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

DISCUSSION

The ætiology 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 ætiology 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. Clegg 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

should be the same in different months. Common sense suggests that the differences of percentages are unlikely to be "chance" happenings and it will be enough to apply an exact test to the set most favourable to the hypothesis of chance deviation—the third set. Applying such a test (see Fisher, Statistical Methods for Research Workers, pp. 94–95) it is found that in random sampling so wide a divergence in favour of the treated would occur about 3 times in 10,000 trials. It is therefore an improbable happening. In one respect, however, treated and controls are not *in pari materia;* the former included a larger proportion of patients with symptoms of not more than one week's duration (44·4, against 33·3). But, as the following table shows and common sense suggests, this is not probably material, unless there were a special process of selection, or self selection—viz., only patients with especially "obstinate" colds presenting themselves for treatment.

—	TREATED			CONTROLS		
	Patients	Recovered	% recovered	Patients	Recovered	% recovered
Symptoms of one week or less ..	75	41	54·7	63	5	7·9
Symptoms over one week ..	20	14	70·0	22	3	13·6

It could, of course, be tested by subtabulation, but, in view of the fact that in the first two series the proportions of treated and controls with symptoms of not more than a week's duration were virtually the same (87·0 and 85·1 %), and in these series the divergence is greater, the arithmetic is needless. We may certainly say that, taken as a series, the probabilities of drawing each pair from a common universe are extremely small.

That conclusion is all that purely statistical reasoning can establish. To revert to the illustration, if an experiment were made with batches of coins fresh from the mint, and their respective percentages of heads differed in such a way that, tested as these data have been tested, a probability of, say, less than 3 in 10,000 emerged that they came from a common universe, no sensible person would infer that the mint coins were biased. He would conclude that either (1) the samples were not *in pari materia* (there had been some "trick" in tossing), or (2) a very improbable event had happened —as it would, on the average, some 3 times in 10,000 trials. He would do so because the a priori improbability of bias in the mint coins is exceedingly great. In our case there is no such a priori improbability that the antibacterial substance might accelerate a cure; that it does do so is a tenable hypothesis. But, and this is the point always to be had in mind, what the statistician has shown is *not* that the odds are so and so many thousands to one in favour of the hypothesis that the antibacterial substance does cure, but only so and so many thousands to one against the chance that such results would emerge without *some* differentiation between the groups. Whether at other times and in groups differently chosen the same differentiation would be found can only be known when further trials have been made.

I am indebted to my colleague, Dr. W. J. Martin, who carried out the arithmetical tests.

INTERSTITIAL EMPHYSEMA AFTER EXTRACTION OF A LOWER MOLAR

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AT 10.10 AM on May 22, 1943, a male postal worker, aged 49, had his lower left second molar extracted under local anæsthesia. The tooth was broken during the first attempt at extraction. A further injection of local anæsthetic was made and the roots successfully extracted, but with difficulty. The patient arrived home at 11 AM, and on looking in a mirror was shocked to find the left side of his face very swollen. At 1 PM he found great difficulty in swallowing solid food. At 2 PM he lay down to sleep but had to sit up because of respiratory embarrassment.

He was seen at 6 PM. At this time the upper line of demarcation of the facial swelling was immediately below the left molar bone, at which point the swelling stood out for about ¾ inch. From this point the swelling gradually increased as it descended to the mandible, and then decreased towards the base of the neck. The upper part of the swelling was firm; on palpation it presented a sensation of sponge rubber, and sounded like it on percussion. Here it was difficult to perceive air crepitus. Below this the swelling was softer and air crepitus was easily audible to the naked ear. On ausculation air crepitus could be heard throughout the entire swelling to the base of the neck. The suprasternal fossa was puffed out with a soft swelling in which crepitus was easily heard. There were no signs of emphysema in or around the orbit. The soft palate on the affected side was bulging over the posterior edge of an upper denture, while the left side of the pharynx was swollen to a point half way towards the middle line. There was no unusual laceration of tissues at the site of extraction, nor was there any suggestion that bleeding had been more than usual. There was no increase in the swelling after he was seen, and in his opinion there had been little increase after he reached home. The condition took a full week to subside.

Prof. H. A. Harris suggests that there was probably a laceration of either the mylohyoid muscle in the floor of the mouth or of the buccinator muscle in the vestibule of the mouth. In the former case, air may pass downwards into the loose deep fascia of the neck and upwards over the mandible anterior to the masseteric fascia and the overlying parotid gland. In the latter case, air may pass medial to the buccinator and backwards towards the pterygomandibular raphe and the soft palate; also lateral to the buccinator in relation to the space occupied by the corpus adiposum buccæ. The passage of air from face to neck or vice versa could take place near the anterior margin of the masseter at the lower border of the mandible, along the loose fascia surrounding the external maxillary (facial) vein and artery.

Two cases of interstitial emphysema after maxillary molar extraction are referred to by Collyer and Sprawson (1942), one reported by Turnbull (1900), and another by Binns (1935). In Turnbull's case a bugler had bugled immediately after the dental extraction, while in Binn's case the patient's wife said that he had tried to blow through a choked pipe shortly after the extraction. Two cases of emphysema after mandibular molar extraction have been reported in America. In the first, reported by Schaefer and Williams (1933), the condition was ascribed to the use of compressed air irrigators. In the second, reported by Hopkins (1935), the extraction was of an impacted molar and apparently required a lengthy operation. Hopkins found the emphysema to extend upwards to the scalp and down to the breasts. Another case, reported in France by Houzeau (1936), followed an easy and complete extraction of a lower right third molar; no explanation was offered.

A case of unilateral interstitial emphysema of the face was reported by Kirby in 1919, but this developed as the result of drying the pulp cavity of an incisor root, to which it was intended to fit a crown, with an electropneumatic hot-air syringe. Extraction was performed after the development of the emphysema. The root was found to have a large apical foramen. Kirby does not state whether it was an upper or lower tooth.

In the case now reported no suction or compressed air was used. The patient said that on the way home he kept the left side of his face covered with his hand because his jaw was aching, and that he kept his mouth closed to prevent cold air getting into his mouth. It is possible that local pressure on the cheek overlying the socket was painful, though general pressure over the side of the face was comforting. Thus, with the mouth kept firmly closed, air may have been driven into the vestibule to blow out the cheeks and keep pressure off the painful socket.

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