cases were untraced is a great disappointment. We hope that they were their best cases, but are we justified in drawing that conclusion ? It may cost a considerable sum per patient to secure information about these 49 cases, but it is more than worth while. Perhaps in sending out letters and trying to secure replies we should call to the attention of these young people that when they ask us to recommend them for jobs we cannot do so unless we know how they are getting along.

I am more sympathetic in completing follow-ups this year than heretofore. At the beginning of 1949 we had 2,145 known subjects living who had been diabetic from childhood. By September 1,258 had been traced. Despite our first, second, and third letters, 2,365 in all, there still remained 50 untraced, but I believe it is only fair to these people and to all of us doctors to learn whether the treatment recommended has been good or bad and to discover whether it could be improved. (By April 1 of this year there were eight untraced.)

Apollinaire Bouchardat, who was born in 1806 and died in 1886, was the first doctor to give hope to the diabetic. He prescribed a palatable diet, taught diabetics, even before Fehling's test was printed, to examine the urine after they ate and thus find out whether a food was beneficial or not. He urged them to take exercise and demonstrated its advantages. Yet Bouchardat (1883), in offering hope for the diabetics, qualified his statement so as not to include children, and wrote that he had never seen a pregnant diabetic woman and, indeed, hardly gives us a hint that he recognized diabetic coma. But he laid the foundation for the treatment we are practising to-day. How pleased he would be to see the advances made, and I can imagine he would agree with me that the next fifty years hold more of promise than the last.

REFERENCES

Barach, J. H. (1949). *Diabetes and Its Treatment*, p. 150. Oxford Univ. Press, New York.

Bouchardat, A. (1883). *De la Glycosurie*, 2nd ed. Germer Baillière, Paris.

Duncan, G. G., Carey, L. S., and Hudson, M. T. (1949). *Med. Clin. N. Amer.*, **33**, 1537.

Fanconi, G., Botsztejn, A., and Kousmine, C. (1948). *Helv. paed. Acta*, **3**, 341.

McKittrick, L. S., McKittrick, J. B., and Risley, T. S. (1949). *Ann. Surg.*, **130**, 826.

Root, H. F. (1949). *Amer. J. med. Sci.*, **217**, 545.

Shepardson, H. C. (1930). *Arch. intern. Med.*, **45**, 674.

White, P. (1949). *Amer. J. Med.*, **7**, 609.

Wilder, R. M., jun. (1949). Ibid., **7**, 625.

A special uniform is being produced by the Ministry of Health for the trained women members of the National Hospital Service Reserve to wear when on duty in hospital. The uniform is of white drill, and different coloured epaulettes and belts will be worn—dark blue for a State-registered nurse, maroon for a State-certificated midwife, green for a State-enrolled assistant nurse, and white for a nursing assistant class 1. The State-registered nurses and midwives will wear caps of the veil type, and the State-enrolled assistant nurses and nursing assistants class 1 will have white close-fitting caps with a turned-up brim in front. Male trained members will wear coloured epaulettes on the white coats provided by the hospitals. The Reserve also includes a section for auxiliary members, whose training is undertaken by the St. John Ambulance Brigade and British Red Cross Society. They wear the indoor uniform of these organizations while taking hospital training or refresher courses. The Reserve is open to women aged between 17½ and 60 and to men between 30 and 60. There are already over 200 trained members and 2,300 auxiliary members in England and Wales.

PROCAINE PENICILLIN: CHOICE OF PREPARATION

BY

R. W. FAIRBROTHER, M.D., D.Sc., F.R.C.P.
Director

AND

K. S. DABER, M.B., Ch.B.
Registrar

Department of Clinical Pathology, Manchester Royal Infirmary

The production of depot or repository preparations has been an important development in penicillin therapy. In view of the rapid excretion of penicillin after the injection of aqueous solutions, the usual method of administration has been by injection at frequent intervals. This is a tedious procedure, causing much discomfort to the patient and a heavy strain on the nursing and medical staff.

Many attempts have been made to overcome these objections. These have involved quite different principles : one scheme is to give large doses (up to 500,000 units) of aqueous penicillin at intervals of 8–24 hours ; another is to delay the renal excretion of penicillin by means of *p*-aminohippuric acid or caronamide ; a third scheme is to delay the absorption of penicillin from the tissues by means of depot or repository preparations. The last method has been mainly adopted in this country for prolonging the blood levels.

The original depot products contained a mixture of beeswax (4–5%) and arachis oil ; with doses containing 300,000 units of penicillin, effective blood levels could be maintained for 8–12 hours. These preparations, being very viscous, were not only difficult to inject but also tended to produce local pain and discomfort. In view of these serious objections the production of procaine penicillin was an important advance (Salivar, Hedger, and Brown, 1948). This preparation is an equimolecular combination of crystalline penicillin G and procaine hydrochloride ; it is a relatively insoluble compound and was originally suspended in arachis oil. Procaine penicillin causes little pain and is easier to inject than the beeswax products ; with the standard dose of 300,000 units, effective blood levels are maintained for 18–24 hours (Jones and Shooter, 1948). It was later found that the effect could be further prolonged by incorporating 2% (w/v) aluminium monostearate in the oily procaine penicillin (Buckwalter and Dickison, 1948) ; Boger and Flippin (1949) claimed that, after an injection of 300,000 units, effective blood levels were present for 4–6 days.

Young *et al.* (1949) tested various procaine penicillin preparations and considered that the monostearate product was superior to the watery or oily preparations for delaying absorption ; they considered that the particle size of the penicillin crystals should not be too large (5–20 μ), and recommended that for the treatment of severe infections the procaine preparation should be combined with a soluble salt of penicillin. Emery *et al.* (1949), using a monostearate preparation with a particle size of 5 μ, obtained satisfactory levels in children for 24–48 hours, but experienced some difficulty in administration owing to the oily nature of the preparation. Wayne *et al.* (1949) confirmed these results, and found that by increasing the dose to 600,000 units assayable blood levels were often obtained after 72 hours.

There is no doubt that procaine penicillin with aluminium monostearate is superior to previous preparations in its capacity to prolong the blood levels, but two important

objections have been made—namely, difficulty in administration owing to viscosity, and, secondly, its unsuitability for the treatment of severe infections owing to the relatively low blood levels attained.

The value of aqueous suspensions of procaine penicillin and reinforced monostearate preparations has consequently been investigated and the results are now reported.

Technique

The various penicillin preparations were given intramuscularly and samples of venous blood were collected at stated intervals. The serum was separated without delay and stored in the refrigerator until required for assay.

The penicillin assay was carried out by the serial dilution method. The dilutions were made in sterile tubes (3 by ⅛ in. : 7.6 by 1 cm.) containing glucose broth which were seeded with a standard drop of an 18-hour culture of the "Oxford" *Staph. pyogenes*; readings were made after 18 hours' incubation at 37° C. and compared with a control series containing known amounts of a standard penicillin (Brindle *et al.*, 1947).

Results

Two different types of preparation, with a particle size of 20 μ or less, were subjected to investigation, the main object of which was to determine the blood levels produced by a standard injection of 1 ml.

The preparations were :—Type A : procaine penicillin (300,000 units) in arachis oil with 2% (w/v) aluminium monostearate, plus crystalline potassium penicillin G (100,000 units) in 1 ml. Type B : aqueous procaine penicillin (300,000 and 400,000 units per ml.).

Type A.—The reinforced product (monostearate procaine penicillin plus crystalline penicillin) contained in 1 ml. a total of 400,000 units of penicillin. The standard dosage of 1 ml. was given to 31 adults, the majority of whom were post-operative cases; in no instance was there any apparent impairment of renal function. A total of 116 estimations were made at times varying from half an hour to 48 hours (Fig. 1).

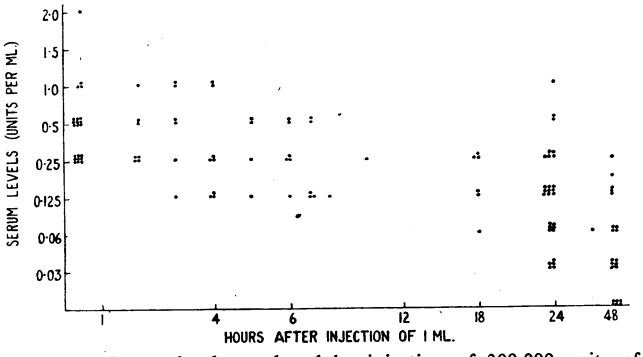

FIG. 1.—Serum levels produced by injection of 300,000 units of procaine penicillin + 2% aluminium monostearate + 100,000 units of potassium penicillin G per ml.

Consistently high levels were obtained throughout the 24-hour period. The immediate response was good, although marked individual variation was shown : during the first hour the readings covered a range of 0.25–2 units per ml., with an average of approximately 0.5 unit per ml. These figures were maintained for several hours and then fell gradually to an average of 0.14 u./ml. at 24 hours, when 28 out of 28 gave an effective level (0.03 u./ml. or greater); after 48 hours 15 out of 21 gave assayable levels. The levels during the initial 4–6 hours were consistently higher than those produced by the same amount of the ordinary monostearate procaine penicillin.

The administration of the preparation presented a slight problem, particularly in cold weather, owing to its viscosity; this was usually overcome by gently warming the bottle and using a 19 S.W.G. needle.

Six patients, some with minor staphylococcal infections, received daily injections of 1 ml. for 4–5 days with satisfactory clinical results. Readings were made at the end of each 24-hour period immediately before the injection of the next dose of penicillin. The results are shown in the Table, together with comparable figures given by the other preparations. Average levels of at least 0.15 u./ml. were maintained throughout.

Table Showing Average Readings with One Daily Dose

Preparation	No. of Patients	Serum Penicillin Concn. (u./ml.) at End of			
		24 Hours	48 Hours	72 Hours	96 Hours
Procaine penicillin, 300,000 units, in arachis oil with 2% w/v aluminium monostearate + potassium penicillin G 100,000 units ..	6	0·156	0·25	0·225	0·375
Aqueous procaine penicillin (300,000 units)	6	0·13	0·219	0·203	0·265
Aqueous procaine penicillin (400,000 units)	11	0·259	0·18	0·205	0·48

Type B.—Two distinct types of aqueous procaine penicillin were subjected to trial : (1) powdered procaine penicillin to which an aqueous diluent is added immediately before use, and (2) a stable suspension containing procaine penicillin in a finely divided state, dispersed by means of wetting and suspending agents. Strictly comparable results were given by both preparations, and therefore the results have been combined in the charts. Two strengths (300,000 u./ml. and 400,000 u./ml.) were investigated, using a standard dose of 1 ml. The particle size was small (20 μ or less), and no difficulty in administration was experienced using a 19 S.W.G. needle.

(*a*) 300,000 units of aqueous procaine penicillin were given to 49 individuals, 29 receiving the freshly prepared suspension and 20 the stable preparation; 111 assays were made at intervals of ½–48 hours (Fig. 2). Relatively high levels (0.25–1 u./ml.) were obtained within ½–1 hour and then maintained for 12–18

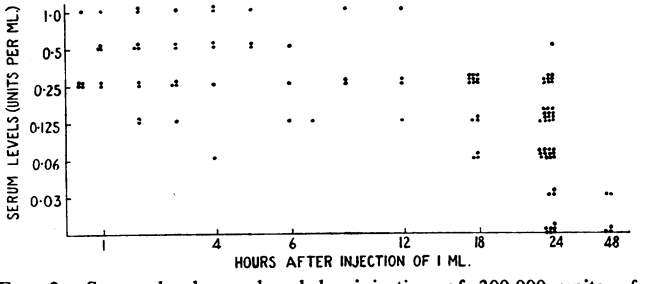

FIG. 2.—Serum levels produced by injection of 300,000 units of aqueous procaine penicillin.

hours. At 24 hours, while the majority gave therapeutic levels, assayable levels were not obtained in 7 out of 44. Six patients received daily injections of 1 ml. for 2–4 days, and readings were taken at the end of each 24-hour period; effective levels were maintained throughout (see Table).

(*b*) The failure of 300,000 units of aqueous procaine penicillin to produce a satisfactory level in all cases at the end of 24 hours confirms previous reports (Whittlesey and Hewitt, 1948; Young *et al.*, 1949). While it has been the general experience that 600,000 units in a dose of 2 ml. give demonstrable levels for at least 24 hours, it was considered that a total dosage of 1 ml. offers definite advantages.

A stable preparation containing 400,000 units of procaine penicillin in 1 ml. was consequently prepared and subjected

to trial; 82 readings at various intervals were obtained from 47 subjects (Fig. 3).

Effective levels were given throughout the 24-hour period; at 24 hours 40 out of 40 gave readings varying between 0.03 and 1 u./ml., with an average of 0.17 u./ml.

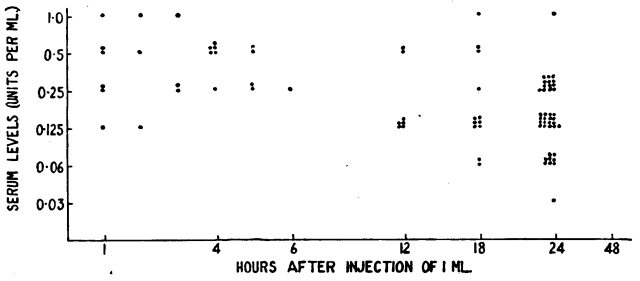

FIG. 3.—Serum levels after injection of 400,000 units of aqueous procaine penicillin.

Eleven patients, five having minor staphylococcal infections, were given 1 ml. daily for 3–4 days (see Table). Effective blood levels were maintained, while the therapeutic response was good in the limited number of cases available for clinical trial.

Discussion

A definite change is taking place in the schedule of penicillin dosage. The original conception of regular doses at frequent intervals is rapidly losing favour: the clinical results are undoubtedly good, but the procedure is tedious and time-consuming, and is often the cause of much discomfort and inconvenience to the patient. The present tendency is to administer large doses at infrequent intervals in the form of either aqueous crystalline penicillin or some repository preparation. The principle governing the use of crystalline penicillin solutions is the intermittent production of high blood levels having a marked bactericidal activity. The object with depot preparations is to maintain an effective blood level throughout the course of treatment. Striking clinical results have been claimed for both forms of preparation (Boger and Flippin, 1949; Griffiths *et al.*, 1949; Tompsett *et al.*, 1949; Weiss and Steinberg, 1949).

The choice of repository preparation is mainly dependent on three important properties—ease of administration, stability, and capacity to sustain the blood levels.

The readiness with which the suspension can be drawn into the syringe through the usual range of needles and then injected into the patient depends on the particle size and viscosity of the suspension. A particle size of 20 μ or less can be readily manipulated, and if such suspensions are shaken vigorously before use clogging of the needle does not occur. Viscosity has proved a serious handicap, which was especially noticeable in the beeswax products. The oily procaine preparations have greater mobility than the beeswax preparations, but nevertheless during cold weather some difficulty in administration is experienced. In consequence the aqueous suspensions have certain advantages for routine use, particularly in general practice.

Stability is another factor worthy of consideration. Products which remain potent for a limited period are wasteful and tend to have a restricted field of application. They are suitable for big clinics but not for the treatment of individual cases. Stable aqueous suspensions of procaine penicillin seem to be of greater practical value than the powdered form requiring the addition of an aqueous diluent before use, as the preliminary manipulation is an unnecessary inconvenience and the potency of the latter product is retained for only a short period.

The penicillin level in the blood is accepted as a convenient index of therapeutic value, and the minimum effective level for sensitive organisms is generally considered to be 0.03–0.06 u. per ml. It is, however, important to appreciate that these are not absolute values. In assessing the significance of blood levels several factors must be considered; these include the severity of the infection, the sensitivity and accessibility of the invading organism, and the nature of the lesion. The levels in the tissues of an acute inflammatory exudate will be much higher than those found in a relatively avascular focus of infection.

There is evidence to indicate that very high concentrations of penicillin may not be desirable. Eagle and Musselman (1948), by *in vitro* tests, demonstrated that the maximum bactericidal effect on *Staph. pyogenes* was obtained by a concentration of about 0.1 u. per ml.; in the experiments, however, organisms constant in number were tested under optimal conditions for penicillin activity. Eagle (1948) suggested that the activity of a given dosage of penicillin is mainly dependent on the time a maximal bactericidal level is maintained: when large doses of aqueous penicillin are given at infrequent intervals much of the penicillin is probably wasted and the interval between doses might be long enough to allow the surviving bacteria to multiply. It is known, however, that the bacteriostatic effect of penicillin persists for some time after the removal of the drug, and also that penicillin tends to persist longer at the site of an inflammatory reaction than in the blood stream, although the local level may not equal the highest found in the blood (Ungar, 1950). It would appear that, while an effective blood level need not always be present, the time when this falls below the therapeutic level should be short.

The results of this trial indicate that both types of preparation fulfil most of the above requirements. The blood levels have not reached the height obtainable with aqueous solutions of crystalline penicillin, but they have tended to remain well above the accepted minimal effective levels. In fact, the levels compare quite favourably with those produced by the old standard form of therapy—i.e., 20,000 units three-hourly (Fig. 4). This dosage schedule has given

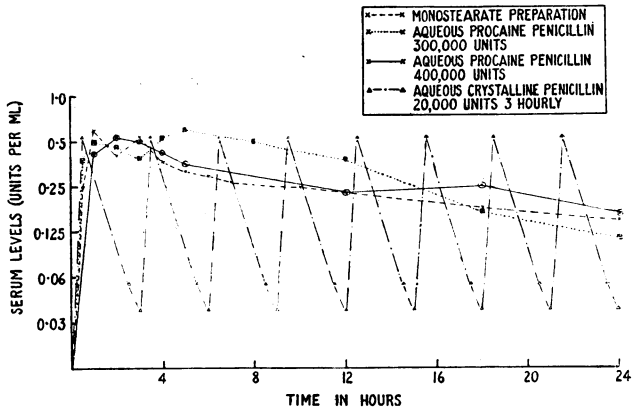

FIG. 4.—Average serum levels over a 24-hour period after a dose of 1 ml. of procaine penicillin, compared with levels given by 20,000 units of aqueous penicillin three-hourly.

excellent results over a period of many years in a wide variety of clinical conditions. A clinical trial has not here been attempted, but the small series of minor infections treated with these depot products have responded well. It does therefore seem reasonable to suggest that these depot preparations have a place in routine therapy. In the case of severe or fulminating infections the initial doses of the

depot preparation may require reinforcement with the crystalline penicillin, but subsequent daily dosage with the depot product should prove adequate.

The development of procaine penicillin has been rapid, and many preparations are now available. There is no doubt that the reinforced monóstearate preparation gives the greatest prolongation of effect in combination with relatively high initial blood levels. It is, however, an oily preparation which presents some difficulty in administration, particularly in cold weather; this is a serious disadvantage for routine use in general practice. It is nevertheless a valuable preparation which should be very useful when it is desirable to give the injection at longer intervals than 24 hours. Considerable prolongation of the blood levels can be achieved by increasing the dosage of the monostearate preparations; but such injections tend to produce local discomfort, and difficulty in administration may be experienced (Peacock and Gillespie, 1950).

The aqueous preparation (400,000 u./ml.) has proved a satisfactory product for daily administration. It is stable, and if well shaken can be injected without difficulty. In this trial effective levels have been consistently maintained in adults for 24 hours after the injection of 1 ml. This should be a convenient preparation for general use.

It is interesting to note that throughout this investigation no instance of hypersensitiveness to the procaine was observed, and that, apart from the initial prick, no local discomfort was reported.

Summary

Blood levels have been estimated in adults after the intramuscular injection of 1 ml. of various procaine penicillin preparations.

With procaine penicillin (300,000 units) in arachis oil with 2% aluminium monostearate plus crystalline potassium penicillin G (100,000 units), effective levels were maintained for the 24-hour period in 28 out of 28 individuals (15 out of 21 gave assayable levels after 48 hours), but some difficulty in administration was experienced.

Aqueous procaine penicillin (300,000 units per ml.) is a convenient preparation, but assayable levels were not produced in 7 out of 44 subjects after 24 hours.

A stable aqueous procaine penicillin suspension (400,000 u./ml.) proved a satisfactory product. It was injected without difficulty and gave satisfactory levels for a 24-hour period in 40 out of 40 cases. This preparation should prove particularly valuable in general practice.

The various preparations of procaine penicillin were kindly supplied by Imperial Chemical (Pharmaceuticals), Ltd., Manchester.

REFERENCES

Boger, W. P., and Flippin, H. F. (1949). *J. Amer. med. Ass.*, **139**, 1131.

Brindle, H., Fairbrother, R. W., and Jackson, F. B. (1947). *Lancet*, **2**, 505.

Buckwalter, F. H., and Dickison, H. L. (1948). *J. Amer. pharm. Ass.*, **37**, 472.

Eagle, H. (1948). *Ann. intern. Med.*, **28**, 260.

—— and Musselman, A. D. (1948). *J. exp. Med.*, **88**, 99.

Emery, J. L., Rose, L. M., Stewart, S. M., and Wayne, E. J. (1949). *British Medical Journal*, **1**, 1110.

Griffiths, E., Jones, P. F., Shooter, R. A., and Heady, J. A. (1949). Ibid., **2**, 958.

Jones, P. F., and Shooter, R. A. (1948). Ibid., **2**, 933.

Peacock, J. H., and Gillespie, W. A. (1950). *Lancet*, **1**, 495.

Salivar, C. J., Hedger, F. H., and Brown, E. V. (1948). *J. Amer. chem. Soc.*, **70**, 1287.

Tompsett, R., Timpanelli, A., Goldstein, O., and McDermott, W. (1949). *J. Amer. med. Ass.*, **139**, 555.

Ungar, J. (1950). *Lancet*, **1**, 56.

Wayne, E. J., Colquhoun, J., and Burke, J. (1949). *British Medical Journal*, **2**, 1319.

Weiss, W., and Steinberg, I. (1949). *Amer. J. med. Sci.*, **217**, 86.

Whittlesey, P., and Hewitt, W. L. (1948). *Proc. Soc. exp. Biol., N.Y.*, **68**, 658.

Young, M. Y., Andrews, G. W. S., and Montgomery, D. M. (1949). *Lancet*, **1**, 863.

FOOD AND MANKIND*

BY

JOHN YUDKIN, M.D., Ph.D., M.R.C.P., F.R.I.C.

Professor of Physiology, University of London

Malnutrition, famine, starvation, have been man's lot since the beginning of his existence. The drive of industrialization which a century ago was expected automatically to fill his life—and his belly—with all his needs has instead been found only to raise quite other problems. Yet in the last decade man's conscience has more and more been awakened to the belief that, with the potential riches at his disposal, the problems of feeding himself and his world family could be solved. These problems may be put in this way: (1) Can the earth produce enough food for its inhabitants? (2) Can the food be equitably distributed among the countries according to their population? (3) Can the food be equitably distributed among the population of each country according to their individual requirements?

World Food Production

Before the war there were indications that the world was already producing too much food. Some of the chief food-producing countries were adopting restrictive practices, such as limiting the areas to be planted with grain or pouring away thousands of gallons of milk. Yet side by side with this were the ever-recurring famines in countries such as India and China, with, in the intervening years, stunted growth, ill-health, pestilence, and misery, affecting more than a third of the world's inhabitants. Those whose conscience was disturbed when they thought of the masses who hungered while food was destroyed began to speak of "poverty in the midst of plenty." It is certainly true that millions might have been fed, and hundreds of thousands might have lived who otherwise starved to death, if the distribution of food could have been better organized. But was there in fact plenty? The answer is most emphatically "No."

With our present nutritional knowledge we can make reasonably intelligent estimates of the amount of food required properly to feed the whole of mankind (Fig. 1). For practical purposes we can say that an increase of food of something like twofold is needed in order adequately to feed humanity. For such an increase to be possible three separate problems must be tackled. First, it is necessary to prevent the wastage and loss of food after it has been produced. Secondly, since by far the greater part of our food comes from the soil, it is necessary to prevent the erosion which is occurring in alarming degrees over most of the world's surface. Thirdly, it is necessary to improve the techniques at our disposal to achieve greater yields of food (Fig. 2).

How much food is lost by pests, infestation, and disease we do not know. One authoritative estimate is that about one-fifth of the total grain is destroyed each year—an amount which would be enough to feed 300 million people. Here is certainly a field for energetic investigation and action. The second problem of increasing food production is that concerned with the loss of good soil. We have only to look at the once fertile fields of Greece, North Africa, and Palestine to realize the devastating results of soil erosion. And a farmer from the Middle West United

*Based on a Public Lecture delivered on November 24, 1949, at King's College of Household and Social Science, University of London.