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* Bainier, called patulin.[1] It was shown in a clinical trial on the common cold in naval personnel that when 95 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 reinvestigated 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 effect of patulin on the common cold.[2] 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 popularly called a "cold" is always, or even usually, due to the same agent either in sporadic cases or in different epidemics. If "colds" can be caused by a diversity of agents, then great differences in the effect of a particular remedy are to be expected between different epidemics and between individual cases. 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 objective signs associated with 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.

To meet the first difficulty 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 the second difficulty the investigation must, in addition to fulfilling the above conditions, include a satisfactory series of control cases. This can only be done by ensuring that alternate cases at each centre are given a spurious treatment which, to the recipient, is indistinguishable from the genuine treatment. To meet the third difficulty the symptoms of the common cold must be defined and their frequency analysed; and from this analysis a series of simple questions must be framed, the answers to which will establish with reasonable certainty whether the patient is suffering from the illness commonly accepted as a "cold." In this latter connexion we had the advantage of studying an unpublished report by Dr. M. L. Rosenheim, Dr. H. A. Burt and Miss Joan Wadge, FRCS, of a previous investigation into a treatment for the common cold. Besides establishing the unrelability of objective signs, both as diagnostic criteria and guides to the progress of the case, their report analysed the frequency of different symptoms. On the basis of their findings the questions on our record card (see figure) were constructed.

1. Patulin in the Common Cold: Introduction by H. Raistrick; Biochemistry and Chemistry, by J. H. Birkinshaw, S. E. Michael, A. Bracken, and H. Raistrick; Preliminary Trial in the Common Cold, by W. E. Gye; Biological Properties and Extended Trial in the Common Cold, by W. A. Hopkins; Statistical Note by M. Greenwood, *Lancet*, 1943, ii, 625.
2. C. H. Stuart-Harris, A. E. Francis, J. M. Stansfeld, *Ibid*, 1943, ii, 684.

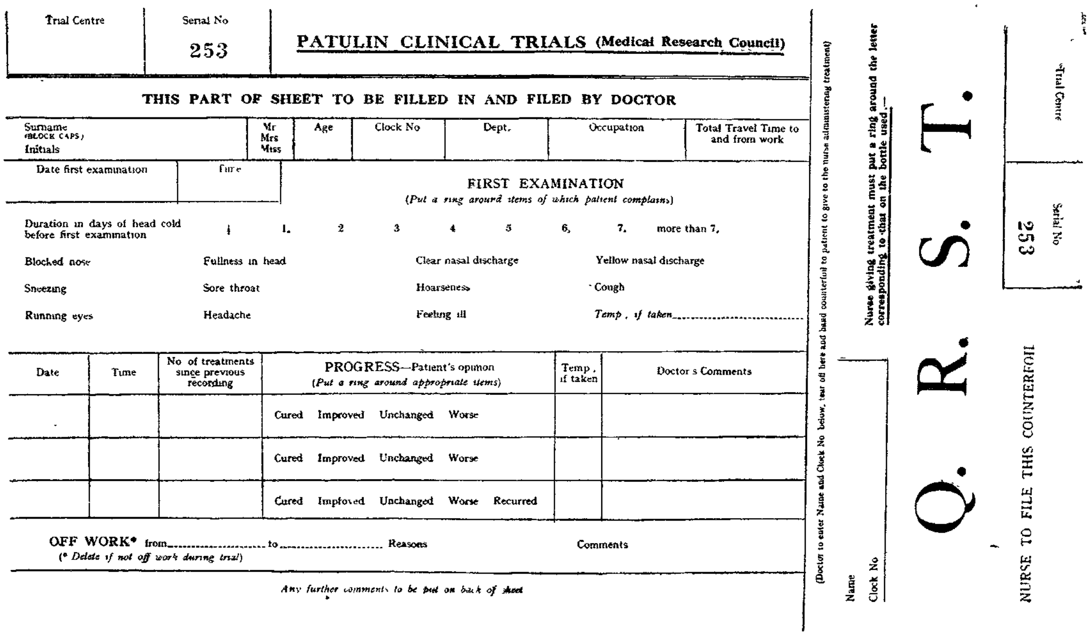
Investigation

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 800 to 1000. 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 organised locally by the medical officer in charge. All persons tested were volunteers. By means of notices and posters, broadcasts in the factory radio, meeting 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 colds were required and not cases of hay-fever, "chronic catarrh" or chronic bronchitis. 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 to be refused save on 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 described 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 contained patulin.

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 condition such as hay-fever or "chronic catarrh." 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 were given. The distinguishing letter of the particular solution given was ringed by the nurse


Trial Centre | Serial No 253 | PATULIN CLINICAL TRIALS (Medical Research Council)

THIS PART OF SHEET TO BE FILLED IN AND FILED BY DOCTOR

Surname (BLOCK CAPS) Initials	Mr Mrs Miss	Age	Clock No	Dept.	Occupation	Total Travel Time to and from work

Date first examination | Time

FIRST EXAMINATION
(*Put a ring around items of which patient complains*)

Duration in days of head cold before first examination ½ 1. 2 3 4 5 6, 7. more than 7,

Blocked nose	Fullness in head	Clear nasal discharge	Yellow nasal discharge
Sneezing	Sore throat	Hoarseness	Cough
Running eyes	Headache	Feeling ill	*Temp., if taken*........

Date	Time	No of treatments since previous recording	PROGRESS—Patient's opinion (*Put a ring around appropriate items*)	Temp., if taken	Doctor's Comments
			Cured Improved Unchanged Worse		
			Cured Improved Unchanged Worse		
			Cured Improved Unchanged Worse Recurred		

OFF WORK* from........ to........ Reasons Comments
(* *Delete if not off work during trial*)

Any further comments to be put on back of sheet

(Doctor to enter Name and Clock No below, tear off here and hand counterfoil to patient to give to the nurse administering treatment)
Name
Clock No
Nurse giving treatment must put a ring around the letter corresponding to that on the bottle used—
Q. R. S. T.
Trial Centre
Serial No 253
NURSE TO FILE THIS 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 one week. At these attendances the MO ringed on the record card one of the words "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 given during 48 hours and then stopped. 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 in a few cases by sniffing up the nose. Neither of 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 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 adapted 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 into each nostril (a teaspoon was 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 instillation in the head-low position. Then sensitivity of the olfactory nerves was tested by odiferous substances, that of the nasal mucous membrane by ammonia. Instillation in the head-low position alone produced complete anæsthesia 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 London, the solutions were made up, 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 strength. Any solution remaining over was collected when the daily delivery of new solutions was made. Solutions were therefore not more than 72 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_1 and T_1 contained 0·2 g. of patulin: ampoules R_2 and T_2 1·0 g. of citrate buffer. Ampoules Q_1 and S_1 contained 0·2 g. of citrate buffer, and ampoules Q_2 and S_2 0·8 g. of the same buffer. These were made into solution daily by dissolving the contents of each pair of ampoules (e.g., T_1 and T_2) 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. These solutions were put up 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 solution actually instilled 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 0·5 part 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.[3] 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, colorimetric and absorption-spectrograph 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 and of 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 need be 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 three recordings, first for patients whose colds were of less than 3 days' duration before treatment was given, and second for those whose colds were of 3 days' or more duration.

TABLE I—ANALYSIS OF 668 CASES TREATED WITH PATULIN AND 680 CASES TREATED WITH THE CONTROL SOLUTION

Treatment	% cured at—			% cured or improved at—		
	24 hrs.	48 hrs.	1 week	24 hrs.	48 hrs.	1 week
Patulin	1·6	13	33	59	73	63
Control	1·2	13	37	64	77	69
Difference	0·4	0 ± 1·9	−4 ± 2·8	−5 ± 2·7	−4 ± 2·5	−6 ± 2·8*

3. In practice it was found that the pH of different samples of the buffer varied between 5·8 and 6·8, with a preponderance 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 6·8.

TABLE II

Treatment	Duration of cold before treatment—					
	less than 3 days			3 days or more		
	% cured or improved at—					
	24 hrs.	48 hrs.	1 week	24 hrs.	48 hrs.	1 week
Patulin	57	71	64	63	76	61
Control	59	74	67	71	81	73
Difference	−2 ±3·5	−3 ±3·2	−3 ±3·5	−8 ±4·2	−5 ±3·8	−12 ± 4·4*

* Statistically significant differences.

Note.—The criterion of "cured" and "improved" was the patient's own opinion.

It will be seen that the success of the treatment was very similar whether patulin or control was given. Probably the most useful result is that obtained at 48 hours. At this time the percentage "cured" was 13% both among controls and patulin-treated, while the percentage of "cured" and "improved" together was 73% for patulin-treated and 77% for those given the control solution.

On statistical analysis only two differences are significant. Both show a slightly higher percentage of cures, or improvement, with the control solution and both occur at the 1 week recording. In view of the fact that no significant differences were found at the 24 and 48 hour recordings, nor at 1 week in the patients with recent colds, it is felt that these differences at 1 week are irrelevant.

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. Himsworth (chairman), Dr. A. J. Amor, Dr. C. H. Andrewes, FRS, Mr. T. E. Cawthorne, Prof. M. Greenwood, FRS, Dr. B. M. Merriman, Dr. H. J. Parish, Prof. H. Raistrick, FRS, Dr. 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 coöperation and assistance.

Trials were carried out in the following establishments and schools:—

	Medical officer in charge
Ministry of Supply ROF's—	
A	Dr. H. P. Warren
B	Dr. H. M. Coulthard
C	Dr. B. Levin
D	Dr. F. Sargent
Post Office	Dr. M. Kennard
	Dr. I. Dixon
	Dr. J. W. Parks
Rolls-Royce, Ltd. at—	
Y	Dr. E. Collier
Z	Dr. N. L. Lloyd
Chloride Electrical Storage Co., Ltd.	Dr. R. E. Lane
Guest, Keen and Nettlefolds, Ltd.	Dr. W. Jeaffreson Lloyd
Vickers-Armstrongs Ltd.	Dr. A. Kerr Clarkson
Enfield Rolling Mills & Cable Works Ltd.	Dr. W. G. S. Pepper
Briggs Motor Bodies, Ltd.	Dr. H. F. Chard
Haileybury College	Dr. C. M. Billington
Rugby School	Dr. R. E. Smith

A STUDY OF TREASON: CORRIGENDUM.—The penultimate sentence in Major A. M. Meerloo's article in our issue of Sept. 2 (p. 321) should read: "Such hatred can be exorcised only by allowing each man freedom to criticise and by creating in him a sense of responsibility for his views." The word *exorcised* was wrongly given.

SIMPLE METHOD OF AMPUTATING THE THIGH

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FOR about thirty years I have used on a large number of cases the following simple method of amputating the thigh.

With a long amputation knife the curved anterior incision is made as for a Carden from condyle to condyle passing halfway between the lower border of the patella and the tuberosity of the tibia. This cut is carried on superficial to the patella and deepened obliquely down to the front of the femur, dividing the periosteum. The posterior incision is then made practically transversely down to the back of the femur, which is reached at a higher level than the skin cut. The linea aspera is freed with scissors and the periosteum pushed up until the femur is bared about 11 inches below the great trochanter. With the aid of a shield retractor the bone is sawn through. The only vessels that usually need ligature are the main vessels, the long saphenous vein, the comes nervi ischiatici and an artery in the substance of the sartorius. A fish-tail division of the sciatic nerve high up inside its sheath is made and the long saphenous nerve cut short. A trident of corrugated rubber is inserted to drain behind and each side of the femur. If any sutures are used it is sufficient to insert two lateral and two terminal ones, but without them the anterior flap falls naturally into perfect position and is retained there by the dressing.

The whole operation takes usually 4–6 minutes but can be done more rapidly; I have completed it in 45 seconds. The advantages of this method are—(1) speed and avoidance of shock; (2) a minimum of muscle is divided, so preventing the plasma loss that is a well-marked feature of many thigh amputations, especially in the presence of inflammation; (3) the small amount of hæmorrhage and the small number of vessels for ligature.

The femur can be divided two inches below the site of election when it is considered wiser to minimise the dissection in anticipation of re-amputation later, but this procedure has in practice rarely been indicated. There is no disadvantage in leaving a theoretical excess of muscle in the stump, because the knee muscles waste with great rapidity. This is recognised in disabilities of the knee-joint, but is perhaps not fully appreciated in thigh amputations; it is usual to cut muscle away to an unnecessary extent.

Even without suture healing and consolidation of the stump is rapid. One officer on whom I did this amputation without sutures for a compound fracture involving the knee-joint, which was full of pus, was fitted with an artificial limb and walked to church to be married 7 weeks after the operation.

SUMMARY

An amputation of the thigh at the site of election is described, using a Carden incision to minimise shock, plasma loss and muscle retraction.

CONGENITAL MALARIA IN ENGLAND

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THE annotation on congenital malaria in THE LANCET of Jan. 29, 1944 (p. 156), prompts me to record a further case which occurred in my practice in 1939–40.

A woman with one child returned to England from India in August, 1939, and was seen when 26 weeks pregnant and found to be healthy. She had had an attack of malaria without identification of the type in 1938. In September, 1939, she developed a tape-worm infection. Early in October, 1939, she developed a temperature after a slight rigor and this was repeated in 48 hours after a severe rigor. Blood examination revealed parasites suggestive of a benign tertian infection. Treatment was instituted with mepacrine and her condition remained satisfactory until three days before the onset of labour (Dec. 1, 1939) when she "felt malarial." On the day of the actual confinement—which was uneventful—she had a rigor and ran a temperature of 103° F. The infant weighed 7 lb. and although rather flabby and thin was active and seemingly healthy. Breast-feeding was possible for only