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 SUB- CUTANEOUS 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 50 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 consider-

able 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.

Its low toxicity when given per os calls for a revision of the maximum dose of scopolamine—and probably of some other alkaloids too—as fixed by the official pharmacopoeias.

In forensic medicine the consequence will be that no injury can be expected from a dose of 3 to 4 mg. of scopolamine given by mouth. (It was only after 8 years that the nurse was taken before a higher court and, on the basis of this investigation, rehabilitated.)

In all the experimental subjects here employed the symptoms characteristic of scopolamine effects were observed to make their appearance in the same chronological sequence: (1) After 15 to 30 minutes, reduction in the rates of the pulse and respiration. (2) After 30 to 45 minutes, dryness of the mucous membranes of the mouth, nose, and throat; a little later, moderate muscular atony and moderate drowsiness. (3) Pronounced dilatation of the pupils was seen only in a minority of the cases—generally beginning after 60 minutes and reaching its maximum after 120 minutes. (4) Symptoms of excitation were seen in a few cases, especially elderly persons, but not until 120 minutes after ingestion of the drug.

After subcutaneous injections of 0.5 mg. the sequence of the symptoms was the same as after peroral administration, but their development was somewhat more rapid and their intensity more pronounced.

CARCINOMA OF THE RECTUM IN SISTERS

BY

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Multiple polyposis of the colon in siblings was first described by Cripps (1882), and Doering (1907) first noted the frequency of malignant change in the condition. The condition is rare, since, although Stewart (quoted by Sawyer, 1940) found polypi in 4% of children, very few of these were multiple. Statements as to the frequency of malignant change vary. In Doering's original series there were 21 carcinomas in 40 cases of polyposis, Sawyer (1940) found malignant change in 40% of cases in a review of several series, while Friedell and Wakefield (1943) found only two carcinomas out of 19 cases. Many of the last series, however, were in children, and would not have been diagnosed without a special search. Genetically determined polyposis may not arise until middle life (Lockhart-Mummery, 1925), and seems to appear earlier in successive generations of the same family (Friedell and Wakefield, 1943). The earlier literature is reviewed by Dukes (1930).

Recently I have observed the following two cases of carcinoma of the rectum in young sisters. One had multiple polyposis of the colon and the other multiple telangiectases. Carcinoma of the rectum in siblings of this age is so rare that one must conclude that there is some connexion between the three conditions. The father of the sisters was killed in 1917, and they were his only children. Their mother is alive, and has three children by a second husband. The eldest of these is 25; all are well, and none have ever had any bowel troubles.

Case Histories

Case 1.—Edith was mentally defective, though she earned her living as a domestic servant. From the age of 4 she was cared for by nuns, who noticed nothing wrong with her bowels. Before this she is said to have had "tuberculous bowels," but her mother can give no grounds for this statement. At the age of 29 she was admitted to hospital with a very vague history of diarrhoea and passage of blood per rectum, was *in extremis*, and died a few days later. At necropsy the body was that of a poorly developed young woman, with foul teeth and many sebaceous cysts of the scalp. There was extensive bronchopneumonia, and a malignant ulcer at the pelvi-rectal junction with metastases in the para-aortic lymph nodes and in the liver. There were many polyps throughout the colon. The intervening mucosa appeared quite normal.

Case 2.—Maud, aged 32, was the sister of Edith. She presented herself at an antenatal clinic, pregnant for the first time, and gave no history of any upset of the bowels. However, a carcinoma of the rectum was discovered, and hysterectomy and colostomy were performed. She died seven months later. At necropsy a mass of growth filled the pelvis, and there were metastases in all the abdominal lymph nodes, the liver, and the peritoneum. Below the hepatic flexure the colon showed numerous minute bright-red telangiectases, each about 2 mm.

across, and separated from the next one by 2 cm. of normal mucosa. The rectum was buried completely in the mass of growth, and the exact origin of the tumour could not be determined.

Comment

From the last Census it appears that there were 3,353,100 women alive at that time between the ages of 25 and 35. In the same year 23 women in the same age group died of carcinoma of the rectum (Registrar-General's Annual Report, 1931). On any system of probability it is extremely unlikely that sisters will die of the same condition which has a death rate of only 2.3 out of a population of some 335,000. There would appear, therefore, to be statistical support for the contention that the conditions found in these women's colons were in some way connected and were also responsible for the development of their carcinomas.

I have to thank Mr. G. F. Stebbing and the Chief Medical Officer of the London County Council for permission to publish the second case, and for the kind invitation to perform the necropsy in Lambeth Hospital, where that patient died.

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Medical Memoranda

Jejunal Diverticulosis Complicated by Haemorrhage

The following case may be considered unusual enough to merit publication.

CASE HISTORY

A man aged 73 was admitted to hospital on May 26, 1945, with a history of severe rectal haemorrhage for 24 hours. The onset was sudden and painless, the blood being dark at first but bright in colour later. He had had no previous attacks and had been in perfect health until three months previously, when he had developed pain in the upper abdomen two to three hours after meals, anorexia, flatulence, and slight loss of weight.

On admission he showed all the signs and symptoms associated with severe haemorrhage; the blood pressure was 80/50 and the haemoglobin 52%. A transfusion of 3 pints (1.7 l.) of blood was given. After passing several melaena stools his condition settled down. The following investigations were carried out: (1) A test meal showed complete achlorhydria. (2) A barium meal revealed a hypotonic but otherwise normal stomach; the diverticula were not visible, but there was slight delay and partial obstruction in the upper jejunal coils. (3) A barium enema showed diverticulosis of the descending and the pelvic colon.

A laparotomy was performed on June 26. Eight diverticula were found in a segment of 14 in. (35.5 cm.) of the proximal jejunum, the first one being situated 4 in. (10 cm.) from the duodeno-jejunal flexure. The largest of these was 1½ in. (3.8 cm.) in diameter and contained a stony-hard and sharp concretion; the diverticulum stood out from the others and was discoloured, while the surrounding mesentery was congested. The rest of the intestinal tract was carefully examined and no further abnormality was found other than diverticulosis of the colon, seen in the skiagram. Resection of the affected loop with an end-to-end anastomosis was performed. A post-operative glucose-saline drip was set up and continuous gastric suction maintained for five days. The patient was discharged from the hospital on Aug. 8, and has been perfectly well since.

DISCUSSION

Diverticulosis of the jejunum is a relatively rare condition, though it is possible that many cases are overlooked, as they are often symptomless and may be difficult to demonstrate at necropsy. By insufflating the intestine *in situ* Rosedale and Lawrence (1936) found 4 cases in 300 consecutive necropsies. The diverticula are of the mucous-membrane-hernia type, similar to those found in the duodenum and colon. They may be single or multiple, as many as 400 having been present in a single case. The upper coils of the jejunum are affected most commonly, but the diverticula may extend on to the ileum. They occur along the mesenteric border where the main arteries pierce the muscular coats, and they push their way between the layers of the mesentery.

The first description appears to have been made in 1807 by Sir Astley Cooper, who found numerous pouches of the jejunum at a post-mortem examination on a man of 65. The aetiology