would be surprising if it were not sometimes associated with acute glomerulonephritis. The association would not necessarily be very frequent. Acute glomerulonephritis has a different age incidence, and in this country it almost always follows infection with a single type of streptococcus (type 12). Erythema multiforme may well be a reaction to infection with many different types of streptococci, as rheumatic fever seems to be. Streptococci of group A were isolated from the throat of one of our patients and another had a raised A.S.O. titre as evidence of preceding streptococcal infection. On the other hand, none of our cases followed the typical course of acute glomerulonephritis; three were normotensive or hypotensive throughout and none had hypertension early in the illness; no patient had a classical onset with headache, generalized oedema, frank haematuria, and oliguria. These observations apply also to the previously described patients referred to in the introduction. It has been said that acute glomerulonephritis often follows an atypical course in older adults, but this may simply imply that there are several different renal diseases referred to by this title at present (Hall *et al.*, 1961).

The histological changes in Case 4 (Fig. 1) are similar to those in the progressive type of acute glomerulonephritis (Ellis, 1942), but are not specific to this condition; they have been described in lupus nephritis (Muehrcke *et al.*, 1957) and in the Schönlein-Henoch syndrome (Heptinstall, 1960). The changes in the glomeruli in Case 5 (Fig. 2) are non-specific.

There were some clinical similarities to Schönlein-Henoch syndrome; two of our patients complained of abdominal pain, and one had persistent occult bleeding from the bowel and transient arthralgia, but the rash in all our patients was unmistakably that of erythema multiforme.

Four of our cases were treated with corticosteroids; in three the skin rash resolved within a few days of the beginning of therapy and in one it recurred during temporary reduction in steroid dosage. Improvement in the renal condition, when it occurred, was less dramatic and slower; it may well have been coincidental.

We conclude that an inflammatory renal lesion with some similarities to acute glomerulonephritis accompanies erythema multiforme in a proportion of cases; that it may lead to fatal uraemia during the acute illness; and that recurrent episodes may produce chronic nephritis. Further study—clinical, bacteriological, and histological—will be required to determine whether the lesion is identical with acute glomerulonephritis after streptococcal infection. The results may well be important in determining whether long-term prophylactic penicillin is indicated in patients with recurrent attacks.

Summary

Five cases are described in which erythema multiforme was accompanied by the onset of a form of nephritis manifested by albuminuria, microscopical haematuria, cylindruria, and uraemia. Hypertension and oliguria were not features of the acute attack.

Two patients died during the acute attack, one progressed to subacute nephritis with chronic uraemia, one developed a nephrotic syndrome and subsequently recovered, and in one the renal abnormalities subsided with the rash.

The histological features in two cases are described.

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REFERENCES

- Ashby, D. W., and Lazar, T. (1951). *Lancet*, **1**, 1091.
Commission on Acute Respiratory Diseases (1946). *Arch. intern. Med.*, **78**, 687.
Costello, M. J. (1947). *J. invest. Derm.*, **8**, 127.
Dresner, E. (1949). *Lancet*, **2**, 1036.
Elliott, W., Hill, M., Kerr, D. N. S., and Ashcroft, R. (1960). *Postgrad. med. J.*, **36**, 230.
Ellis, A. (1942). *Lancet*, **1**, 1.
Finland, M., Jolliffe, L. S., and Parker, F., jun. (1948). *Amer. J. Med.*, **4**, 473.
Foerster, D. W., and Scott, L. V. (1958). *New Engl. J. Med.*, **259**, 473.
Gairdner, D. (1948). *Quart. J. Med.*, **17**, 95.
Hall, M., Kerr, D., Smart, G., Ashcroft, R., Elliott, W., and Swinney, J. (1961). *Brit. J. Urol.*, **33**, 41.
Hebra, F. (1866). *On Diseases of Skin*, vol. 1, p. 285. New Sydenham Society, London.
Heptinstall, R. H. (1960). In C. V. Harrison's *Recent Advances in Pathology*, 7th ed. Churchill, London.
Lever, W. F. (1944). *Arch. Derm. Syph. (Chicago)*, **49**, 47.
Levitt, L. M., and Burbank, B. (1953). *New Engl. J. Med.*, **248**, 530.
Muehrcke, R. C., Kark, R. M., Pirani, C. L., and Pollak, V. E. (1957). *Medicine (Baltimore)*, **36**, 1.
Osler, W. (1888). *N.Y. med. J.*, **48**, 675.
— (1900). *Brit. J. Derm.*, **12**, 227.
— (1914). *Brit. med. J.*, **1**, 517.
Robinson, H. M., jun., and McCrumb, F. R., jun. (1950). *Arch. Derm. Syph. (Chicago)*, **61**, 539.
Ustvedt, H. J. (1948). *Acta med. scand.*, **131**, 32.
Welsh, A. L. (1948). *J. invest. Derm.*, **10**, 401.

CHRONIC BRONCHITIS

CONTROLLED TRIAL OF ISOPRENALINE AND CHYMOTRYPSIN BY INHALATION

BY

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The aim of the trial was twofold; firstly, to assess the ability of finely divided chymotrypsin with isoprenaline by inhalation to relieve airways obstruction; and, secondly, to assess its ability to liquefy sputum and thus increase the quantity expectorated when presented alternatively as a fine dry powder or suspended in an inert propellant.

The patients were admitted to hospital for the duration of the trial. The clinical material consisted of 35 male patients aged 30 to 65 years. All the patients had had winter cough and sputum for at least three years, and had been off work at least once, during that period, with bronchitis.

Method

Every patient received each of the two methods of presentation of the chymotrypsin and isoprenaline for a period of five days. Each of these periods was preceded by three days "control" during which no treatment was given. Whether a patient should start with the powder or with the suspension was determined from a list based on random numbers. None of the patients had antibiotic therapy of any kind.

Analysis of the primary objective was carried out sequentially according to one of the designs described by Armitage (1957). After 31 men had been admitted, the sequential plan indicated that the trial should stop. At this stage a further four men were already receiving treatment. The trial was then continued until these men had completed their course of treatment, no new patients being admitted.

During the trial three men had to be withdrawn from treatment (as explained later). The subsequent analysis is based on the 32 men who completed the trial.

The inert propellant suspension was presented in a pressurized ampoule with a metering valve at the outlet permitting a dose of 0.05 mg. of isoprenaline sulphate and 1 mg. of chymotrypsin to be dispensed at each operation. The dosage schedule was 0.1 mg. of isoprenaline with 2 mg. of chymotrypsin administered before breakfast, at noon, and before retiring.

The medicament powder mixture was presented in a cartridge containing 0.1 mg. of isoprenaline sulphate with 0.1 Anson unit of chymotrypsin. The powder was expelled from the cartridge by the use of a rubber bulb and a trip-valve mechanism actuated by the negative pressure of inspiration. One cartridge was used before breakfast, one at noon, and one before retiring. All specimens of sputum were collected in dry waxed containers. The weight of a 24-hour collection was recorded daily and expressed as a percentage of the average in the preceding control period.

A "Garthur expirograph" with a 9.5 L bell and a circumferential speed of 1 cm. a second was used to estimate the forced expiratory volume in the first second (F.E.V.₁). Six estimations were carried out at the end of each control and each therapy period, and the result was expressed as a mean of six readings. In the therapy periods, at least three hours were allowed to elapse between the last dose of the medicament and the estimation of the F.E.V.

The main criterion used in the sequential analysis of the trial was the percentage improvement in the F.E.V.₁ after taking chymotrypsin and isoprenaline for five days as compared with that in the preceding control period. For each patient the decision "better with powder" (or suspension) was made if the percentage improvement was more than 10% greater for one than the other—for example, a patient who improves his F.E.V.₁ by 20% with the suspension would only be regarded as "better with powder" if his improvement with it was at least 30%. This order of difference was decided on clinical grounds; smaller differences were allocated to a group "same on both treatments."

As already stated, the F.E.V.₁ was measured before the chymotrypsin-isoprenaline treatment was given with either the powder or suspension. Each of these readings gave a baseline for comparison with readings taken at one minute, three minutes, three hours, and six hours after the corresponding treatment was given. Improvements in the F.E.V.₁ at these times were calculated as percentages of the relevant baseline figure.

Results

The particular sequential chart used had the following properties:

If the two treatments were equally effective in improving the F.E.V. after five days' therapy there was only a 1 in 20 chance of wrongly concluding that one of them was better.

There should not be more than 30 patients in the trial who were "better"—that is, had a 10% greater improvement—on one form of administration than the other. While this does not set an exact limit on the total number of patients in the trial, it does impose some restriction on the number which, in any case, seemed reasonable in terms of the available hospital clinical resources.

If one form of administration was so good that 85% of patients with a preference were "better" on that treatment, there would only be a 1 in 20 chance of not recognizing that it was better.

With the criterion of improvement used, 12 out of 32 patients were the same on both treatments. By the time the boundary of the Chart was reached, 16 men had been better on one form of administration than the other; these were equally divided into eight better with the powder and eight better with the suspension. The conclusion from the sequential trial is that there was no significant difference between the two forms of administration. The results after five days on each treatment, in all 32 men, are shown in Table I.

Chart showing results of sequential trial.

To answer the question whether either form of administration improved the F.E.V.₁, comparisons were made with the corresponding values for the control periods in all 32. For the suspension, the average improvement after five days' treatment was +2.6% with a standard error of 3.5%. For the powder, the results after five days' treatment were slightly worse than before treatment, the average improvement being -0.9% with a standard error of 3.3%. In neither case is the result significantly different from zero. In other words, we have no evidence to suggest that chymotrypsin and isoprenaline sulphate mixture produces a long-term increase in the F.E.V.₁ by whichever method it is administered.

Sputum weights were on the average decreased during treatment with isoprenaline and chymotrypsin, although not significantly so. With the suspension, results were 6.6% lower than control (standard error 4.3%) and with the powder, 2.1% lower than the control (standard error 6.6%). The difference between these results, 4.5%, had a within-patient standard error of 7.3%, and this was not significant.

The immediate effect of treatment on the F.E.V.₁ is summarized in Table II. At one minute both methods of administration improve the F.E.V.₁ by 17.4% and 14.7% respectively; these two figures do not differ significantly. At three minutes the improvements are slightly greater, at 18.5% and 18.1%. Thus chymotrypsin and isoprenaline initially increase the F.E.V.₁

TABLE I.—Results in 32 Men After Five Days of Treatment

	Suspension	Powder
Average F.E.V. ₁ before treatment ..	1.08 litres	1.13 litres
Average percentage improvement ..	+2.6%	-0.9%
Standard error	3.5%	3.3%
Average sputum weight before treatment ..	37.1 g.	37.7 g.
Average percentage increase ..	-6.6%	-2.1%
Standard error	4.3%	6.6%

to a significant and marked extent, but the mode of administration is immaterial. By three hours after treatment, however, results are on the average just the same as before treatment; by six hours after treatment the F.E.V.₁ is actually lower in the 32 men than before treatment, but not by a significant amount.

In those patients who had never used chymotrypsin before the trial there was no evidence of any immediate toxic reactions. Four patients, however, had to discontinue therapy within four weeks and one within 12 weeks of starting; in the four cases there was a marked increase in the breathlessness and wheezing closely associated with the inhalation of the medicament.

TABLE II.—F.E.V.₁ After Treatment

	Suspension	Powder
Average F.E.V. ₁ before treatment ..	1.12 litres	1.15 litres
.. percentage increase at 1 minute ..	17.4 ± 3.6	14.7 ± 2.5
.. 3 minutes ..	18.5 ± 3.8	18.1 ± 2.5
.. 3 hours ..	0.1 ± 3.0	-0.1 ± 1.9
.. 6 ..	-0.8 ± 3.0	-4.7 ± 2.5

The remaining patient developed a very hoarse voice accompanied by a very dry irritating cough which made sleep almost impossible. One patient had to be taken out of the trial while in hospital. He became acutely breathless on starting the therapy, and his forced vital capacity (F.V.C.) decreased by half. A further attempt at inhalation in this individual, using half the previous dose of chymotrypsin without isoprenaline sulphate, produced an immediate fall in the F.V.C., but not to such an alarming extent. On further questioning it became apparent that this patient had used chymotrypsin with isoprenaline for a period of six weeks, some months before entering the trial. A further patient had to be removed from the trial as he completely failed to co-operate, and a third because of an acute exacerbation of his bronchitis in the control period.

Discussion

For therapy to be satisfactory in chronic disease it must be effective, free from toxicity, not requiring to be used frequently, and any apparatus connected with it must be reliable and easy to use. We did not find any evidence of improvement in the breathing in the long-term experiment (Table I). In the short-term experiment there was an improvement of statistical significance in the F.E.V.₁ at three minutes, in the case of both the powder and the suspension. However, it was of a transient nature in both instances, and had disappeared by three hours, while at six hours the F.E.V.₁ was worse than it had been before therapy. This rather suggests a rebound phenomenon. It has been stated by other authors that the administration of isoprenaline with an effective size of 1 to 5 μ , in a dosage of 0.15 mg., will produce a significant increase in the F.E.V.₁ for one to three hours (Robinson *et al.*, 1958b), but this has not been our experience at the interval of three hours or longer. It is reasonable to suppose that if the sputum underwent liquefaction it would be coughed up more easily, and that the viscosity would be reduced and the quantity expectorated increased. Indeed, this is what has been found by Robinson *et al.* (1958a). These authors reported that in 39% of their cases the sputum was increased in quantity, and that there was evidence of reduced viscosity. We did not carry out viscosity estimations, but our results show a decrease in the average daily quantity of sputum expectorated.

In regard to the question of toxicity, we had to discontinue treatment in the long-term follow-up in five cases for what appeared to be allergic reactions. It has been recognized for some time that there is always a possibility of allergic reactions to both chymotrypsin and trypsin, although it has always been thought to be less likely to occur with the former. Cases have been reported by Maclaren and Aladjem (1957), Fullgrabe (1957), Lichtman (1957), and Liebowitz and Ritter (1960).

One of our cases developed a very severe non-specific laryngitis and tracheitis. Similar cases of hoarseness have been reported by Robinson *et al.* (1958a), although these authors make the point that the three patients in question were on a "high enzyme dosage." On the basis of subjective performance and ease of use, the majority of the patients preferred the suspension with the pressurized ampoule. Therefore it would appear to us that the above therapy in the present dosage does produce short-term improvement in ventilatory capacity but not more than might be expected by isoprenaline alone. There is nothing in the present evidence to suggest that chymotrypsin in the above dosage will facilitate the expectoration of sputum. There is evidence that chymotrypsin is apt to produce both allergic reactions and also non-specific laryngotracheitis.

Summary

Thirty-five male patients were admitted to a chemotherapy trial using chymotrypsin and isoprenaline sulphate presented as a fine dry powder or suspended in an inert propellant.

The indices of assessment were sputum weight and F.E.V.₁.

Sequential analysis indicated no therapeutic difference between the powder and the suspension.

There was no evidence that the weight of the sputum in the therapy period was different from that in the control period.

The F.E.V.₁ was significantly increased at three minutes after both therapies. At six hours there was a reduction of the F.E.V.₁ below that of the control period which was not statistically significant.

Five patients had to discontinue therapy subsequently on account of allergic reactions. One patient discontinued therapy on account of severe non-specific laryngotracheitis.

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REFERENCES

- Armitage, P. (1957). *Biometrika*, **44**, 9.
- Fullgrabe, E. A. (1957). *Ann. N.Y. Acad. Sci.*, **68**, 192.
- Lichtman, A. L. (1957). *Ibid.*, **68**, 196.
- Liebowitz, D., and Ritter, H. (1960). *J. Amer. med. Ass.*, **172**, 159.
- Maclaren, W. R., and Aladjem, F. (1957). *J. Allergy*, **28**, 89.
- Robinson, W., Woolley, P. B., and Altounyan, R. E. C. (1958a). *Lancet*, **2**, 821.
- (1958b). *Ibid.*, **2**, 819.

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