46% of those on 20 PH. Changes in radiographic appearances were independently assessed by a radiologist unaware of the treatment of any patient. Two-plus or three-plus improvement was seen in 54% of SH and 42% of 20 PH patients. There were two radiographic deteriorations and one death on each treatment. None of the above differences is statistically significant.

The proportion of patients bacteriologically negative, both on direct examination and on culture, at a single examination at three months was 65% for the SH series and 66% for the 20 PH series.

Bacillary resistance to isoniazid was found in 2 of 39 culture-positive SH patients tested at three months, compared with 0 of 29 similar 20 PH patients. Bacillary resistance to streptomycin was found in 1 of 38 culture-positive SH patients, and to P.A.S. in 1 of 28 similar 20 PH patients.

It is concluded, *judging solely from the results at three months*, that P.A.S. (sodium) 20 g. daily plus isoniazid 200 mg. daily is a very effective combination of drugs, both clinically and bacteriologically; it ranks with the most efficacious treatments so far studied—namely, streptomycin 1 g. daily plus isoniazid 200 mg. daily and streptomycin 1 g. daily plus P.A.S. (sodium) 20 g. daily.

A supplementary clinical comparison of all the 219 patients on streptomycin plus isoniazid and all the 172 on P.A.S. plus isoniazid confirms the clinical efficacy of combining P.A.S. with isoniazid. However, patients on streptomycin plus isoniazid gained a little more weight, and a higher proportion showed substantial radiographic improvement.

A preliminary analysis of results of sensitivity tests on each of the four treatments shows that P.A.S. (sodium) 10 g. daily plus isoniazid 200 mg. daily may prove to be a bacteriologically effective combination for at least three months. On the other hand, treatment with streptomycin 1 g. twice a week plus isoniazid 200 mg. daily is apparently less effective than streptomycin 1 g. daily plus isoniazid 200 mg. daily in preventing the development of bacterial resistance to isoniazid over a three-month period.

ACKNOWLEDGMENTS

The hospitals and the doctors co-operating in the phase of the trial reported here are as follows:

Hospitals.—Aberdeen City Hospital; Aintrec Hospital; Ashludie Hospital, Monifieth; Ayrshire Central Hospital, Irvine; Bangour Hospital, West Lothian; Black Noddy Hospital, Braintree; Brierton Hospital, West Hartlepool; British Legion Sanatorium, Nayland; Brompton Hospital; Broomfield Hospital, Chelmsford; Canadian Red Cross Memorial Hospital, Taplow; Clare Hall Hospital, Herts; Connaught Military Hospital; Cumberland Hospital, Surrey; Dumfries and Galloway Sanatorium; East Fortune Hospital, East Lothian; Edgware General Hospital; Edinburgh City Hospital; Foxhall Hospital, Ipswich; Glenafton Hospital, Ayrshire; Hammer-smith Hospital; Heathcote Hospital, Leamington Spa; Heathfield Hospital, Ayrshire; Hillingdon Hospital; Holywood Hall Sanatorium, Bishop Auckland; Inverurie Hospital, Aberdeen; Kettlewell Hospital, Kent; King Edward VII Sanatorium, Midhurst; King George V Hospital, Godalming; King George's Sanatorium for Sailors, Hants; Lenham Sanatorium, Kent; Llangwyfan Hospital, Denbigh; Mcarnskirk Hospital, Renfrewshire; Mount Pleasant Hospital, Middlesex; Newcastle General Hospital; North Middlesex Hospital; Poole Sanatorium, Middlesbrough; Robroyston Hospital, Glasgow; Romsley Hill Sanatorium, Worcestershire; Royal Victoria Hospital, Edinburgh; St. Albans City Hospital; St. Helen's Hospital, Ipswich; St. Helier Hospital, Surrey; Seaham Hall Sanatorium, Sunderland; Southfield Hospital, Edinburgh; Westcliffe Hospital; West Heath Sanatorium, Birmingham; Woodend Hospital, Aberdeen; Woolley Sanatorium, Northumberland; Yardley Green Hospital, Birmingham.

Physicians.—Drs. P. G. Arblaster, M. Barry, D. Bell, W. Biagi, W. M. Borthwick, J. T. Boyd, L. E. Burkeman, K. M. Chalmers, J. A. Chamberlin, C. W. Clayton, R. C. Cohen, A. H. C. Couch, Professor J. W. Crofton, Drs. R. Cunningham, V. Davies, V. F. Dawkins, M. K. Dhole, J. W. Duerden, T. A. Watkin Edwards, I. Emslie, W. J. Ferraby, P. Forgas, M. A. Foulis, R. Fraser, M. A. Gallagher, J. E. Geddes, I. W. B. Grant, J. S. B. Greenfield, L. A. Hardie, W. C. Harris, H. F. Harwood, M. Hemming, E. V. Hess, J. A. Hill, F. Hodgkiss, N. W. Horne, J. V. Hurford, G. Hurrell, J. E. M. Hutchinson, Lieutenant G. J. Jones, Drs. G. Penrhyn Jones, R. Sinclair Kennedy, G. M. Lewis, G. M. Little, L. C. Lum, E. G. Sita Lumsden, G. R. W. N. Luntz, Lieutenant-Colonel J. Mackay-Dick, Drs. W. MacDermid, N. MacFarlane, D. G. McIntosh, G. R. McNab, A. T. Mason, W. T. Miller, K. Murray, W. A. Murray, P. J. O'Rourke, J. P. Parkinson, Hayden J. Partington, W. C. Pinkney,

A. C. P. Ritchie, J. B. Robinson, J. T. Nicol Roe, Hector J. T. Ross, I. D. Ross, J. D. Ross, J. B. M. Runciman, F. A. H. Simmonds, D. H. Smith, J. Morrison Smith, J. Stevenson, C. J. Stewart, P. Stradling, G. J. Summers, J. Sumner, J. O. Taubman, D. Teare, H. E. Thomas, O. F. Thomas, B. C. Thompson, H. R. Thomson, Sir Geoffrey S. Todd, Drs. H. J. Trenchard, F. W. A. Turnbull, M. Walton, W. F. Wheeler, A. B. White, F. L. Wollaston, W. L. Yell, D. van Zwanenberg, and the consultant staff of Brompton Hospital (registrar, R. N. Johnston).

Bacteriologists and Pathologists.—Drs. C. S. Anderson, D. F. Barrowcliff, R. Blowers, D. M. H. Cogman, R. T. Cooke, J. E. Craik, P. B. Cronc, J. C. Dick, Professor A. W. Downie, Drs. J. M. Dunbar, W. J. Godden, T. E. W. Goodier, W. I. Gordon, J. Harper, J. F. Heggie, E. D. Hoare, Captain C. H. Jones, Drs. E. R. Jones, P. Kidd, M. Laidlaw, G. Laws, J. T. A. Lloyd, A. Macdonald, J. Marks, P. H. Martin, A. Messer, D. A. Mitchison, Squadron-Leader A. D. Moore, Drs. E. Nassau, J. W. Nicholas, W. H. A. Pictou, R. Pilsworth, Squadron-Leader J. S. Porterfield, Drs. A. I. D. Prentice, I. A. Purdie, K. Rafinski, R. W. Riddell, J. M. Robertson, B. R. Sandiford, F. E. T. Scott, A. G. Signy, T. Skeoch, J. Smith, P. J. Taylor, W. K. Taylor, A. T. Wallace, R. F. Welch, W. Whitelaw. The bacteriologists and pathologists form a laboratory sub-committee under the chairmanship of Professor R. Cruickshank.

Dr. E. H. Bailey, Southern Group Laboratory, supplied culture medium where desired. Dr. D. A. Mitchison's laboratory, Postgraduate Medical School of London, served as reference laboratory for drug-resistance tests.

The above cannot be a comprehensive list of all the doctors who have contributed to the results reported here, nor has it been possible to name the many laboratory technicians who have done detailed and valuable work. The Tuberculosis Chemotherapy Trials Committee expresses its thanks to all members of hospital staffs who have assisted in the investigation, particularly for their willing response to the urgent requests for information for inclusion in this report.

The Research Committee of the Tuberculosis Society of Scotland was of considerable assistance in initiating the trial in Scotland. The Edinburgh team is in receipt of a research grant from the Royal Victoria Hospital Tuberculosis Trust. The figure was drawn by Miss P. Carter, of the Department of Medical Illustration, Guy's Hospital.

REFERENCES

- Medical Research Council (1952). *British Medical Journal*, 2, 735.
— (1953a). *Ibid.*, 1, 521.
— (1953b). *Lancet*, 2, 213.
— (1953c). *Ibid.*, 2, 217.

DESENSITIZATION TO STREPTOMYCIN AND P.A.S.

BY

JOHN CROFTON, M.D., F.R.C.P.

From the Department of Tuberculosis and Diseases of the Respiratory System, University of Edinburgh

It is not proposed to discuss in detail in this paper the symptoms of hypersensitivity to streptomycin or P.A.S. (para-aminosalicylic acid), but only to emphasize that desensitization is possible. In patients sensitized by treatment with streptomycin or P.A.S. desensitization is usually easy, and has been referred to briefly elsewhere (Crofton, 1953). It is much more difficult to desensitize individuals sensitized to streptomycin by handling it in the course of their work, and I have seen no previous report of this being successfully accomplished.

Desensitization of Streptomycin-handlers

The recent statement from the Ministry of Health (1953) indicates that a number of people whose duty involves the handling of streptomycin become sensitized to the drug. In many cases the degree of sensitivity is very high; a nurse may not only be unable to administer streptomycin injections but may be unable to work in a ward where they are given or enter a room where the injections are prepared. The previous literature on this subject has been well reviewed in the Ministry of Health report and will not be recapitulated here. The present report is only to emphasize that even individuals highly sensitive to streptomycin can be desensitized, and to describe two cases in which this has been done.

Case 1

A ward sister aged 37 had no family or personal history of allergy. Two years before admission to hospital she had begun giving streptomycin injections, and during the five

months before the onset of symptoms one year previously she had been giving injections daily to between two and nine patients. She had not worn rubber gloves. One year before admission she began to notice swelling of the peri-orbital tissue of the right eye, which reached its maximum two hours after giving streptomycin injections. (She had previously lost her left eye in an accident.) These symptoms gradually increased, and eight months before admission a patch test with streptomycin was done on her back. This resulted in severe local reaction and also local redness and swelling around her right eye. By this time she had become so sensitive that she was liable to develop the reaction whenever she went into the ward, and she had to be put off work. Even then she found that a flare occurred in the eye if she went to visit one of her friends who was changing after coming off duty.

At the time of admission she had not been in contact with streptomycin for some time, and there were no abnormal physical signs. An intradermal test with 50 μ g. of streptomycin in 0.1 ml. produced a local reaction with oedema 4 by 4 mm. in diameter and an erythema 20 by 18 mm. at six hours. One hour after the injection there was a reaction in the eye, with reddening and itching of the right cheek. She was placed on diphenhydramine hydrochloride, 50 mg. three times a day, and then two injections of distilled water were given, without reaction, on successive days. Thereafter she had a first injection of 10 μ g. of streptomycin. The next day she said she felt slightly unwell, but there was no local reaction. It was thought that this feeling might be due to overdosage with diphenhydramine, and this was reduced to 50 mg. twice a day. On the following two days intramuscular injections of 20 and 50 μ g. successively of streptomycin were given without incident. On the 4th day 100 μ g. was given, but 16 hours later she developed redness and oedema of the right eyelids. This lasted for two days. No streptomycin was given until the evening of the second day, and diphenhydramine was increased to three times a day.

On the 6th day after starting treatment the dosage of streptomycin was reduced to 50 μ g. On the 7th and 8th days no injections were given as there was still slight desquamation of the right eye but no oedema. On the 9th day 100 μ g. was given again with no reaction. On the 10th day 200 μ g. produced oedema and redness of the upper eyelid six hours later. On the following day this dose was repeated with an extra dose of diphenhydramine and there was no reaction. On the 12th day the dose was stepped up to 300 μ g. and produced no reaction. On the 13th day, following 500 μ g., there was marked swelling and oedema of the right eyelids, and 2½ hours after the injection she was hardly able to open the eye. At the same time the patch test on her back which had been done eight months previously became red and hot. On the 14th day this reaction had subsided and the 500- μ g. dose was repeated. The reaction in the back and eye occurred again, but less severely than previously, and on the evening of the 15th day the 500- μ g. dose was repeated with no reaction. With the succeeding doses of 600, 800, 1,000, and 1,250 μ g. there was no reaction, but with 2-, 3-, and 4-mg. doses there was very slight swelling and itching of the eyelids.

On the 23rd day 6 mg. produced no reaction, but there was a slight one with the 10-mg. dose the next day. This had subsided by the evening of the 25th day and 12 mg. was given. Thereafter 20, 30, 50, and 100 mg. were given without incident, but 0.2 g. on the 30th day was followed by redness and itching. There was no reaction to 0.3 g. on the 31st day, but there was a slight reaction to 0.5 g. on the 32nd. Thereafter 0.7 g. and 1 g. were given without any reaction. Diphenhydramine was then stopped. For a couple of days she complained of headache and nausea, but this was relieved by giving 50 mg. of diphenhydramine on the third day. The next day there was some recurrence, which was relieved by giving glucose in a diphenhydramine capsule. Thereafter there was no further trouble. A further injection of 1 g. was given after the cessation of diphenhydramine treatment, and there was no reaction.

The intradermal test with 50 μ g. of streptomycin was then repeated and there was no reaction whatsoever. Gauze soaked in 50% streptomycin solution was strapped on her back for 24 hours with no reaction. She was therefore regarded as having been desensitized, and returned to work in tuberculosis wards. Three years later she has had no recurrence of trouble. She has on the whole avoided giving streptomycin injections herself, but has occasionally done so, taking the precautions we have previously outlined (Crofton and Foreman, 1948).

Summary of Case 1.—A nursing sister aged 37 became sensitized to streptomycin after giving injections for about a year. The sensitivity consisted of redness and swelling around the right eye, and was so severe that she was unable to enter a room in which one of her colleagues was changing after coming off duty. Skin tests confirmed the streptomycin sensitivity and desensitization was carried out by giving ascending daily intramuscular injections of streptomycin over 35 days, the first injection being 10 μ g. and the last 1 g. Minor reactions occurred during the course of desensitization. She has subsequently worked for three years in tuberculosis wards without incident. This patient was a sensible woman and could probably have been desensitized as an out-patient, but she was admitted to hospital, partly because I had not carried out such desensitization previously and partly because the sanatorium in which she worked was situated a long way away.

Case 2

An assistant nurse aged 47 had no personal or family history of allergic conditions. In February, 1948, she had begun giving streptomycin injections, up to about 28 a day. Rubber gloves were available but were seldom worn. In November, 1948, she began to develop conjunctivitis and periorbital swelling. In January, 1949, a streptomycin patch test was said to have been positive. Subsequently she did not handle streptomycin herself, but continued to work in the tuberculosis wards. In May, 1949, the condition recurred and by September she had also developed a dermatitis of the arms and hands. Thereafter she ceased work in the wards and during this time had almost no trouble. In January, 1952, she had a recurrence on the eyes and on the arms. Just before the onset of this she had passed through a room where streptomycin injections were being prepared. An intradermal injection of 25 μ g. of streptomycin resulted in an erythema 9 by 10 mm. at 24 hours, almost no reaction being present at six hours. The patient had a difficult personality. It did not prove possible to desensitize her as an out-patient and she was consequently admitted to hospital.

Mepyramine maleate, 100 mg. three times a day, was given and desensitization was begun with an intramuscular dosage of 50 μ g. Daily doses of 75, 100, 200, and 400 μ g. were given without incident. When given 500 μ g. and subsequent doses of 800 and 1,600 μ g. the rash became a little worse, with slight itching on the forehead. The 1,600- μ g. dose was therefore repeated for five days, until the reaction subsided. On the 14th day 2 mg. was given. There was again some reaction, so 1.6 mg. was given on the 15th day and no injections on the 16th or 17th. Owing to the persistence of reactions three further injections of 2 mg. were given between the 18th and 20th days, 2.5 mg. on the 21st, 3 mg. on the 22nd, and 3.5 mg. on the 23rd and 24th. On the 25th to the 29th days no injections were given, because of persistent dermatitis. Then 3.5 mg. was again given.

Subsequently the dose was raised slowly with occasional intermissions of a day or two days and on several occasions repetition of doses. The doses (in mg.) on successive days were 4, 4, 4, 4.5, nil, 5, 5.5, nil, 5.5, 6, 6.5, 7, 7.5, nil, nil, 7.5, 8, 8.5, 9, 9, nil, nil, 9, 9.5, 10, 12, 14, 16, nil, 18. At this stage there was again a slightly more severe reaction, exaggerated by her difficult personality, and no injections were given for three days. The reaction subsided and injections were resumed: 18, 19, 20, 22, 24, 25, 27, 30, 32, 34, 38, 43, 50, 70, 75, 85, 100, 120, 120, 150, 180, nil, nil, 180.

nil, 200, nil, 220, 220, 240, 260, 280, 300, 330, 360, 380, 400, 420, 450, 500 mg. At this point an error was discovered, most unfortunate but of some interest. It was found that, by mistake, desensitization had been carried out with dihydrostreptomycin sulphate instead of with streptomycin sulphate. Streptomycin sulphate was substituted and, foolishly, the same dose as the previous dose of dihydrostreptomycin was given—that is, 500 mg. There was a very severe reaction. Although the temperature rose only to 98.8° F. (37.1° C.), there was a brisk generalized rash, erythema, slight oedema of the eyes, and great exacerbation of the peripheral dermatitis. Injections were stopped for five days until the reaction had subsided and everyone had calmed down.

Desensitization was then recommenced with streptomycin sulphate, starting with 50 µg. It was found possible to increase the dose quite rapidly, indicating that the dihydrostreptomycin had at least partially desensitized the patient to streptomycin. The dose was increased from 50 µg. to 5 mg. within nine days. There was a slight reaction at this stage, and subsequent doses of 5, 8, 10, 15, and 25 mg. were given without reaction. A dose of 45 mg. resulted in a slight reaction lasting three days, but the dose was increased from 45 to 140 mg. within the succeeding week. At 140 mg. a small patch of dermatitis appeared on the chin and no injections were given for four days. Over the next 25 days the doses were increased from 150 mg. to 1 g. with no significant incidents. Mepyramine maleate was then stopped and intradermal tests were repeated with 100 µg. of streptomycin. There was no reaction. A piece of gauze soaked in 50% streptomycin was then applied to the back for 24 hours without any reaction. Desensitization had therefore apparently been accomplished. Unfortunately, in spite of this, the patient refused to return to work in the wards, and it has not been possible to test out in practice the success of the desensitization.

Summary of Case 2.—An assistant nurse aged 47, who had developed a streptomycin dermatitis and who was highly sensitive to the drug, was desensitized to dihydrostreptomycin by being given daily intramuscular injections, rising from 50 µg. to 0.5 g. over fifteen weeks. At this stage streptomycin was substituted, resulting in very severe reaction. Desensitization was recommenced with streptomycin over the succeeding eight weeks, in which the intramuscular dose was increased gradually from 50 µg. to 1 g. Intradermal and patch tests of streptomycin were negative at the end of the desensitization period, but the patient refused to return to work in tuberculosis wards.

Comment

It seems clear, therefore, that desensitization in individuals whose skin has become sensitized to streptomycin by contact is quite feasible, although it may take several months and minor reactions may occur. It is probable that the patient's mentality may have something to do with the speed with which desensitization is attained. In the first case the patient was a sensible woman and, in spite of some minor reactions, desensitization was readily achieved in a period of 35 days, excluding the time utilized in doing tests. The second patient had a difficult personality and tended to exaggerate her reactions. In consequence, even allowing for the error over dihydrostreptomycin, desensitization took much longer. It was apparent that there was some cross-desensitization to dihydrostreptomycin and that the initial use of that substance for desensitization had resulted in partial desensitization to streptomycin, for subsequent desensitization to streptomycin itself took only eight weeks. It is felt that, with a sensible individual, it should be quite feasible to carry out desensitization on an out-patient basis. This in fact has been done elsewhere, using methods similar to those described (personal communication, Dr. Michael Gibson).

Desensitization of Patients

In patients undergoing treatment with streptomycin and P.A.S. hypersensitivity reactions are well known. The com-

monest manifestation is fever, usually occurring 10 to 25 days after starting treatment. Any fever at this stage of treatment should be regarded as a hypersensitivity reaction until proved otherwise. Rashes may be seen, with or without fever. When such a reaction occurs chemotherapy should be stopped. Continuation in spite of a warning fever has resulted in severe liver damage, encephalitis, or other serious hypersensitivity reactions, especially in the case of P.A.S. When the reaction has subsided one may test for hypersensitivity by giving 0.5 g. of streptomycin. If the patient is hypersensitive symptoms such as mild fever, a rash, or itching of the skin occur within an hour or two. If there is no reaction a dose of 1 g. is given in order to make certain. When the reaction, if any, has subsided, a half-dose of P.A.S. (usually 2.5 g.) is given, for the patient may be sensitive to both drugs. Again a reaction will usually occur within an hour or two. If there is none a full dose (5 g.) is repeated two or three times to make certain.

Desensitization is then begun. If the patient is sensitive to both drugs it is well to desensitize to P.A.S. first, as resistance to this drug develops less readily; after desensitization normal doses of P.A.S. can then be used to cover the desensitization to streptomycin. It is usually adequate to start with 0.5 g. of P.A.S., working up to the full dose by daily increments over 10 to 14 days. With streptomycin an initial dose of 0.1 g. is usually low enough, and this can be increased to 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1 g. in the succeeding days, desensitizing over 10 to 14 days. In both cases, if there is any reaction the last dose is repeated after the reaction has subsided.

Personally I have encountered no difficulties in a large number of patients desensitized; it is a very much easier matter than the desensitization of streptomycin-handlers. The following patient is an example. She was sensitive to both drugs and was a little more difficult than usual to desensitize, but presented no major problems.

Case 3

A female schoolteacher aged 23 was admitted with pulmonary tuberculosis of recent origin. She was started on streptomycin, 1 g., and P.A.S., 15 g. daily, the latter being increased to 17 g. within a few days. She had a slight fever up to 99° F. (37.2° C.) or a little above. On the 22nd day the temperature rose to 100.6° F. (38.1° C.) in the evening; it was normal the next morning, but rose to 104° F. (40° C.) that evening, with a bright red morbilliform rash over the body. P.A.S. was stopped and the next day the temperature subsided. That evening she received the normal dose of streptomycin and the temperature again rose to 104° F. (40° C.), with rigors, exacerbation of the rash, and Raynaud's phenomenon in the fingers. Streptomycin was then stopped also and an antihistamine drug given. The temperature was normal next day and the rash cleared within two days. A test dose of 2.5 g. of P.A.S. resulted in a faint rash and itching of the skin one hour later. Two days later a test dose of 0.5 g. of streptomycin resulted in pains in the arms and flushing of the face and conjunctivae. Both these reactions subsided within 12 hours.

Desensitization to P.A.S. was begun with 0.5 g. the first day in a single dose, 0.5 g. four times on the 2nd day, 0.5 g. five times on the 3rd day, 1 g. four times on the 4th day (slight itching of skin). On successive days the following doses were then given, each five times a day: 1.5, 2, 2.5, and 3 g. On the last-mentioned dose there was slight prickling of face and legs lasting one to two hours after each dose, but the dose was maintained and within ten days could be raised to 17.5 g. a day. Desensitization to streptomycin was then begun with 0.1 g. on the first day. Slight prickling of the legs occurred with this dose and with the 0.2-g. dose the next day. The latter was repeated, as was the 0.4-g. dose a few days later, but the full 1-g. dose was reached on the 12th day. P.A.S. was continued throughout the desensitization to streptomycin. Thereafter there was

no further trouble. Chemotherapy was continued for over a year, during which she had a segmental resection of the residual disease.

Summary of Case 3.—A female patient aged 23 developed a high temperature and a morbilliform rash after 22 days on streptomycin and P.A.S. Test doses proved she had become sensitive to both drugs. The daily dose of P.A.S. was gradually increased from 0.5 g. to 15 g. over 11 days; 10 days later it was raised to 17.5 g. Streptomycin doses were increased from 0.1 to 1 g. daily over 12 days. Subsequently she continued both drugs for over a year without incident.

Summary

Desensitization of streptomycin-handlers who have become hypersensitive to the drug is difficult but quite feasible. Two cases are reported.

By contrast, patients who acquire hypersensitivity to streptomycin or P.A.S. during treatment are usually readily desensitized. As an example a case is described of a patient hypersensitive to both drugs.

My thanks are due to the residents and nursing staff at Hammersmith Hospital, London, the Northern General Hospital, and Southfield Hospital, Edinburgh, who carried out the day-to-day treatment of these patients.

REFERENCES

- Crofton, J. W. (1953). *Proc. roy. Soc. Med.*, **46**, 584.
— and Foreman, H. M. (1948). *British Medical Journal*, **2**, 71.
Ministry of Health (1953). *Ibid.*, **2**, 39.

EFFECT OF HEXAMETHONIUM BROMIDE ON THE CEREBRAL CIRCULATION IN HYPERTENSION

BY

H. A. DEWAR, M.D., M.R.C.P.

*Assistant Physician, Royal Victoria Infirmary,
Newcastle-upon-Tyne*

S. G. OWEN, M.B., M.R.C.P.

*Late Luccock Research Fellow in Medicine, King's College,
University of Durham, Newcastle-upon-Tyne*

AND

A. R. JENKINS, B.Sc.

*Late Assistant Biochemist, Royal Victoria Infirmary,
Newcastle-upon-Tyne*

The fall in total peripheral resistance which occurs after the administration of the ganglion-blocking agent hexamethonium bromide is not distributed equally between the vascular areas of the body; there follows, therefore, a redistribution of peripheral blood flow. Thus the flow to the foot and toes is greatly increased, while that to the calf segment of the leg muscles is diminished; vascular resistance in the liver decreases enough to maintain the blood flow at its previous level (Freis *et al.*, 1952). The more complex changes in the kidneys have been described by these and other authors (Kirkendall and Culbertson, 1952; Mackinnon, 1952; Miles *et al.*, 1952; Moyer *et al.*, 1952). The effects upon the cerebral and coronary circulations are of particular importance, considering how serious might be the risk of impairment of the blood supply to heart or brain in hypertensive patients. Crumpton and Murphy (1952) have shown that in dogs with experimental renal hypertension the vascular resistance in the coronary system is slightly re-

duced by hexamethonium and that the mean coronary blood flow is maintained. These authors have further outlined the results of their studies of the cerebral circulation in six patients with hypertension and grade III to IV retinopathy before and after blood-pressure reduction with hexamethonium bromide. The present investigation covers the same field in a series of hypertensive patients, in all of whom the changes in the fundi were classified as grade II (Keith-Wagener-Barker) with the exception of one case of malignant hypertension and grade IV retinopathy (Patient 2).

Methods

The studies were carried out on six patients with arterial hypertension who had been admitted to hospital for treatment with subcutaneous hexamethonium bromide. The nitrous oxide technique of Kety and Schmidt (1945, 1948) as modified by Scheinberg and Stead (1949) was employed, constant-rate samples over the ten-minute periods being withdrawn by means of an electrical device (Dewar *et al.*, 1953). In three cases cerebral venous blood was sampled through a needle introduced direct into the superior jugular bulb (Myerson *et al.*, 1927; Gibbs *et al.*, 1945); in the remainder cerebral venous blood was obtained through a cardiac catheter inserted into the left antecubital vein, the technique of which has been described elsewhere (Dewar *et al.*, 1953). Mean cerebral blood flow (C.B.F.) was calculated according to the formula:

$$\text{C.B.F. in ml. per 100 g. brain per minute} = \frac{\text{CV}_{10} \times S \times 10}{\int_0^{10} (A-V) dt}$$

where CV_{10} is the concentration of nitrous oxide in the cerebral venous blood in volumes % at the end of the ten-minute period, S is the partition coefficient of nitrous oxide between brain tissue and blood (known to be unity), and $\int_0^{10} (A-V) dt$ is the integral of the arterial-cerebral venous nitrous oxide difference for the period as determined from the difference between the nitrous oxide concentrations of the integrated arterial and cerebral venous samples.

Blood-pressure readings were made by the auscultatory method in the arm held at heart level, and the mean arterial blood pressure (M.A.B.P.) for each ten-minute period was calculated by adding one-third of the average pulse pressure to the average diastolic reading. The cerebral vascular resistance (C.V.R.) was taken as the quotient of M.A.B.P. divided by the mean C.B.F. In four cases analyses for oxygen content were made on the integrated arterial and cerebral venous samples and the cerebral oxygen consumption (CMRO_2) calculated by dividing the product of the mean arterio-venous oxygen difference ($A-\text{VO}_2$) and mean C.B.F. by 100. The gas analyses were made in a Van Slyke-Neill manometric apparatus, and were all performed by one of us (A. R. J.). Two estimations of blood flow were made on each patient, separated by at least 25 minutes. The conditions of the second were identical with those of the first except for the prior administration of hexamethonium bromide by intravenous or subcutaneous injection in a dose sufficient to cause significant blood-pressure reduction. The second estimation was not begun until the blood pressure had stabilized at its new level. The results of the studies are shown in the Table.

Hexamethonium bromide produced an average fall in the M.A.B.P. of 30% ($t = 4.7$, $P < 0.01$). This was accompanied by a 28% decrease in the C.V.R. ($t = 3.7$, $P < 0.05$), which in four instances fell to a value within the normal range (Kety and Schmidt, 1948). No significant change occurred in the mean C.B.F. during the period of blood-pressure reduction, successive estimations showing close agreement. (In each pair this was in fact within the range of twice the theoretical standard error of the method as performed by us—Dewar *et al.*, 1953.) In the four cases in which this was estimated, no essential alteration occurred in the $A-\text{VO}_2$ difference, nor in the rate of CMRO_2 . These results agree with those obtained by Crumpton and Murphy