CLINICAL TRIAL OF PATULIN IN THE COMMON COLD

REPORT OF THE PATULIN CLINICAL TRIALS COMMITTEE, MEDICAL RESEARCH COUNCIL.

In November, 1943, a report was published of the chemical properties and clinical effects of a metabolic product of Penicillium patulum Bialler, called patulin. It was shown in a clinical trial on the common cold in which 30 patients treated with patulin were compared with 85 controls, the advantage to the treated patients was such that it would usually be regarded as statistically significant. The results obtained were considered encouraging, but no definite claims were made.

The discovery of an effective treatment for the common cold being a matter of such great practical importance; it was clearly desirable that this suggestion be investigated as soon as possible. This was rendered the more necessary because, shortly after the publication of the first report, a second and independent group of workers stated that they had been unable to demonstrate any advantage of patulin treatment. The Medical Research Council, therefore, undertook an extensive reinvestigation of the claims regarding patulin, and the results are here reported.

The ease with which the effects of a therapeutic agent on a particular illness can be determined is primarily dependent upon the precision with which that condition can be defined. Such definition of the common cold presents considerable difficulties. First, there is no reason to believe that the condition is a single disease or even a disease entity. Second, the duration of colds is not constant but varies, not only between different epidemics but also between different patients in the same epidemic, making the assessment of treatment difficult. Third, the signs and symptoms of the common cold are too variable to serve as criteria of its presence or progress; a cold manifests itself mainly by subjective symptoms and, in consequence, diagnosis rests mainly upon the statements of the untrained patient.

The first difficulty of the investigation must test large numbers of patients, must take place at several widely separated places, and must continue long enough to exclude the possibility that a single brief epidemic is being studied. To meet these difficulties the investigation was supplemented by control conditions, making the assessment of treatment difficult.

The present report of the trial of patulin in a large number of patients, together with other investigations, are a step forward in the elucidation of the pathology of the common cold.

Investigation

Therapeutic trials have been carried out in 11 factories with a total population of approximately 90,000 and in three units of the Post Office with a population of approximately 15,000. These were widely distributed. In these trials the test solutions were instilled into the nostrils; but 2 additional trials were carried out, using a spray technique of administration, in 2 public schools with a population of approximately 500 to 1600. A pilot trial was carried out in a London factory in December, 1943, and early January, 1944. The main trials ran from Jan. 18 to April 11, 1944; although the trial in any particular unit did not continue throughout this period, trials in several were always in progress at any one time.

Selection of cases.—The trial at each place was supervised and organized locally by the medical officer in charge. All personnel, whether w.c. or non-w.c. patients, by means of notices and posters, broadcasts in the factory radio, meetings with works committees, and similar means, the existence of the test was brought to the notice of employees, and all with colds were asked to come to the medical department for treatment. Care was taken to ensure that volunteers were aware of the experimental nature of the trial and that they should honestly state whether or not the treatment had been effective. It was made clear that only cases of common cold were to be included in the trial and that cases of hay fever, "chicken cold," or chronic catarrh or bronchitis were excluded. If on any morning more volunteers attended than could be dealt with, then those with colds of shorter duration were asked to remain. Rarely had suitable cases been refused, so that the opening day or two of the trial when there was usually a rush of volunteers. Cases were accepted on the basis of the patient's description of the symptoms; clinical examinations were only made when there was reason to exclude some other condition.

Recording.—Patients were seen by the MO before receiving treatment from the factory nurse or sick-bay attendant. The MO remained ignorant which of the test solutions the patient received and neither the MO nor the nurse knew which w.c. or non-w.c. patients.

At the first attendance the MO filled in the record card and satisfied himself that the patient was in fact suffering from the common cold and not from some other condition. If the case was one of hay fever or "chicken cold" he then detached the counterfoil and gave it to the patient who took it to the nurse in an adjoining room. The nurse gave out the test solutions in strict rotation, each patient receiving his own bottle of solution from which all treatments and got cases of hay fever, "chicken cold," or chronic catarrh were excluded.

The distinguishing letter of the particular solution given was ringed by the nurse on the counterfoil.
on the patient's counterfoil. The record sheet and counterfoil were filed separately by the MO and nurse respectively.

The patient returned to report progress to the MO at 24 hours, 48 hours, and once a week. At these attendances the patient was given, under anaesthesia, the three solutions: "cured," "improved," "unchanged," "worse," or "recurred," whichever accorded with the patient's statement of his condition.

**TREATMENT**

At the first attendance the technique of treatment was demonstrated to each patient by the nurse or attendant, who also gave the patient a leaflet of instruction. In all cases treatment was started, and dressing was changed, within 24 hours. In most cases the patient was given 3 treatments by the nurse in the surgery at 4-hourly intervals, on each of 2 consecutive days. He was instructed to carry out the treatment at the same intervals, and in exactly the same way at home, getting a friend or relative to help him. The number of treatments given at home naturally varied so that the total number received in the 48 hours ranged from 8 to 12. All treatments, whether at work or at home, were given from the same bottle of solution, which was in the patient's own charge.

In the published reports of the preliminary clinical trials of patulin, the solution was administered by spraying or instilling into the nostrils of those whose noses were infected. Not all these methods seemed suitable for large-scale trials. Spraying requires special apparatus, impossible to supply in quantity during war-time, and in the hands of inexpert persons it may be inefficient. Sniffing of solutions up the nose is potentially dangerous in that it may spread infection to adjoining sinuses. We had to find a simple, efficient and safe method which did not require special apparatus.

On the advice of Mr. T. E. Cawthorne, FRCS, we adopted the technique introduced by Proetz and called the "head-low position." The patient lies supine on a couch with the head hanging freely over the end. He breathes through his mouth and a teaspoonful of solution is run slowly along the nose (a teaspoonful is used because of the difficulty of supplying pipettes for patients to take home). The patient remains recumbent for about a minute, then sits up slowly and refrains from blowing his nose for an hour or so. Experiments to test the comparative efficiency of this method were carried out by Mr. Cawthorne. A solution of cocaine was introduced into the nostrils of a series of volunteers by four different methods—dropping, spraying, sniffing, and instilling. Cocaine is, however, potentially toxic (a teaspoonful of the olfactory nerves was tested by olfactory substances, that of the nasal mucous membrane by ammonia. Instillation in the head-low position alone produced complete anaesthesia and thus appeared to be easily the most efficient way of bringing fluid in contact with the whole nasal mucosa. This technique was therefore adopted for all trials save those in the two public schools. There sprays were available with skilled personnel to use them. In these two trials the opportunity was taken to reproduce exactly the conditions of the clinical trials previously reported.

**DISPENSING**

Previous experience had convinced us that, in a trial of this nature, it is of great importance that both the medical personnel and the patients be prevented from guessing which of the two treatments is genuine and which spurious. It had further been learnt that two solutions are not sufficient to prevent this. In this present trial, therefore, four solutions were used, two of which (R and T) contained patulin and two (Q and S) were simply solutions of the buffer salts used in dispensing patulin.

An important consideration was that patulin solutions should be reasonably fresh. In the pilot trial, which took place in 1941, the solutions were made up and dispatched to the factory that afternoon and given out next day. The strength of the patulin was 1/10,000 in a phosphate buffer as used by previous investigators. The control was a solution of phosphate buffer of the same pH and concentration, and was dispensed in the same way. Samples were collected when the daily delivery of new solutions was made. Solutions were therefore not more than 24 hours old at the time of the last treatment in the 48 hours. This method of dispensing, however, was clearly impracticable for the main trials in units widely distributed over the country. For these both patulin and buffer were dispensed in the solid state.

Cases of eight ampoules were prepared. Ampoules R, S and T contained 0·2 g of patulin; ampoules Q and T were 1·0 g of citrate buffer. Ampoules Q and S contained 0·2 g of citrate buffer, and ampoules Q and S were merely solutions made up by dissolving the contents of each pair of ampoules (e.g., RQ and T3 in one litre of cold distilled water. The strength of these patulin solutions was thus 1/5000 in a 0-1% solution of buffer; the control solution was 0-1% buffer solution. The bottles were packed in 10 oz. bottles, each of which carried directions for use and the appropriate distinguishing letter on a tie-on label of a distinctive colour. On handing one of these bottles to the patient the coloured tie-on label was torn off and put in a box. Thus, by counting the labels in the box at any one time, the nurse dispensing treatment could check whether the four solutions, Q, R, S, and T, were in fact being given out in strict rotation. Any unused bottles remaining at the end of the day were discarded.

The solutions were consequently not more than 60 hours old at the time of the last treatment in the 48-hour period. The solution was not used by the patient as dispensed: he was instructed to add to each dose an equal quantity of warm water immediately before using. The strengths of the solutions as actually distilled were therefore: patulin, 1/10,000 in a 0-05% solution of buffer; control, 0-05% buffer solution.

The buffer was devised to give a pH of 6-0 in distilled water. It consisted of approximately 15-5 parts of sodium citrate and 10 parts of citric acid (the exact proportions must be determined by trial owing to slight variations in pH of sodium citrate) thoroughly ground together and subsequently passed through a fine sieve. In the main trials and the latter part of the pilot trial, citrate buffer was used in preference to phosphate buffer because it was found that the latter could not easily be worked on the machines for dispensing powders into ampoules. Bacteriostatic, colormetric and absorption-spectrophotograph tests showed that citrate buffer preserved the stability of patulin in the dilution used for, at least, the time required.

Further, patulin has been recovered quantitatively from such solutions.

**Results**

In the various units 1449 patients were treated, but 101 record forms were rejected for reasons such as doubtful diagnosis, refusal to carry out treatment and absence from work. Thus 1348 were available for analysis of and these 668 were treated with patulin and 680 with the control solution. The results from each unit have been analysed separately so as to reveal any differences due to time and place. As, however, no significant differences were found, only the combined results for all units are given here. Table I shows the percentage of cases cured and cured and improved at the 24 hours, the 48 hours and 1 week recordings. Table II shows the percentage of cases cured and improved at the 48 hours and 1 week recordings for patients who had colds of less than 3 days' duration before treatment was given, and second for those whose colds were of 3 days' or more duration.

3. In practice it was found that the pH of different samples of the buffer varied between 6±5 to 6±7 and that even after storage of samples having a pH of 6±0. This variation however does not affect the validity of the results since it has been shown that patulin is sufficiently stable in a citrate buffer of pH 6±0.
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Similarly, in the two public-school units where the spray technique was used no significant differences in effects were found between the control and the patulin solution. In these two trials, however, only 49 cases were available for analysis.

Summary

In a large clinical trial of patulin in widely distributed areas in Great Britain and lasting from the beginning of December, 1943, to the middle of April, 1944, no evidence was found that patulin is effective in the treatment of the common cold.

The Patulin Clinical Trials Committee had the following membership: Prof. H. P. Hinsworth (chairman), Dr. A. J. Andrewes, Dr. C. H. Ingrams, Dr. T. E. Catwhorne, Prof. M. Greenwood, Drs. R. B. Merriman, Dr. H. J. Parish, Prof. H. Raisbeck, Drs. W. L. Scott and Dr. P. D'Arcy Hart (secretary). Dr. Joan Faulkner was appointed assistant-secretary and supervised the actual trials.

The committee is indebted to Dr. W. J. Martin for help in the statistical analysis of the results, to the Therapeutic Research Corporation for providing and dispensing the agents to be tested, and to the management, medical staffs and workers in the several factories where trials were carried out for their ready cooperation and assistance.

Trials were carried out in the following establishments and schools:

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<td>Dr. R. P. Warren</td>
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A STUDY OF TREATMENT: CORRIGENDUM.—The penultimate sentence in Major A. M. Meeloo's article in our issue of Sept. 2 (p. 321) should read: “Such hatred can be excoriated only by allowing each man freedom to criticise and by creating in him a sense of responsibility for his views.” The word excoriated was wrongly given.