drug and dummy tablets were allocated at random to the 93 patients in Aberdeen and 76 in Preston who took part initially in the trial. All were adult males; their ages ranged from 42 to 72 in Aberdeen and 35 to 65 in Preston, but most of them were in the older age-groups. They were expectorating mucoid sputum only, and during the period of the trial no other treatment was given. If the patient's condition deteriorated, and his doctor wished to give other treatment, he was withdrawn from the trial. All the patients were given a bottle containing enough tablets for a course of two tablets three times a day for a month, and they were instructed to swallow the tablets whole (not chew them) before meals. They were told that the tablets were a new treatment for their complaint which would not harm or upset them in any way and that if any other treatment was required during the month's trial period this would be given. The doctors were given 10 bottles, as it was thought they would each find this number of patients to treat, but not all did so. The order of issue of treatment and control bottles was randomized by means of random numbers and the key was not known to those taking part in the trial until its completion.

The response of the patients was recorded by the doctor by the severity of the following symptoms and signs at the beginning and the end of each week in the four-week trial period—dyspnoea, wheeze, cough, sputum, rales, and rhonchi. These symptoms and signs were recorded as absent or +, ++, or +++, according to severity. Obviously some assessments had to be made by the patients (for example, cough, sputum, and dyspnoea) others (for example, rales and rhonchi) were made by the doctor.

Result

Three of the patients in Aberdeen were lost from the trial, leaving 46 who were given the drug and 44 controls. Two of the Preston patients were lost from the trial, leaving 36 on the drug and 38 controls, so that when the Aberdeen and Preston patients are amalgamated there were 82 who were given the drug and 82 the "dummy" tablets.

The response of the patients to the drug and the dummy tablets was examined as follows. The severity ratings for each symptom and sign at the beginning and end of the trial were compared. Slight improvement was counted as a decrease of +, and considerable improvement as a decrease of ++ or +++ (there were very few of the latter). The deterioration categories were defined similarly from increases in pluses. For convenience of presentation and analysis the response of the patients was summarized by a "mean score." In calculating this, considerable and slight improvements were scored as +2 and +1 respectively, and considerable and slight deterioration by -2 and -1, while "no change" was scored zero. For example, for dyspnoea, those on methyl cysteine hydrochloride were classified as follows: 10 showed considerable improvement, 25 slight improvement, 45 no change, and 2 were slightly worse—therefore the mean score = $10 \times 2 + 25 \times 1 + 45 \times 0 - 2 \times 1 = 43/82 = 0.52$ (see Table I).

TABLE I.—Number of Aberdeen and Preston Patients by Response of Different Symptoms to Treatment

Response	Dyspnoea	Wheeze	Cough	Sputum	Rales	Sibilant Rhonchi	Sonorous Rhonchi
<i>Methyl Cysteine Hydrochloride</i>							
Considerable improvement ..	10	6	5	6	6	6	6
Slight improvement ..	25	38	47	42	16	30	21
No change ..	45	35	26	28	52	41	48
Slightly worse ..	2	3	3	6	8	5	7
Considerably worse ..	—	—	1	—	—	—	—
Total ..	82	82	82	82	82	82	82
Mean score ..	0.52	0.57	0.63	0.59	0.24	0.45	0.32
<i>Control</i>							
Considerable improvement ..	12	8	8	4	2	2	5
Slight improvement ..	26	29	28	24	10	29	19
No change ..	41	35	30	41	65	42	50
Slightly worse ..	3	9	15	13	4	8	8
Considerably worse ..	—	1	1	—	1	1	—
Total ..	82	82	82	82	82	82	82
Mean score ..	0.57	0.41	0.33	0.23	0.10	0.28	0.26

For all symptoms and signs except dyspnoea the mean scores were higher for the treated patients than for the controls (Table I). The largest differences were for cough and sputum: *t* tests of the differences in mean scores for these symptoms between patients treated with methyl cysteine hydrochloride and dummy tablets give values which are significant at the 5% level for both cough and sputum. (Cough *t* for 162 degrees of freedom was 2.36; $P < 1\%$. Sputum *t* for 162 degrees

of freedom was 3.00; $P < 5\%$.) Differences in response between the drug-treated and control patients for the other symptoms and signs are not near significance.

The information for cough and sputum is summarized in Table II, where it can be seen that for cough 63% of those on the drug were placed in the improvement categories compared with 44% receiving the control,

TABLE II.—Response of Aberdeen and Preston Patients. Cough and Sputum

Response	Cough				Sputum			
	Drug		Control		Drug		Control	
	No.	%	No.	%	No.	%	No.	%
Improvement ..	52	63	36	44	48	59	28	34
No change ..	26	32	30	37	28	34	41	50
Worse ..	4	5	16	19	6	7	13	16
	82	100	82	100	82	100	82	100

and for sputum 59% on the drug were placed in the improvement categories compared with 34% on the control tablets. Moreover, 19% receiving control tablets were placed in the worse category for cough compared with 5% on the drug, and for sputum 16% of the controls were worse compared with 7% on the drug. There was no evidence that the effect of treatment with the drug on cough and sputum varied with the age of the patient or the duration of the bronchitis, nor was there any fortuitous association between the division of patients and the doctor's standard of assessment which might cause the differentials found. Doctors did not have equal numbers of active and control bottles, and not all were able to use the 10 bottles.

Comment

There is some evidence from this trial that the responses of the patient to the drug and the dummy tablets differ, the only significant difference being the greater reduction in cough and sputum for patients on the drug. This effect could be due to a depressant action on the cough reflex, but there is no evidence that the drug has this pharmacological action, and the reduction in cough and sputum may well reflect a direct action of the drug on the bronchial mucosa. It is planned to study this possibility further; first, in animals, by observing the effect of the drug on the histology of the pulmonary tree after it has been injured by an irritant gas, and, secondly, in chronic bronchitis, by regular assessment of sputum cytology as an indirect index of bronchial healing, as basal and columnar cells are regularly seen in the sputum of patients with active bronchitis.

The difficulties in assessing the value of new substances in the treatment of chronic diseases that are subject to spontaneous variation in clinical state are well known. Large-scale trials have shown that about 35% of those suffering from such varied complaints as angina pectoris, seasickness, anxiety and tension, or the common cold, could be cured by giving a placebo tablet of plain glucose (Burn, 1960), and in this trial it is noteworthy that some improvement in the control group was recorded in respect of all symptoms and signs—for example, 44% receiving the control showed improvement in cough and 34% improvement in sputum. Reduction in cough and sputum was reported in 66% of cases when methyl cysteine hydrochloride was given in an uncontrolled trial (Vaughan Hudson, 1960, unpublished), but many

sources of error are possible in ascribing the benefit to the drug when it is administered in this way—such as spontaneous improvement, desire on the patient's part to please the doctor, and the difficulty in assessing subjective symptoms such as dyspnoea, cough, and sputum. Some of these disadvantages are overcome by using the double-blind method, but difficulties still exist, such as the accurate assessment of subjective symptoms. Measurement of sputum volume was rejected from this trial as being impracticable because none of the patients were in hospital and many were working. Moreover, failure on the part of the patient to use a container every time sputum was produced could lead to misleading inaccuracy.

Summary

A total of 164 male chronic bronchitics in Aberdeen and Preston expectorating mucoid sputum took part in a double-blind controlled trial using methyl cysteine hydrochloride ("acdrile") and a placebo.

The response was assessed by the patient's general practitioner by the severity of the following symptoms and signs at the beginning and at the end of each week in a four-week period—dyspnoea, wheeze, cough, sputum, rales, and rhonchi. Those having methyl cysteine hydrochloride showed a greater reduction in cough and sputum compared with the controls, this difference for both cough and sputum being significant at the 5% level. Differences in response between the drug and control patients for the other symptoms were not significant.

This trial was made possible by the co-operation and interest of the general practitioners in Aberdeen and Preston, to whom our thanks are due. Our thanks are also due to Mr. R. Vaughan Hudson, who suggested and sponsored this trial. We also thank Berk Pharmaceuticals Ltd., London, for a generous supply of active and dummy tablets.

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Soon after the publication of the Younghusband Report the Association of General and Family Caseworkers, the Association of Psychiatric Social Workers, and the Institute of Almoners set up a Standing Joint Committee to consider the implications of this report for these three professional groups. This committee has now prepared a report, *The Professional Social Worker in Local Authority Health and Welfare Services*, and has sent a copy to all local authority health and welfare departments in England, Wales, and Northern Ireland. Copies are available (1s., post free) from 42 Bedford Square, London W.C.1.

EFFECT OF ORAL ALPHA-CHYMOTRYPSIN ON SPUTUM VISCOSITY

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The use of crystallized trypsin when applied topically for the digestion of necrotic debris and liquefaction of thick viscid exudates has been reported on numerous occasions. After the good results obtained in thinning fluid by the intrapleural use of trypsin, the enzyme was used as an aerosol for the liquefaction of viscid bronchial secretions. Several papers (Roettig *et al.*, 1952; Limber *et al.*, 1952; Peck and Levin, 1952; Unger and Unger, 1953a, 1953b; Yates and Goodrich, 1953; Wilson and Stevenson, 1957) have been published showing that trypsin as an aerosol may decrease the viscosity of sputum. More recently, crystallized alpha-chymotrypsin, when administered intramuscularly, has been reported to be effective in respiratory conditions such as bronchial asthma, bronchitis, and sinusitis (Parsons, 1958; Teitel *et al.*, 1960; Taub, 1960).

Intramuscular injections are not always convenient and the availability of a tablet containing the proteolytic enzyme, specially formulated for oral administration and intestinal absorption, has many advantages over intramuscular administration. Several papers have been published on the effect of oral alpha-chymotrypsin ("chymoral") in the reduction of inflammation and oedema, and as a mucolytic agent in upper respiratory conditions (Teitel *et al.*, 1960; Taub, 1960; Billow, 1960). The proteolytic enzyme does not digest living tissue since both serum and viable cells contain specific enzyme inhibitors.

A common feature of chronic bronchitis is the distress caused by the expectoration of tenacious sputum, and an easily administered substance capable of producing sputum liquefaction would be a welcome addition to the drugs and antibiotics already in regular use.

The only available literature (Taub, 1960; Teitel *et al.*, 1960) reporting the mucolytic action of oral alpha-chymotrypsin makes no mention of a controlled investigation, and therefore a small-scale double-blind trial was carried out to assess the mucolytic activity of this compound. As chronic bronchitics are renowned to be influenced for good, at least temporarily, by any new preparation, it was decided to estimate progress by a measurement of the stickiness of the sputum, thus avoiding any subjective statements from the patient. It seemed a valid assumption that the stickiness of sputum could be expressed in terms of a viscosity measurement.

Materials and Method

Patients known to be suffering from chronic bronchitis were picked at random, without regard to age or sex, from the clinic records and divided into two approximately equal groups. A four-weeks supply of two