

gave a good night's rest but symptoms returned next morning. During the second day nasal douching was carried out three times, but in spite of immediate relief to nasal blockage the cold was not cured. On the afternoon of the third day the cold finally cleared up. On the evening of the third day one small fleck of green pus was obtained by blowing the nose.

Thus the cold was not cured in the early stages but relief from nasal stoppage was obtained; this early period of a cold may be the period of virus infection and if it is it may be said from this closely observed case that patulin has no effect on the virus. The secondary stage of infection with gram-positive and gram-negative organisms was completely prevented and since it is an almost invariable rule that the purulent process continues with me for at least a week, patulin proved to be of great value.

IV. Biological Properties: Extended Trial in the Common Cold

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Preliminary experiments have been carried out to estimate the action in vitro of patulin against a number of the more common pathogenic aerobic organisms. For the reasons put forward by Fleming (1938) the bacteriostatic power of the drug has been estimated rather than its bactericidal action. In order that the results might be comparable with those obtained with other mould products the method adopted was, in the main, the serial dilutional technique used by Oxford (1942) in a similar investigation.

Serial dilutional method.—Standard heart broth at pH 7.2 containing 2% glucose, 1% peptone and 0.5% NaCl was used as the basal medium. The solution of patulin was prepared by weighing 25 mg. of the substance into a 100 c.cm. flask, adding 90 c.cm. of sterile distilled water and dissolving by gentle warming. The resulting solution was then quickly brought to boiling-point, cooled rapidly and brought up to the 100 c.cm. mark with sterile water. This gives a 1:4000 solution of patulin. The sterile basal medium was tubed in 4 c.cm. quantities and to each tube was added graded dilutions of patulin—e.g., 1 c.cm. of 1:4000 solution added to 4 c.cm. of medium gives a 1:20,000 dilution; 0.8 c.cm. of 1:4000 solution plus 0.2 c.cm. of sterile water a 1:25,000 dilution, and so on, using increasing quantities of sterile water and decreasing quantities of patulin solution. Thus each tube contained 5 c.cm. of liquid, 1 c.cm. of sterile water being added to the control tube. Different strengths of patulin solution were prepared as the work proceeded and they became necessary.

Both cultures obtained from the National Collection of Type Cultures and organisms isolated in the laboratory where the investigation was carried out were used for testing. In the former case three successive generations (each of 24 hours) were grown in the basal medium before the test was carried out.

The tubes containing the sterile basal medium plus the dilutions of patulin were inoculated from glucose-broth cultures of the test organisms, a standard loopful (0.004 c.cm.) to each. Except in the case of weakly growing organisms all cultures were diluted 1 in 1000 in the sterile basal medium before use. After sowing, the cultures were incubated for 24 hours at 37° C. and were then examined. Complete inhibition of growth was shown by the absence of any turbidity, partial inhibition by a growth which was obviously less than that in the control tube.

All tests were carried out in duplicate and have been repeated using different samples of patulin.

Experimental Findings

From table I it will be seen that patulin possesses bacteriostatic powers against a number of gram-positive and gram-negative aerobic organisms. The position with regard to the anaerobes is still under investigation but preliminary results show that the substance is active against this group also.

Compared with other mould products which have been isolated during recent years, patulin differs from penicillin, gramicidin and citrinin in that it shows no selective differentiation between gram-positive and gram-negative microbes. In this respect the drug is comparable with penicillic acid, and indeed the inhibitory figures pub-

lished for the latter compound (Oxford 1942) are very similar to those shown in table I. Patulin is very much less active than is penicillin against gram-positive organisms, but the position is reversed with regard to the coli-typhoid salmonella group. For example, while patulin gives complete inhibition of *Salmonella typhi* at a dilution of 1 in 50,000, and complete inhibition of *Bacterium coli* at a dilution of 1 in 33,000, the figures for penicillin (Abraham et al. 1941) are 1 in 10,000 and less than 1 in 1000 respectively. In the same way, with the dysentery group patulin is a more efficient growth inhibitor than penicillin, the figures for *Bact. dysenteriae* Shiga being 1 in 50,000 for the former drug and 1 in 20,000 (Abraham et al. 1941) for the latter.

Effect of serum.—In order to estimate the inhibitory effect, if any, of serum the dilution tests were repeated with the addition of 10% fresh human serum. *Staphylococcus aureus*, *Streptococcus pyogenes* and *Strep. pneumoniae* were used as test organisms and the results obtained are shown in table II. In no instance was any inactivation observed.

Effect of pus.—In view of the projected trials of the substance in the treatment of common cold, it was important that its activity in the presence of pus should be estimated. This was carried out using "pus broth" as described by Florey and his colleagues (1941), and with *Staph. aureus*, *Strep. pyogenes* and *Strep. pneumoniae* as test organisms.

The pus was first "thinned" by incubation at 37° C. for 3 days, and after centrifugation one part of the supernatant fluid was diluted with two parts of broth to give a 33% pus broth. After filtration through a Seitz EK filter

TABLE I—BACTERIOSTATIC ACTION OF PATULIN USING 2% GLUCOSE BROTH

| Test organism | Limiting dilution for inhibition | | | Notes |
|-------------------------------|----------------------------------|---------|---------|---------------------------------|
| | Complete | Partial | None | |
| <i>Staph. aureus</i> .. | 50,000 | .. | 80,000 | Coag. + ve from abscess |
| Ditto .. | 33,000 | .. | 50,000 | Coag. + ve from osteomyelitis |
| Ditto .. | 33,000 | 50,000 | 100,000 | Two strains: NCTC 3095 and 3750 |
| Ditto .. | 50,000 | .. | 100,000 | NCTC 3761 |
| <i>Strep. pyogenes</i> | 80,000 | .. | 100,000 | Lancefield A from throat |
| Ditto .. | 33,000 | 50,000 | 80,000 | NCTC 2432 |
| <i>Strep. viridans</i> .. | 33,000 | .. | 50,000 | NCTC 3166 |
| <i>Strep. pneumoniae</i> | 80,000 | .. | 100,000 | Group 3 |
| <i>S. typhi</i> .. | 50,000 | .. | 80,000 | .. |
| Ditto .. | 50,000 | .. | 80,000 | NCTC 2128 |
| <i>S. typhi. para A</i> | 80,000 | 100,000 | 150,000 | .. |
| <i>S. typhi. para B</i> | 50,000 | .. | 80,000 | .. |
| Ditto .. | 33,000 | .. | 50,000 | NCTC 14 |
| <i>Bact. coli</i> .. | 33,000 | 50,000 | 80,000 | NCTC 86 |
| <i>B. dysenteriae</i> Flexner | 80,000 | .. | 100,000 | .. |
| <i>B. dysenteriae</i> Shiga | 50,000 | 80,000 | 100,000 | .. |
| <i>B. proteus</i> .. | 33,000 | 50,000 | 80,000 | NCTC 401 |
| <i>M. catarrhalis</i> .. | 80,000 | 100,000 | 150,000 | .. |

varying dilutions of patulin were added to this broth, which was then inoculated in the usual way with the test organisms, incubated for 24 hours at 37° C. and examined. Pus broth without the addition of patulin was used as a control and the test was carried out in parallel with 2% glucose broth.

The results in table II show that in no instance was any antagonistic effect observed.

Effect on leucocytes.—The in-vitro effect of patulin on the phagocytic activity of leucocytes has been tested using the method described by Thrower and Valentine (1943).

Saline dilutions of the drug were prepared ranging from 0.4% to 0.0125%; 0.2 c.cm. of each dilution was added to an equal volume of reconstituted blood and the tubes were incubated at 37° C. for 3 hours. A tube containing saline

TABLE II—DILUTION TESTS, SHOWING THAT SERUM AND PUS DO NOT INTERFERE WITH BACTERIOSTATIC EFFECT OF PATULIN

| Test organism | Highest dilution producing complete inhibition | | |
|-----------------------------|--|--------------------------|-----------|
| | 2% glucose broth | Glucose broth +10% serum | Pus broth |
| <i>Staph. aureus</i> .. | 33,000 | 33,000 | 33,000 |
| <i>Strep. pyogenes</i> .. | 80,000 | 80,000 | 80,000 |
| <i>Strep. pneumoniae</i> .. | 80,000 | 80,000 | 80,000 |

without the addition of the drug was used as the control. After 3 hours incubation a standard drop of heat-killed three-hour staphylococcal broth culture was added to each tube; the tubes were then shaken and incubated for 30 minutes. After incubation, films were made from each tube and a count was made, noting (a) the number of cells containing cocci and (b) the number of ingested cocci in 100 phagocytes.

The results showed that at 0.05% of patulin phagocytosis is inhibited; it is reduced at 0.025% but unaffected at 0.0125%.

Acute toxicity for laboratory animals.—Patulin has been administered intravenously to mice weighing between 20 and 25 g.; the results are set out in table III. Deaths occurring within 3 days were recorded. The average lethal dose is in the region of 0.5 mg. per 20 g. With the higher dosage levels (1 mg. and 1.5 mg. per 20 g.) most of the animals appeared ill within 2 hours of the injection and died within 6 hours. In a number of instances death was immediately preceded by convulsions, in one case so severe as to fracture vertebræ. On autopsy the lungs were found to be oedematous and

TABLE III—DETERMINATION OF LETHAL DOSE IN MICE

| Intravenous dose (mg./20 g.) | No. of mice | Deaths within 3 days | Mortality % |
|------------------------------|-------------|----------------------|-------------|
| 0.25 | 30 | 5 | 16.6 |
| 0.5 | 20 | 13 | 65 |
| 1.0 | 20 | 17 | 85 |
| 1.5 | 5 | 5 | 100 |

grossly hæmorrhagic. On section the capillaries showed acute dilatation and the alveoli were packed with red cells. Similar capillary damage, but to a less degree, was seen in the liver, spleen and kidneys. Histological examination of the brain showed oedema, congestion of the vessels and a round-cell infiltration.

The average lethal dose for a 20 g. mouse when the substance is administered subcutaneously is also in the region of 0.5 mg. When this amount is given dissolved in 0.2 c.cm. of water death usually takes place within 24 hours. Changes similar to those described when the intravenous route was used were found on autopsy. With smaller doses (0.25 mg. and 0.125 mg.) the mice survived but injection was followed first by oedema of the tissues and later by necrosis at the site of inoculation.

The findings in a rabbit are very similar. After an intravenous injection of 50 mg. (0.25 mg. per 20 g. body-weight) the animal went into convulsions and died at 14 hours. At autopsy, pleural and pericardial effusions were present and the organs showed the same changes as in the mice.

Treatment of the Common Cold

All epidemiological studies on the common cold go to show that the disease is prevalent throughout the world and that it is a very important factor in the morbidity-rate. In the United Kingdom the complaint is responsible for more absenteeism and loss of efficiency than any other disorder or group of disorders. Although a cold is usually regarded as a nuisance rather than a serious complaint, there can be no doubt that repeated attacks (and the average incidence is two attacks per person per annum) lead to serious and sometimes disabling complications.

For years past a cure for the common cold has been sought, and numerous so-called specifics have had their

advocates. None of these specifics, however, has fulfilled its early promise, and, as the saying goes, if a cold is treated energetically it will get well in seven days, while if left to itself it will get well in a week.

When patulin was isolated and preliminary tests in vitro had shown that it possessed bacteriostatic powers against a number of gram-positive and gram-negative organisms, a few observers decided to give the drug a personal trial in the treatment of common cold. The results were encouraging and it was felt that the substance merited further trial in a larger group, under controlled conditions. An investigation was therefore arranged in coöperation with the authorities at a large naval depot.

Common cold is a generic term applied to a number of conditions affecting the respiratory tract, and it was essential for an investigation such as this that some limited definition of a cold would have to be adopted and that only those cases which conformed to that definition should be included in the series. The definition adopted was in the main that of Horder (1932)—an acute specific catarrh involving the upper respiratory tract, and in most cases the nose and pharynx. A cold runs a benign course of 3–10 days, with pyrexia and constitutional disturbance. Horder allows some degree of sinusitis, laryngitis or tracheitis in his definition, but patients presenting themselves with such complications on first attendance were not included in this series. Moreover, patients with severe headache, body aches, and in whom the diagnosis between influenza and common cold was indefinite were excluded. Thus the type of case treated was an acute or subacute rhinitis with or without pharyngitis, and with or without slight pyrexia and constitutional disturbance—in other words, what the man in the street, who may be sneezing, with his nose “stuffed up” or running and a dry throat, and is feeling thoroughly miserable, calls a “cold in the head.”

The investigation was carried out in two parts:

Group 1.—A controlled series in which half the patients were treated with patulin and half with a control fluid.

Group 2.—In which selected observers suffering from colds were given supplies of patulin and asked to keep careful notes of their progress.

PREPARATION AND ADMINISTRATION

Patulin keeps well in a phosphate buffer solution adjusted to pH 6. This buffer solution is prepared as follows:

27.231 g. acid potassium phosphate (‘Analar’) is dissolved in a litre of distilled water; 57 c.cm. of N/10 sodium hydroxide is added to 250 c.cm. of the phosphate solution; the resulting solution is well mixed and then made up to a litre with distilled water.

The stock solution of patulin is prepared by dissolving 0.050 g. of the substance in 5 c.cm. of the buffer solution and diluting to 100 c.cm. with sterile distilled water. This stock solution keeps well; a supply which was kept for 3 months showed no evidence of deterioration. For ready use one part of the stock solution is diluted with nine parts of sterile distilled water to give a 1:20,000 solution of substance; two parts with eight parts of water to give a 1:10,000 solution, and so on. The solutions for use were prepared freshly each day and were used within twenty-four hours. The strengths used were 1:20,000 in the first batch, 1:10,000 in the second, and 1:5000 in the third batch. In group 2 a 1:10,000 solution was supplied.

The solution of patulin was applied locally to the nasal passages and nasopharynx. Patients in group 1 were treated by a sick-berth attendant who sprayed the nose and throat with a De Vilbiss atomiser. Patients in group 2 either sniffed it up from the palm of the hand or instilled it into the anterior nares with a pipette; some of the patients in this group also gargled with the solution. The patients in group 1 were treated every 4 hours. Some of the patients in group 2 applied the treatment every 2 hours, others every 4 hours. Approximately 4 c.cm. of fluid was used on each occasion, and in most cases treatment was continued for 24–48 hours. A few patients in the first batch were treated for three days, but in the later batches 48 hours was taken as the limit. The control fluid used in group 1 was equally diluted buffer solution.

RESULTS IN GROUP 1

Treatment of group 1, which was subdivided into three batches, was carried out at a Naval depot. Colds were rife at the time, and after a broadcast on the subject ample volunteers were forthcoming. The patients were first examined and the form here illustrated was filled up; if they conformed to the definition of common cold they were then directed to an attendant who treated alternate cases with a solution of patulin and the remainder with the control fluid.

Date / / 43. Name _____ Age _____ Rating _____
 Headache _____ Shivering _____ Coryza _____
 Body pains _____ Sore Throat _____ Cough _____
 Other symptoms _____
 Contact ? _____ Subject to colds ? _____
 Present condition :— T. P. R.
 Eyes _____ Nose _____
 Fauces _____
 Chest _____

| Date. | Time. | Treatment. | Progress. |
|-------|-------|------------|-----------|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

Duration of symptoms before treatment _____

Duration of symptoms after treatment _____

COMMENTS :—

Form used in Group 1. The reverse has space for the findings on direct examination and culture of the nasopharyngeal swab.

The patients themselves did not know that the series was being controlled and were under the impression that they all had had the same treatment. With the third batch, to prevent the possibility of any bias on the part of those conducting the trials, until the results of treatment had been assessed, none of them knew which was the treated group and which the control.

Treatment was repeated four-hourly during the day, and the patients were seen at the end of 24 hours and again at the end of 48 hours, at which times improvement or otherwise was assessed. The assessment of results was by no means easy, for a cold, apart from rhinorrhoea, has but few objective signs, and one was forced to rely largely on the patient's statement. However, every effort was made to check a patient's statement that he was cured by physical examination and by interrogation as to why he had said so.

As might be expected, a certain number of men, both treated and controls, had made up their minds that they were going to be cured, and claimed complete alleviation of their symptoms when asked how they felt. Further questioning in such cases elicited the fact that although they felt better they were still suffering from such symptoms as some nasal discharge, a stuffed-up nose in the morning, &c. Only those men who, after questioning, were found to be completely symptom-free, and who, on examination, had no objective signs were classified as cures. In the first batch an attempt was made to divide the patients into three groups; cured, improved and worse, but because of the difficulty in assessing improvement this method was abandoned, and patients in the subsequent groups were classified as cured or not cured. For convenience in statistical analysis, the figures obtained in the first batch have been treated in a similar fashion, the improved and worse cases being classified as "not cured." The results obtained are shown in table IV; it will be seen that in each batch the treated patients show a much higher percentage of cures than do the controls.

A large number of the cured patients noticed a great improvement after the first application of patulin, and were completely cured within 24 hours. The response to treatment could almost be described as dramatic; men who had been feeling miserable with a constant nasal discharge and a raw throat during the day and a stuffed-up nose on waking in the morning, reported 24 hours after treatment had been begun that they felt quite fit and that their nasal passages were dry and clear.

Other patients improved more gradually, but experience showed that if complete cure did not take place within 48 hours it was unlikely that patulin would have any apparent effect on modifying the course of the cold.

No ill effects were observed after treatment. Some patients (especially those in batch 3, when a 1:5000 solution was used) complained of a transitory stinging in the nose, immediately after they had been sprayed, and a number noticed that for about half an hour after treatment they had a profuse nasal discharge. That these effects were not due either to the buffer solution or to mechanical action is shown by the fact that none of the patients in the control group reported similar symptoms.

The failures may be divided into two groups—(a) patients who did not improve in any way, and (b) patients who showed transitory improvement which was not maintained or in whom complications developed. The second group is of some interest and mention may be made here of a relevant personal experience.

For many years I have had at least one severe cold each winter. These attacks may be described as typical common colds; they start with vague malaise, a dry throat and slight pyrexia and are closely followed by sneezing, profuse nasal discharge and completely blocked nasal passages on waking in the morning. The acute symptoms usually persist for 4–5 days and are followed by a purulent nasal discharge which lasts for about a week. A few years ago one of these attacks culminated in a severe pan-sinusitis, which, however, cleared up with conservative treatment. During the time that patulin was undergoing clinical trials I noticed the premonitory symptoms of a cold, and 12 hours later when the attack had fully developed I started treatment using a 1:10,000 solution of patulin every 4 hours. Next morning—i.e., some 20 hours later—I woke up feeling completely cured and without a trace of nasal discharge or blockage of

TABLE IV—RESULTS IN GROUP 1

| Batch and month | TREATED | | | CONTROLS | | |
|-----------------|----------|-----------|-------------|----------|-----------|-------------|
| | Patients | Recovered | % recovered | Patients | Recovered | % recovered |
| 1. January | 54 | 24 | 44 | 41 | 1 | 2.4 |
| 2. February | 23 | 16 | 70 | 26 | 3 | 12 |
| 3. April | 18 | 15 | 83 | 18 | 4 | 22 |
| Total | 95 | 55 | 58 | 85 | 8 | 9.4 |

the nasal passages. The same night, however, symptoms of sinusitis (pyrexia, pain close to the inner canthus of the eye, together with generalised headache and vomiting) made their appearance.

Two of my colleagues had similar experiences; after the use of patulin they noticed distinct but temporary improvement, but shortly afterwards both developed sinusitis; like myself, both had had previous attacks. It is probable that any focus which the solution cannot reach will keep the infection active in the nasal passages, and some of the failures in the treated group may have been due to the existence of a previous sinusitis. In 2 patients clinical and radiological evidence of such a condition was found; neither of these patients improved, but neither became worse nor complained of symptoms suggestive of an acute sinusitis.

RESULTS IN GROUP 2

Some 14 patients complaining of colds were given supplies of patulin and asked to keep notes of their progress. Of these, 10 reported a complete and rapid recovery. Of the remainder, one felt much better and 3 noticed no improvement whatsoever. Typical case-histories of the cured cases are as follows.

CASE 1. (Notes supplied by Dr. M. Maizels.)—A married woman, who usually has two bad winter colds, which always develop in the same way: thickness in nose, running eyes, sore throat. The cold is bad for 3 days and clears up in about 3–4 days. On the evening of Feb. 2 she noticed dryness and stuffiness of the nose and sore throat. Next morning she felt she had a very heavy cold coming—sneezing, fullness in ears, serous discharge from nose, eyes watering and throat dry at the back, but felt well in herself. She feels sure that this would have developed typically without treatment. Treatment began at 12 noon on Feb. 3; patulin was instilled as drops in the nose and snuffed up from the hand; the throat was gargled with patulin. Snuffing and gargling were repeated at 2.15, 4.15 and 6.15 PM on Feb. 3 and on the morning of Feb. 4. At 5 PM on Feb. 3, the patient said, her nose was streaming and the cold was getting worse. She woke up on Feb. 4 quite well.

CASE 2.—A man, who reported with a "streaming cold" of one day's duration. The predominating symptoms were malaise, headache, profuse nasal discharge and sore throat. Examination revealed a subfebrile temperature, slight faucial inflammation and acute rhinitis. Treatment consisted of 1:10,000 patulin every 4 hours during the day, and 24 hours after beginning treatment the patient reported that he was completely symptom-free. This was confirmed by examination. As a sufferer from colds he was convinced that his cold would have dragged on for a week or longer had he not been treated.

CASE 3.—A man, who reported with a heavy cold of several days duration. The predominating symptoms were a thick purulent nasal discharge during the day and completely blocked nasal passages, together with a sore throat, on waking in the morning. Treatment consisted of 1:10,000 patulin every 4 hours during the day. After the first application the discharges became very profuse and watery; 48 hours later all discharge had ceased and the nasal passages were clear and dry.

In addition to these cases, 27 WRNS personnel were treated with patulin. The results are given in the following report by the officer in charge of the trials.

"The first bottle of the substance was provided for my office staff and myself to try. The results were so successful that other officers asked to be allowed to use it, and have sent their ratings for treatment. As far as possible we have used it, as instructed, before a cold has lasted more than 24 hours.

"Twelve officers and 14 ratings have reported completely successful results after not more than 24 hours' treatment. Included among these was a girl motor-transport driver who has had a series of very heavy colds; not a single attack has developed since she has used the solution. One officer and one rating reported partially successful results. Both of these are subject to colds which seem deep-rooted and last for 2–3 weeks. Both reported that the treatment gave them considerable relief and made them feel much less heavy headed, but the cold itself did not clear up immediately. The one real failure was in an officer who gets very heavy colds, accompanied by aches and pains and usually a rise in temperature. It did not seem to have any definite effect in her case."

BACTERIOLOGY

The bacterial flora of the nasopharynx was investigated in a number of patients in the controlled series. Swabs were taken before treatment was started and again when the patient was discharged cured, and an attempt was made to estimate both whether any organism predominated in the series as a whole, and whether any change took place in the bacterial flora after treatment.

All the swabs examined yielded a mixed growth, and, although different organisms predominated in different individuals, no one organism was predominant in the series. The most commonly found microbes were *Strep. pneumoniae*, *Micrococcus catarrhalis*, and streptococci, both alpha and beta. The series was too small to warrant any definite conclusions, but the impression gained was that after treatment with patulin a distinct reduction of organisms took place.

Five cases of clinical influenza were treated with a 1:10,000 solution of patulin, used in exactly the same way as in colds. In these cases the onset was sudden, headache and generalised body pains were the predominating symptoms, and apart from a dry cough the respiratory tract was not affected. Pyrexia per-

sisted for 4–5 days. The course of the disease did not appear to be influenced in any way by the drug.

DISCUSSION

The aetiology of the common cold is not yet fully understood. Some workers adhere to the virus hypothesis, while others are convinced that organisms such as pneumococci, *M. catarrhalis*, streptococci, &c., are primary causes. With the aetiology and pathology of the complaint in such an unsatisfactory position it is difficult to give any considered opinion on the merits of a new curative agent, and the task is made more difficult because the duration and severity of colds varies enormously with the individual, time and place, and because the common cold is a self-limited disease.

For these reasons it is felt that although the results of the trials described in this paper are encouraging, no definite claims can be made for patulin until it has been given more extended trial in different localities.

Summary

Patulin is about equally bacteriostatic to both gram-positive and gram-negative organisms; it is much less active than penicillin against gram-positive organisms but much more so against gram-negative ones.

The bacteriostatic power of the substance is unaffected by the presence of serum or pus.

The phagocytic activity of leucocytes is unaffected by a 1 in 8000 solution, but inhibited by a 1 in 2000 solution.

The lethal dose for mice is about 0.5 mg. per 20 g. body-weight, whether the substance is given intravenously or subcutaneously. Subcutaneous administration produced necrosis at the site of injection.

During the first four months of this year patulin was given a trial in the treatment of common colds which were prevalent at a naval establishment in the south-east of England. Solutions of the substance were sprayed into the nose or snuffed up from the hand.

The results obtained were encouraging, 57% of the treated cases recovering completely within 48 hours, compared with only 9.4% of the controls.

No ill effects were observed.

My thanks are due to Professor Raistrick for supplies of patulin; to the Royal Naval authorities, both executive and medical, at the depot where the trials were carried out for their coöperation; to Surgeon Lieut.-Commander H. W. Clëgg for his help in the animal toxicity tests; and to SBPO Geoffrey Smith, who assisted me both in the bacteriological work and clinical trials.

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v.—Statistical Note

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The purely statistical question which arises in Commander Hopkins's work is a simple one—assuming that the treated and control populations do not differ in any material way, except in regard to the fact of treatment, what is the probability that such divergent percentages of cure would emerge?

It is evident that if two batches of pennies are tossed, the respective percentages of "heads" are likely to differ, and the probability that any particular difference, or a greater difference, would occur can be readily calculated. The principle involved in this stock case is fundamentally the same as in our problem, subject to a consideration I shall discuss later on.

The fundamental data are given by Hopkins in his table IV. The three sets—January, February and April—are not *in pari materia* and must not be aggregated. There is no reason why the proportion of cures