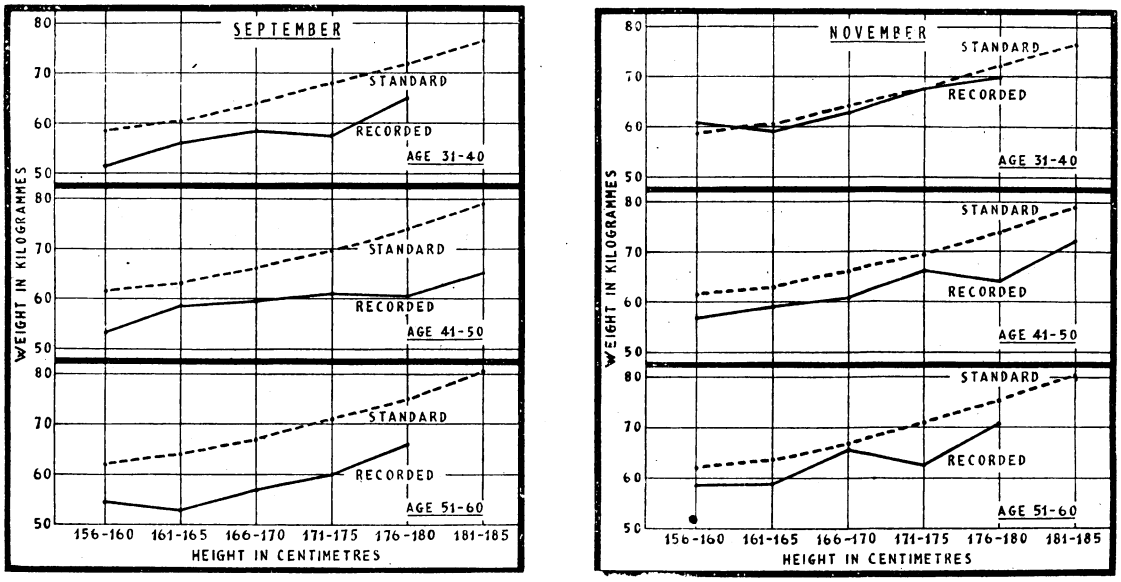

FIG. 2.—Heights and weights of male factory workers in Vienna, 1945. (The standard for body weight is that of Davidson and Anderson.)

Industrial Workers

In Fig. 2 the body weights of workers in a large factory in the XIth district of Vienna have been plotted against heights. The total of approximately 600 workers were split into the three age groups shown. The figures used as standard for body weight are those of Davidson and Anderson (1940). The first part of Fig. 2 suggests that in September a loss of weight between 8 and 10 kg. had occurred, with the greater loss having been suffered by the older men. The second part of the figure indicates that by November the youngest group of men had attained a weight equal to the standard, while in all cases an increase had occurred. Although weighings were carried out with the work-people in shirt and trousers and without shoes, we cannot completely exclude the possibility of an increase in weight due to heavier underclothes worn in the colder weather.

Conclusions

Although there was a substantial improvement in the food supplies of Vienna between September and November, 1945, the full nutritional requirements have not yet been provided. So far as protein is concerned the total amount available appears to be adequate except for the lowest ration category of "normal consumer," although it is possible that the proportion of animal protein may be insufficient. The shortage of fat in the diet, although perhaps of little physiological significance, is a measure at least of unpalatability.

A comparison of the intake of vitamins A and C in September and November is of interest. In the earlier month the official ration supplied no vitamin A or vitamin C at all, but, since people could procure at least a small amount of vegetables for themselves, their diet was partially protected. In November, however, the official ration was designed to supply adequate quantities, but as potatoes were scarce and vegetables almost unobtainable, the actual diet available was worse than before. In order, at least in part, to make good this deficiency the British authorities are proposing to issue vitamin tablets throughout their sector. These tablets will also supply a supplement of riboflavin. To meet the calcium deficiency it is proposed, as was mentioned earlier, to add chalk to the bread.

Summary

A dietary survey carried out in Vienna in November, 1945, showed that the food eaten by normal consumers provided about 1,700 calories daily; factory workers obtained approximately 2,200 calories, and children 10 years old about 2,000 calories. All the diets were deficient in calcium, vitamin A, and riboflavin, and there was a shortage of vitamin C for the children. A survey of the weekly food consumption of 97 Vienna families broadly confirmed these results and suggested that the average *per capita* diet supplied about 2,000 calories daily.

The weights of Vienna school-children showed no drop below the standard for age, while a slight excess in height appeared to exist. A group of factory workers seemed to have increased in weight since September.

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THE "IONIZATION" OF PENICILLIN

BY

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The practice of using solutions of penicillin for the treatment of infected wounds by ionization seems to be on the increase, and some authors—notably von Sallmann (1943), Struble and Bellows (1944), and Dunnington and von Sallmann (1944)—using this method for eye infections have claimed satisfactory results. Before these results can be accepted it must be shown that penicillin in solution behaves as an electrolyte. A series of experiments was therefore designed to test this hypothesis, and the results, which are reported in this paper, suggest that it is untenable. No attempt was made to determine the specific conductivity of penicillin in solution, but it seems amply clear that, even if the molecule does move, the rate will be so slow that a therapeutic concentration in the tissues will not be obtained, and there is a strong possibility that the penicillin will be destroyed by the products of electrolysis of other electrolytes present.

Methods

In all experiments the apparatus shown in Fig. 1 was used. The strength of the penicillin solutions was between 25 and 50 units per ml.—a convenient concentration for estimation by the cup method employed; where a penicillin-agar base was used, slices were cut off and dropped on to seeded plates and the penicillin content estimated from the diameter of the zone of inhibition, as in the cup method.

Where an indicator was required B.D.H. 4110 was used, as this dye has no inhibitory effect on penicillin. All the water employed in the experiments was redistilled from alkaline $KMnO_4$ in an all-glass apparatus.

Experiment 1.—The glass tube was filled with the redistilled water. The maximum current was passed for two hours. During this time the current increased from 0.05 to 0.15 milliampere. The test was

repeated with a solution of sodium penicillin in redistilled water (25 units per ml.). The milliammeter readings increased from 0.10 to 0.15 in two hours.

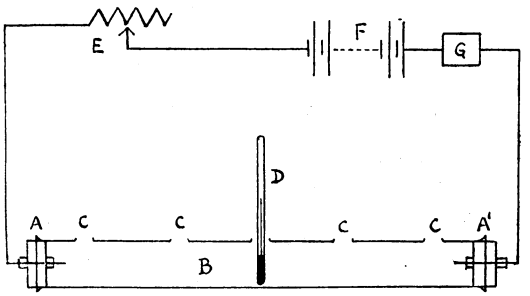

FIG. 1.—Apparatus used for all experiments.—A, A', Non-polarizable platinum electrodes, 14 cm. apart. B, Glass tube, 1 cm. bore. C, Holes in tube for sampling. D, Thermometer. E, Variable resistance for controlling current. F, High-tension battery, 240 volts. G, Milliammeter.

The addition of penicillin to the water leads to only a slight initial increase in the amount of current passing through it. Penicillin is therefore either a very poor conductor or a non-conductor; in the latter case the slight increase in current might well be due to impurities in the drug.

Experiment 2.—The glass tube was filled with sodium penicillin solution (25 units per ml.) and the maximum current passed for two hours. Samples of the solution from the region of the anode and

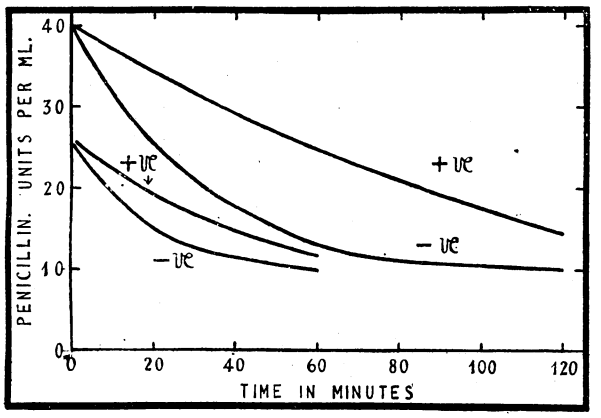

FIG. 2.—Experiment 2: showing rate of loss of penicillin at the anode (+) and cathode (−). Aqueous solution; two tests.

of the cathode were tested for penicillin activity at intervals. The results of two tests are shown in Fig. 2, where it can be seen that the penicillin is destroyed at both electrodes, although more rapidly at the cathode.

Experiment 3.—Experiment 2 was repeated with addition of the indicator, B.D.H. 4110, to the solution. The colour changes showed that the solution at the anode rapidly became acid (*p*H 4) and at the cathode became alkaline (*p*H 10). At the end of 15 minutes these changes were complete in the respective halves of the tube. Test sampling from each end of the tube for penicillin activity was carried out, and the results obtained were identical with those of Experiment 2.

The indicator therefore has no effect on the penicillin. The destruction of the penicillin is probably due to the gross *p*H changes in the solution, which themselves may be due to the electrolysis of impurities in the penicillin.

Experiment 4.—In order to slow down the rapid ionic movement demonstrated by the *p*H changes in Experiment 3, the tube was filled with 3% agar in redistilled water containing B.D.H. 4110 and 50 units of sodium penicillin per ml. The current was maintained at 10 mA for 23 minutes. The agar column was 120 mm. long, and at the end of the experiment the colour change at the anode indicating *p*H 4 was 35 mm. long and at the cathode (*p*H 10) 20 mm. long. Plating of disks of the agar at the end of the experiment showed that at the anode, where the *p*H was reduced to 4, only 3 units penicillin per ml. remained, and at the cathode only traces of penicillin were detected. In the central part of the column, where the reaction remained neutral, 50 units per ml. were recoverable from all parts, no shifting towards either electrode being demonstrated. This experiment again suggests that the penicillin destruction, when it occurs, is due to gross *p*H changes.

In none of the foregoing experiments do the conditions of test resemble those which would be encountered in *in vivo* methods. As practically all body fluids contain sodium chloride and most tissues other chlorides, the experiments were repeated in the presence of the former salt, and, as will be shown, this leads to even more rapid destruction of the penicillin.

Experiment 5.—The tube was filled with 0.9% NaCl in redistilled water containing various concentrations of sodium penicillin. These were subjected to various strengths of current, and the penicillin content was determined at intervals by the cup method, as in the previous experiments. The results are shown in Fig. 3. It will be

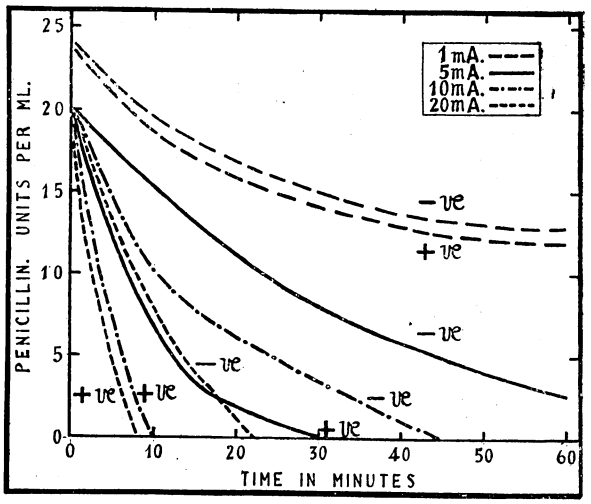

FIG. 3.—Experiment 5: solutions of penicillin in saline. Showing rate of loss of penicillin at anode (+) and cathode (−) at different current strengths.

seen that the penicillin is destroyed more rapidly at the anode (in watery solutions the reverse is true), and this is probably due to the presence of chlorine. Also the greater the current the greater the rate of destruction of penicillin. For instance, at 20 mA 20 units per ml. are destroyed within 10 minutes (anode), while at 5 mA 20 units per ml. are destroyed in 30 minutes (anode). The tests also show that the rate of destruction of penicillin in a solution of NaCl is more rapid than when no NaCl is present. The temperature of the solution being ionized rose in all these tests but never exceeded 21° C.

Experiment 6.—The tube was filled with a column of agar containing 0.9% NaCl, 50 units per ml. of sodium penicillin, and indicator B.D.H. 4110. The current was passed at 10 mA for 20 minutes, and at the end of this time the agar was sliced and plated. The penicillin had been completely destroyed where colour changes had occurred in the agar, but in the central part of the column, where the *p*H was about 7, there had been no detectable loss or movement of penicillin.

Compared with Experiment 4 these results show that ionization in agar containing penicillin and NaCl leads to more rapid destruction of the penicillin in the region of the electrodes. Again there is no evidence that penicillin behaves as an electrolyte.

Discussion

No claim is made that these experiments are exhaustive, but the results seem to justify an assumption that any attempts to ionize penicillin into the body are doomed to failure. Penicillin appears to be either a very poor conductor or a non-conductor—an observation confirmed by the failure to demonstrate any movement of penicillin during the passage of an electric current through a solution of its sodium salt. If penicillin is a conductor, albeit a very poor one, it should be possible to demonstrate ionic movement by suitable *in vitro* experiments; even if this can be done the movement will be relatively slow, and it is doubtful whether a therapeutic concentration could ever be obtained in the tissues. Again, all tissue fluids contain sodium chloride, and, as has been shown *in vitro*, the products of electrolysis of this salt are highly lethal to penicillin; naturally free chlorine and sodium hydroxide are not formed in the tissues during electrolysis, and at the moment one cannot

say whether the experimental results *in vitro*, in this respect, are applicable to *in vivo* methods.

High concentrations of penicillin were not used in the experiments because they would have had to be grossly diluted in order to estimate the amounts present. This dilution would have introduced unnecessary errors into the estimations.

Summary

Penicillin is either a non-conductor or a very poor conductor (Experiment 1).

It has been impossible, in the conditions described, to demonstrate any movement of penicillin under the influence of an electric current (Experiments 4 and 6).

The presence of the products of electrolysis of sodium chloride in the *in vitro* experiments led to the rapid destruction of penicillin. It is not known how far this observation can be applied to *in vivo* methods.

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DIFFERENCE IN THE EFFECT OF SCOPOLAMINE ON PERORAL AND SUBCUTANEOUS ADMINISTRATION

BY

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Particular circumstances brought it about that in my department (dermatology) we had occasion to carry out a series of systematic studies on the effect of scopolamine given by mouth in doses of 3–4 mg.—i.e., 6 to 8 times the Danish maximal dose (0.5 mg.)—and to compare it with the effect of 0.5 mg. given subcutaneously.

Effect of 3–4 mg. Given by Mouth

One of my patients, a nurse admitted for a severe *x*-ray burn, had some time before been sentenced to prison for an attempt to poison her matron, being accused of having poured some scopolamine in her coffee. The sentence aroused an enormous sensation in Denmark, and many persons offered voluntarily to act as experimental subjects in order to try out the effect of scopolamine given in moderately increased doses by mouth (3–4 mg.). This was the amount of scopolamine with which the attempt at poisoning was claimed to have been made. An experiment with the peroral administration of 10–15 mg. to the sentenced woman had given merely moderate, not serious, symptoms of the well-known type, and hence further experiments were to be looked upon as safe. In the literature no instance of death from ingestion of scopolamine has been reported—not even with doses as high as 500 mg. and 300 mg.

The 30 persons employed for these experiments were chiefly nurses, aged from 30 to 69.* In the majority of the subjects the only conspicuous symptom was a moderate dryness of the mucous membranes, accompanied by some drowsiness. The development and intensity of the symptoms may be recorded summarily as follows. In no instance was a stronger effect observed.

1. *Heart Action.*—After 15 to 30 minutes a moderate fall in the pulse rate appeared, often accompanied by a minor rise in the rate of respiration.

2. *Mucous Membranes.*—After 30 to 40 minutes a distinct dryness of the mucous membranes of the mouth and throat was noticed.

3. *Muscles.*—A little later a moderate laxity of the muscles was observed. Convulsions or rigidity were not seen in any instance. A couple of subjects stated, however, that they had some slight jerky sensations in the legs.

4. *Pupils.*—Dilatation of the pupils is said to be the most characteristic symptom of scopolamine action, and hence the subjects were examined very closely for the appearance of this symptom at intervals of 15 minutes. In 19 cases no distinct dilatation could be demonstrated; in 3 cases only, this phenomenon reached a considerable size (7.5 mm.)—after about two hours—and was accompanied by lowered reaction to light. The dilatation of the pupils subsided but slowly.

5. *Sensorium.*—The action on the sensorium was limited to a slight drowsiness in some subjects. The two oldest, aged 69 and 65, presented a slight degree of excitation, with loquacity and giddiness, resembling that seen in moderate alcoholic intoxication.

6. *After-effects.*—Most of the subjects noticed no after-effect at all and slept well during the following night. A few felt a little tired next day, and two noticed a slight dryness of the throat. On the following day a moderate dilatation of the pupils could still be demonstrated in a few of the subjects examined.

After this experiment 4 additional persons were given 4 mg. of scopolamine by mouth. The symptoms were not particularly more pronounced than in the preceding group.

Peroral and Subcutaneous Methods Compared

It was most interesting to compare the features of intoxication here observed when the same subjects were given a subcutaneous injection of 0.5 mg. of scopolamine. In this way it became practicable to settle the question about the proportional effect of scopolamine given perorally and subcutaneously. These experiments were carried out on 14 persons. Only two of them showed an effect of scopolamine identical with that observed after ingestion of 3 mg., perhaps even a little weaker. In the remaining 10 subjects the effect was distinctly stronger after injection of the remedy, in most of the cases even considerably stronger, and it appeared more rapidly too, showing the following picture:

1. The pulse rate and the frequency of respiration were not influenced much more strongly here, but the effect appeared sooner.

2. The dryness of the mucous membranes was noticeably more pronounced, in several cases even much more pronounced—so that, for instance, the subject could not swallow a biscuit without intake of water.

3. Also the effect on the musculature was greater here, and in several subjects it was so marked that it was difficult for them to keep on their feet.

4. Dilatation of the pupil was quite distinct in 8 of the 10 subjects, and impairment of the reactivity of the pupil was demonstrable in 7 cases, considerable in 2.

5. Drowsiness and sleepiness appeared in nearly all the subjects, often accompanied by an inconveniencing dizziness. Symptoms of excitation and confusion were observed in 4 subjects. As mentioned already, the character of this symptom was that of a "drunk." A couple of subjects had slight hallucinations. The symptoms of excitation always made their appearance rather late—at the earliest after two hours.

6. Also the after-effects were decidedly stronger after subcutaneous injection than after ingestion.

Later two of the nurses who had been given 4 mg. of scopolamine by mouth were submitted to an additional test for the effect of 0.5 mg. of the remedy injected subcutaneously. The effect here was about the same as that observed in the 12 subjects first examined.

If we wish to give a numerical expression for the decrease in the effect when scopolamine is given per os instead of subcutaneously, it is obvious that on an average the effect then is at least 6 times weaker, or rather, perhaps, 8 times weaker.

Conclusion and Summary

The effect of 3 or 4 mg. of scopolamine given by mouth to 34 healthy adult subjects was generally rather weak—much weaker than would be expected *a priori* according to the doses officially established as maximal for peroral administration. In a majority of the subjects the effect has to be characterized as insignificant, as chiefly it was limited to a slight dryness of the mucous membranes of the mouth and throat.

A comparative study was made of the variation in the effect of scopolamine when given subcutaneously and per os to 14 of the same persons. The doses here employed were 0.5 mg. given subcutaneously and 3 mg. (in two cases 4 mg.) given by mouth. In 12 cases the effect of 0.5 mg. injected subcutaneously was stronger—in several cases decidedly stronger—than that of 3 or 4 mg. given by mouth. In only two cases was the effect of 3 mg. perorally equal to or perhaps a little stronger than that of 0.5 mg. given subcutaneously.

Judging from these results the efficacy of the drug given by mouth may be reckoned on an average to be about one-eighth of its efficacy when injected subcutaneously.

* For further details see *Nordisk Med.*, 1944, **20**, 793.