Q-T interval was markedly reduced. I am indebted to Dr. Bunjé, lecturer in medicine, for reports on these.

The post-operative condition of the majority of patients was satisfactory, but they tended to lie still for prolonged periods and required careful watching to ensure a clear airway. Recovery is not so rapid as after nitrous oxide and pethidine, but less sedatives are required post-operatively.

Summary

Chlorpromazine has been used before and during induction of anaesthesia in 150 serious-risk patients in a tropical hospital with a view to reducing the incidence of sudden alterations in blood pressure due to over-sensitive autonomic reflexes occurring during major operations. It was not found possible to obtain figures which would show an obvious improvement over the standard technique using nitrous oxide and pethidine, and premedication with the opium alkaloids and scopolamine. Nevertheless, the drug is still being used, especially as a premedication before chest surgery. Overdosage is associated with hypotension and responds readily to a L-noradrenaline (levophed) infusion.

I am indebted to Messrs. May and Baker for initial supplies of largactil.

REFERENCES

- Almy, T. P., and Laragh, J. H. (1949). *Amer. J. Med.*, **6**, 507.
 Barlow, M. B., Ginsberg, H., and Gottlich, J. (1953). *S. Afr. med. J.*, **27**, 242.
 Best, W. R., Muehrcke, R. C., and Kark, R. M. (1952). *J. clin. Invest.*, **31**, 733.
 Calesnick, B., Smith, N. H., and Beutrer, R. (1951). *J. Pharmacol.*, **102**, 138.
 Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M., and Koetschet, P. (1953). *Arch. int. Pharmacodyn.*, **92**, 305.
 Dawes, G. S., and Comroe, J. H., jun. (1954). *Physiol. Rev.*, **34**, 167.
 Dougherty, T. F., and White, A. (1944). *Endocrinology*, **35**, 1.
 Finkelstein, M., Spencer, W. A., Hammer, C. S., and Alberst, S. N. (1954). *Fed. Proc.*, **13**, 354.
 Goldstein, M. S., et al. (1952). *Amer. J. Physiol.*, **171**, 92.
 Hills, A. G., Forsham, P. H., and Finch, C. A. (1948). *Blood*, **3**, 755.
 Keating, V. J., and Hill, K. (1955). In preparation.
 Laborit, H. (1954). *Int. Rec. Med.*, **167**, 315.
 Meltzer, L. (1947). Thesis, University of the Witwatersrand. Quoted by Barlow (1953).
 Melville, K. I. (1954). *Fed. Proc.*, **13**, 386.
 Meyer, R. J. (1953). *J. clin. Endocr.*, **13**, 123.
 Mosinger, M. (1952). *Médecine et chirurgie pathogéniques—cancer*. Masson, Paris.
 Roche, M., Hills, A. G., and Thorn, G. W. (1949). *J. clin. Endocr.*, **9**, 662.
 Sawyer, C. H., and Parkerson, G. R., jun. (1953). *Endocrinology*, **52**, 346.
 Swingle, W. W., et al. (1938). *Amer. J. Physiol.*, **123**, 659.
 Thorn, G. W., et al. (1948). *J. Amer. med. Ass.*, **137**, 1005.
 Trent, J. C., and Gaster, E. (1944). *Ann. Surg.*, **119**, 954.
 Uvnäs, B. (1954). *Physiol. Rev.*, **34**, 608.
 Wiggers, H. C., et al. (1947). *Fed. Proc.*, **6**, 226.
 Wyman, J. B. (1953). *Proc. roy. Soc. Med.*, **46**, 605.

The assistance which the World Health Organization gives to educational institutions, particularly to medical schools, is reviewed in the *Chronicle of the World Health Organization* for May (Geneva, 1s. 9d.). Political and economic changes resulting in a sudden shortage of senior teaching personnel, or recognition of academic insufficiency in their institutions, may induce governments to ask W.H.O. to assign them a visiting professor. During 1954 thirty-eight such assignments were made and a total of 515 "professor-months" spent on the project. Short visits by eminent scientists to underdeveloped countries were also arranged. The aim of the visiting professor is to help develop the local staff and to train someone to succeed him. The greatest deficiencies have been in the medical schools, where during 1952-4, 227 "professor-months" have been spent. A card index of experienced teachers willing to go abroad under W.H.O. auspices has been prepared, as well as an inventory of equipment needed for teaching medical subjects, in which the cost of each article is indicated. Where needed, medical literature, laboratory apparatus, and diagnostic and therapeutic instruments are sent with the professor, who trains the local faculty to use them. In Burma, Ethiopia, and Nepal institutions have been set up for training auxiliary staff to help in health work.

DESENSITIZATION OF NURSES ALLERGIC TO PENICILLIN

REPORT OF A CASE

BY

B. J. O'DRISCOLL, M.D.

Physician, Central Hospital, Galway

"The position with regard to desensitization is confused. Some dermatologists state roundly that it is useless" (Ministry of Health, 1953). The chief object of the present article is to prove that nurses can be desensitized to penicillin—although desensitization of a nurse may be somewhat more difficult than desensitization of a patient.

When penicillin was first used for treatment it was thought to be completely non-toxic. Although time has on the whole justified this assumption, it was soon found that some patients are already, and that others become, hypersensitive to the antibiotic. The Ministry of Health report shows that many nurses have had to abandon their career on account of sensitivity to penicillin.

Review of the Literature

O'Donovan and Klorfajn (1946) successfully desensitized a patient by giving repeated doses of penicillin by mouth. Peck et al. (1947) evolved a technique for desensitization by giving progressively larger subcutaneous doses of penicillin. Garai (1949) found that a patient who was sensitive to sodium and potassium penicillin was insensitive to the calcium salt, and desensitized him with gradually increasing subcutaneous doses of calcium penicillin. Kalz and Prichard (1952) published reports of cases of penicillin sensitivity that were relieved by antihistamines. Maslansky and Sanger (1952) found that penicillin is less likely to cause reactions when it is mixed with an antihistamine. They believed that the addition of the antihistamine rendered the penicillin less prone to cause reactions. Beck (1953), however, showed that an antihistamine is as effective in preventing reactions to penicillin when it is given intramuscularly before the penicillin as when it is given mixed with it.

Roberts (1953) desensitized three workers in a penicillin-manufacturing plant with increasing doses of penicillin, using antihistamines to control the reactions and continuing the maximum doses for several months at decreasing intervals. Crofton (1953) showed that the antihistaminic action of diphenhydramine hydrochloride ("benadryl") did not interfere with the desensitizing property of streptomycin. Balme and Dormer (1954) were similarly able to eliminate the antihistamine from a mixture of mepyramine maleate ("anthisan") and penicillin when they had given maximum doses of the antibiotic to a penicillin-sensitive patient.

Case Report

On February 19, 1954, a nurse aged 24 was referred for treatment because her face swelled every time she came near penicillin.

She started training in April, 1949. One year later her eyelids swelled occasionally. Some months after this her eyelids swelled immediately she took penicillin tablets for a sore throat, and the swelling lasted for some days. It was then she noticed that the swelling of the eyelids always occurred after she had given penicillin injections. Consequently she avoided giving penicillin, so far as possible, during the remainder of her training. When she had qualified as a general nurse she did her midwifery training. During that time she never handled penicillin and her face never troubled her. In February, 1953, she took up duty in a nursing-home. Two weeks later her eyelids began to swell, and in a further

week she had to give up her work as her eyes were nearly closed. The swelling remained for a week, although she took mepyramine maleate tablets. In December, 1953, tired of idleness, she decided to give nursing another trial. She went back to duty in the nursing-home, and, although a considerable quantity of the antibiotic was used there, she avoided giving penicillin injections. One hour after she had gone home from work on her first day's duty her eyelids began to swell. She had not done any nursing from that time until she was referred for treatment.

A person who was presumably insensitive to penicillin was used as a control in all the tests.

Patch Test.—Fifty per cent. penicillin soaked in lint strapped to the back for 24 hours produced no reaction.

Intradermal Tests.—The patient waited in an office while the dilutions were made up in the following manner in the ward. One mega unit of penicillin was diluted to 10 ml. with distilled water so as to give a solution of 100,000 units per ml. Then 1 ml. of this was aspirated into a syringe and distilled water was aspirated up to the 10-ml. mark, giving a dilution of 10,000 units per ml. Dilutions of 1,000 and 100 units per ml. were similarly prepared: (1) 10 units of penicillin in 0.1 ml. of distilled water produced no reaction; (2) 100 units produced no reaction; and (3) 1,000 units caused a brawny swelling 5 cm. in diameter surrounded by a large area of redness in four hours, and the eyelids became itchy and swollen. On the following day, as the eyes were nearly closed, chlorcyclizine hydrochloride ("histantin"), 100 mg., was given by mouth three times daily and the swelling disappeared in a few days.

Desensitization

The nurse was treated as an out-patient, as she was not keen on entering hospital. All penicillin was given into the deltoid muscles at the patient's request. The following doses were given, on succeeding days except where otherwise stated.

(1) 200 units (0.2 ml. of the 1,000 units per ml. dilution). This was double the amount of the strongest dilution that did not produce a reaction in the skin test.

(2) 400 units: no reaction.

(3) 1,000 units: no reaction.

(4) 2,000 units: the eyes were itchy in the evening but felt normal the following morning.

(5) 2,000 units: no reaction.

(6) (a) A 50-mg. chlorcyclizine tablet given before penicillin, before lunch, and before tea. This dose was repeated daily. (b) Penicillin, 4,000 units: no reaction.

(7) 10,000 units: the eyes were red and itchy six hours later and were normal the following morning.

(8) (a) Two 50-mg. chlorcyclizine tablets given three times a day and repeated daily. (b) Penicillin, 10,000 units, no reaction.

(9) 20,000 units caused intense burning and swelling of the eyelids. On the following day, as the eyelids were still swollen, no injection was given. Promethazine hydrochloride ("phenegan"), 50 mg. at night, was prescribed in addition to 100 mg. of chlorcyclizine thrice daily.

(10) Next day 20,000 units: no reaction.

(11) 30,000 units caused the eyelids to become red and itchy.

(12) 30,000 units two days later: no reaction.

(13) 40,000 units: slight itching of eyelids.

(14) 60,000 units: itching of eyelids.

(15) 90,000 units: slight reaction.

(16) 130,000 units: slight reaction.

(17) 190,000 units: slight reaction.

(18) 250,000 units: (a) the eyelids were very itchy and swollen; (b) the skin became itchy, red, and swollen at the site of the skin tests; (c) granular swellings appeared between the fingers like cheiropompholyx; and (d) the patient was very nervous and trembling, and the pulse rapid.

(19) 250,000 units again two days later: reaction was similar to that on the previous occasion but not so severe.

(20) It was decided to try the effect of injecting an antihistamine intramuscularly, and no further antihistamines were given by mouth. (a) 100 mg. of antazoline ("antistin") intramuscularly, (b) 350,000 units of penicillin immediately afterwards pro-

duced no reaction. The patient said that she had felt drowsy while taking the antihistamines by mouth but was quite alert now.

(21) 700,000 units after antazoline, 100 mg.: the eyes itchy for a few hours.

(22) Antazoline, 100 mg. intramuscularly; penicillin, 700,000 units, caused no reaction.

(23) Antazoline, 100 mg., and penicillin one mega unit: no reaction.

(24) Antazoline, 50 mg., and one mega unit of penicillin: no reaction.

(25) Antazoline, 25 mg., and one mega unit of penicillin: no reaction.

(26) Antazoline, 10 mg., and one mega unit of penicillin: no reaction.

(27) One mega unit of penicillin without antihistamine caused no reaction.

Final Tests.—Penicillin, 10,000 units intradermally, caused the same reaction in the patient and the control. It consisted of redness about 2 cm. in diameter at the site of injection and had disappeared on the following day. This was probably due to chemical irritation of the penicillin. On April 26 the nurse took up duty in a fever hospital. She has given a considerable amount of penicillin and has had no reaction for more than a year. On December 9 10,000 units of penicillin intradermally caused no reaction apart from that produced in the control.

Discussion

It is obvious that a nurse can be desensitized to penicillin. Inadequate doses explain at least some of the failures in penicillin desensitization. For example, Farmer (1953) did not go beyond 5,000 units, and it is not surprising that contact symptoms recurred.

Antihistamines are far more effective in preventing reactions when given intramuscularly. Thus, antazoline, 100 mg. intramuscularly, was more effective in preventing a reaction in this case than promethazine, 50 mg., and chlorcyclizine, 300 mg., by mouth. This is surprising, as promethazine is 14 times more potent by mouth than antazoline (Wilson and Schild, 1952). It is not necessary to give the antihistamines in the same syringe with the penicillin, although this technique may have the advantage of reducing the number of injections.

Thus the technique recommended is to begin with double the dose of penicillin which caused no reactions in the tests. Keep doubling the dose every day until a reaction occurs. Then give an antihistamine intramuscularly either before or in the same syringe as the penicillin. This procedure has been found to shorten dramatically the time required to effect desensitization to streptomycin and *para*-aminosalicylic acid.

One may ask, Is desensitization permanent? Certainly, inadequate desensitization does not last; Crofton (1953), however, says that a nurse has been free from symptoms for three years after he had desensitized her to streptomycin. It may be possible to desensitize a nurse by giving increasing doses of penicillin by mouth, using antihistamines to control reactions.

The negative patch test in this case is possibly explained by the hypothesis that it is the blood vessels in the dermis which are sensitized, as suggested by Farmer (1953). A patch test applied where the skin was most sensitive to penicillin would probably have been positive; this, however, would have necessitated the callous procedure of applying the penicillin to the face.

Summary

Tests show that it is possible to desensitize a nurse who otherwise would have to give up her profession on account of reactions to penicillin. Previous failures were possibly due to inadequate dosage.

Details of the technique used in a successful case are recorded. Twenty-seven injections of progressively

increasing doses of penicillin were given, usually at daily intervals, and antihistamines were used to prevent reactions.

Antihistamines are much more effective when administered intramuscularly; indeed, if one gives them by that route from the time the first reaction occurs one may desensitize a nurse in a fortnight.

Patch tests are not reliable.

REFERENCES

- Balme, H. W., and Dormer, A. E. (1954). *British Medical Journal*, 1, 500.
Beck, C. A. (1953). *J. Amer. med. Ass.*, 153, 1170.
Crofton, J. (1953). *British Medical Journal*, 2, 1014.
Farmer, P. W. (1953). *Med. J. Aust.*, 2, 820.
Garai, F. (1949). *J. Amer. med. Ass.*, 141, 25.
Kalz, F., and Prichard, H. (1952). *Arch. Derm. Syph. (Chicago)*, 65, 568.
Maslansky, L., and Sanger, M. D. (1952). *Antibiot. and Chemother.*, 2, 385.
Ministry of Health Report (1953). *British Medical Journal*, 2, 39.
O'Donovan, W. J., and Klorfain, I. (1946). *Lancet*, 2, 444.
Peck, S. M., et al. (1947). *J. Amer. med. Ass.*, 134, 1546.
Roberts, A. E. (1953). *Arch. industr. Hyg.*, 8, 340.
Wilson, A., and Schild, H. O. (1952). *Clark's Applied Pharmacology*, 8th ed., p. 79. Churchill, London.

Medical Memoranda

Absolute Neutrophil Leucopenia after Uncontrolled Use of Amodiaquine

A very wide range of drugs have been found capable of causing depression of the myeloid functions of the bone marrow with the development of agranulocytosis. So far as I am aware, no case has been reported following the administration of amodiaquine (4-(3-diethylaminomethyl-4-hydroxyanilino)-7-chloroquinoline). In view of the widespread use of this very effective schizonticide in malaria, the case reported below stresses a possible danger in its uncontrolled administration without medical supervision.

CASE HISTORY

A female European child aged 2 years was seen in the out-patient department of Wankie Colliery Company, Southern Rhodesia, on April 21, 1954. The mother said that the child had been suffering for the past two weeks with vague malaise, fretfulness, loss of appetite, and occasional bouts of "fever." The last attendance of the child as an out-patient had been in the previous January, when she was suffering from a pyuria and had been treated with a fortnight's course of sulphadimidine. The dosage had unfortunately not been recorded, but the white blood cell count at the time was 6,900 per c.mm., with a normal differential count. The child was pale, well nourished, and afebrile, and on clinical examination all systems appeared to be normal. Routine haematological examination on April 21 showed Hb, 73%; white cells, 6,400 (polymorphs 4%, lymphocytes 75%, monocytes 12%, eosinophils 9%).

The mother did not return for the results of the examination as instructed, but brought the child back some 36 hours later, when the white cells numbered 5,500 (polymorphs 0.5%, lymphocytes 85.5%, monocytes 10%, eosinophils 4%).

When both parents were cross-questioned about giving any medicines at all to the child, they admitted that as they thought the child's "fever" was due to malaria they had been giving her a half-tablet (100 mg.) of amodiaquine twice daily for the five days prior to her first attendance at hospital. The evening of that same day they gave her another 100 mg. and the following morning and evening two further 100-mg. doses.

The child was admitted to hospital and started on a course of benethamine penicillin (N-benzyl-β-phenylethylamine salt of penicillin G), 300,000 units every second day. On May 24 a tibial puncture was carried out and examination of the bone marrow showed a general picture of normal cellularity

with the predominant cells lymphocytes and all granulocytes decreased. There was an apparent arrest at the myelocyte stage.

The differential marrow cell count (500 cells) was as follows:

Cells	Average Normal Range (Whitby and Britton, 1950)	Patient
Neutrophil polymorphs	8.0-20%	2.0%
" metamyelocytes	15.0-25%	5.5%
" myelocytes	10.0-26%	12.0%
Eosinophils (total)	2.5-16%	4.0%
Basophils	0.0-1%	0.25%
Promyelocytes	0.5-5%	0.75%
Myeloblasts	1.0-4%	0.5%
Lymphocytes	15.0-40%	50.0%
Monocytes	0.5-5%	8.0%
Plasma cells	0.0-3%	1.0%
Haemocytoblasts	0.0-1%	0.25%
Proerythroblasts	0.0-4%	0.5%
Early and intermediate normoblasts	3.0-12%	5.0%
Late normoblasts	2.5-10%	10.0%
Megakaryocytes	No figure	0.25%
Myeloid-erythroid ratio	4.1:13.1	1.7:1

It was assumed that the condition was due to the uncontrolled administration of amodiaquine and that the prognosis was reasonably good now the drug had been withdrawn. Penicillin was continued and efforts were made to obtain a supply of pentose nucleotide. This drug was very difficult to obtain both in Rhodesia and in the Union of South Africa, and it was four days before enough arrived to begin treatment. During this period there was little change in the daily white cell counts, which ranged between 3,800 and 5,000 per c.mm., with a polymorph count between 4% and 6%. The general condition remained good, no focus of infection developed, and she remained afebrile. Administration of pentose nucleotide was started on June 30 at a dosage of 2 ml. intramuscularly twice daily. The summarized white cell counts for the next four days are given below (differential counts to 300 cells).

Date	W.B.C. per c.mm.	Polys.	Lymphs.	Monos.	Eosins.	Meta-myelocytes
30/4/54	5,400	2.0%	83.3%	12.6%	1.6%	0.3%
1/5/54	5,800	2.5%	83.5%	12.0%	2.0%	—
2/5/54	5,000	0.3%	90.7%	8.0%	1.0%	—
3/5/54	6,000	—	76.0%	19.0%	5.0%	—

During the whole period except for the examinations on April 21 and 23 the Hb remained within the range of 80%–85% and platelets were plentiful. The daily dosage of pentose nucleotide was increased on July 2 to a daily total of 5 ml. and on the 3rd to 6 ml. The patient was transferred to Bulawayo General Hospital on the 3rd. The day following her arrival a follicular exudate was noticed on the tonsils which on culture revealed a mixed growth of *M. catarrhalis* and scanty non-haemolytic streptococci. She was then given procaine penicillin, 300,000 units 12-hourly, and the dosage of pentose nucleotide was increased to a daily total of 8 ml. in four divided doses.

Neutrophils reappeared in the peripheral blood the day after admission. The tonsillar infection quickly subsided. From May 5 to 10 the white cells fluctuated between 7,000 and 9,000 per c.mm. and the polymorph count between 8% and 10%.

A slow but steady improvement followed for the next ten days, and on May 15, when treatment was discontinued, the white cells numbered 16,500 per c.mm. and the polymorphs stood at 67%.

COMMENT

The cause of the neutropenia was in all probability due to the uncontrolled administration of amodiaquine in a dosage of 200 mg. daily for seven days. A possible factor is that there may have been some residual depression of the bone marrow following the course of sulphadimidine some three months earlier, when a leucopenia had been noted. The parents were emphatic that the child had been given nothing but amodiaquine except an occasional half aspirin tablet. They also stated it was the first time the child had been given amodiaquine. It is of interest to note that the father, who had been dosing himself heavily and irregularly with amodiaquine (1–2 g. daily), showed a mild leucocytosis