tion of knowledge already well established regarding the hazards of transfusion therapy, accidents from this cause need not arise.

In neither of these instances was the transfusion of whole blood so pressing that advantage could not have been taken of existing laboratory facilities for blood-matching by trained laboratory staff. These cases serve as a reminder that this must be done whenever circumstances permit if the best service is to be given to the patient. As soon as plasma prepared during the war years was found to carry a risk approaching 10% of inducing hepatitis in the recipient, preliminary plasma transfusion whilst the matching of blood was being undertaken, or as the sole emergency transfusion for cases of moderate haemorrhage, wisely fell into disrepute. Now that the transfusion of "small-pool" plasma carries little greater risk of transferring the hepatitis virus than does a transfusion of whole blood, and, alternatively, satisfactory plasma substitutes, dextran and polyvinylpyrrolidone, are available, we believe with Discombe (1952) that greater use should be made of such fluids for the avoidance of incompatible transfusions.

Immune antibodies active against transfused corpuscles of the patient's own ABO group are particularly likely to be present in the circulation of recipients who have had jaundiced or stillborn babies, or who have reacted adversely with a rigor, jaundice, or haemoglobinuria to a previous blood transfusion. Even in a dire emergency, therefore, such as a domiciliary "flying-squad" emergency, where the transfusion of unmatched whole blood may seem entirely warranted, strenuous efforts should be made to have blood specially matched against the patient's serum when there is a history suggesting the presence of immune antibodies. It is such patients that one of us (Tovey, 1950) has proposed should be termed "dangerous recipients," and in each of the above cases the patient's history would have placed her in this category.

Dangerous recipients run a particular risk in that if they are Rh-positive the immune antibodies they have developed may well be of the type anti-c or anti-e, and thus active against Rh-negative corpuscles (cde/cde). Or, should the recipient be Rh-negative with Rh antibodies (anti-D) in her serum, an Rh D-positive bottle of blood which has been misgrouped or mislabelled "Rh-negative" may give rise to a serious haemolytic transfusion reaction. Moreover, in some instances incompatibility from immune antibodies can be detected *in vitro* only by methods of direct matching which are too complicated to employ as a routine, such as an indirect antiglobulin technique or a titration procedure using bovine albumin. It is important, therefore, that clinicians obtain a history of the outcome of previous pregnancies or transfusions from any patient about to be transfused. Should the history indicate the patient to be a dangerous recipient, blood should not be transfused until it has been matched by the special procedures mentioned. Whenever possible, the danger in the event of an emergency transfusion should be anticipated, and as soon as it is known that a patient has given birth to a jaundiced or stillborn baby or has suffered a serious reaction to transfusion a full serological examination should be carried out to determine whether immune antibodies are present, and, if so, their exact type.

In neither of the above patients, although their histories indicated the need, had such serological investigations been made before the transfusion accidents. Although Gunz (1946) drew attention to the need for a standard history sheet to accompany every request for transfusion, and such a sheet has been employed by regional transfusion centres for the past six years, many hospitals are still not taking this precaution as a routine for their cases for transfusion.

Case 2 further illustrates that, although a patient may be transfused without serious reaction with blood of a certain ABO and Rh group, this does not mean that a later transfusion of blood of the same ABO and Rh group will be similarly unaccompanied by reaction. It is important to bear in mind that the transfusion of blood can result in

the stimulation of dangerous antibodies, and any further blood for transfusion should invariably be matched on a freshly taken sample of the recipient's serum if more than 48 hours have elapsed since a previous transfusion.

We are grateful to Dr. M. Gillespie and Dr. J. S. Campbell, of the South-west Regional Transfusion Service, and to Dr. A. E. Mourant and Dr. D. Parkin, of the M.R.C. Blood Group Reference Laboratory, for help with the serological investigations.

REFERENCES

- Discombe, G. (1952). *Lancet*, 1, 734.
Gunz, F. W. (1946). *British Medical Journal*, 1, 601.
Tovey, G. H. (1950). *Practitioner*, 164, 171.

SENSITIVITY OF AUTONOMIC GANGLIA TO HEXAMETHONIUM IN HYPERTENSION

BY

JAMES CONWAY, M.B.

Senior Lecturer in Physiology, Charing Cross Hospital
Medical School

The introduction of hexamethonium bromide (H.M.B.) by Paton and Zaimis (1949, 1951) as a substance which blocks the transmission of nervous impulses across the synapses of autonomic ganglia presented a potentially valuable therapeutic means of controlling hypertension. The specificity of its action on autonomic ganglia makes it also a most valuable tool in the study of the autonomic nervous system, and this property is used here to study the underlying mechanisms producing hypertension. Repeated doses of hexamethonium bromide or bitartrate* are given intravenously, and the following points are observed:

- (1) the sensitivity of the blood pressure to depression by autonomic blockade;
- (2) the level to which the diastolic blood pressure may be depressed; and
- (3) the dose required to affect the pupillary light reflex.

The first indicates the state of activity of the autonomic ganglia controlling blood vessels, and incidentally the suitability of patients for treatment. The second gives the minimal diastolic pressure which is used to differentiate various types of hypertension. This term is used in the sense defined by Frew and Rosenheim (1949), as the pressure maintained by the inherent tone of the blood vessels and circulating pressor substances, and corresponds to the term blood pressure "floor" of Ferris *et al.* (1948). Both of these authors used tetraethylammonium bromide (T.E.A.B.) to block autonomic ganglia.

Material

Tests were performed on patients who had been in hospital for at least seven days, and in one-third of the cases repeated tests were performed to establish the reliability of the method. The admission of patients to hospital was made for the investigation and treatment of hypertension or renal disease, and was quite independent of the present study. Cases with heart failure, extreme renal failure, or a history of recent thromboses were excluded.

The clinical diagnosis of essential hypertension was made after exclusion of other causes. Renal hypertension was assumed to be present if evidence could be obtained of

*All doses are expressed as those of the dibromide salt. Messrs. May and Baker kindly gave supplies of the bitartrate used in this investigation.

previous renal disease or associated toxæmia of pregnancy. In all cases a standard amylobarbitone sedation test (White, 1944) was performed, and in a quarter of the cases a test using T.E.A.B. was performed.

Methods

After a single injection of H.M.B. the effect on the blood pressure is found to be maximal within five minutes; repeated injections give a progressively diminishing effect. To minimize the effect of the biological variation in sensitivity to drugs a number of repeated doses were given in preference to a single standard dose. After a single injection it is also found that there is a transient overswing in the fall of pressure which exaggerates the fall in blood pressure particularly when larger doses are used. All blood-pressure readings are taken by the same person, using the auscultatory method and the diastolic pressure taken at the fifth phase—that is, as all sound disappears. This is necessary because the fourth phase often disappears when the blood pressure falls. Attention is paid to the diastolic pressure, as this gives more constant responses and the end-point can easily be defined, whereas the systolic pressure is more variable and sometimes shows a progressive fall in pressure.

The Test.—The procedure outlined gives reliable results and is free from complications. The patients, after being told precisely what is going to be done, are placed in quiet surroundings lying *absolutely flat* except for one pillow under the head for comfort. Blood pressures are taken every ten minutes until a resting level is established, when the first injection of 10 mg. of H.M.B. is given intravenously and pressures are read at three-minute intervals for 15 minutes. Thereafter injections of 25 mg. are made at 15-minute intervals until the maintained reduction in diastolic pressure does not exceed that of the previous dose by more than 8 mm. Hg. This is usually achieved by doses of 35–60 mg.—that is, second or third injections. The dose producing 75% of the fall in diastolic pressure is recorded as the *effective hypotensive dose*. If the blood pressure does not respond to a dose of 35 mg. it will not do so to larger doses. This was demonstrated by the additional doses it was necessary to give in order to block the ciliary ganglion. The dose at which the response of the pupils to light is slight and unsustained is recorded as the *effective pupillary dose*. When large doses (exceeding 85 mg.) are given there is sometimes a secondary slight fall in blood pressure. This is not closely related to the injections, and is partly accounted for by the onset of somnolence and the prolonged immobilization of the patient. For this reason, blood-pressure readings are taken at half-hourly intervals after the completion of the test until an upward trend of pressure is established. The results of some earlier tests in which there were minor variations in procedure have been used.

Precautions.—Mild fainting sometimes occurs when the first, and rarely the second, dose produces a profound and

rapid fall in pressure. This is readily overcome by raising the foot of the bed. No patient has lost consciousness, and it has not been necessary to give pressor drugs. On three occasions when the blood pressure fell considerably after both the first and the second injection it was thought prudent to stop the test, although the patients did not complain of ill effects. Postural hypotension persists for a variable time after the test, and patients are not allowed out of bed or to sit upright in bed until the following morning.

In spite of a considerable reduction in blood pressure in some patients there has been no evidence of thrombosis occurring during the period of hypotension or afterwards. No symptoms due to the paralysis of other organs under the control of the autonomic nervous system were encountered.

Results

A total of 69 tests have been performed on 46 patients with hypertension, and in addition tests were carried out on a control series of 12 patients suffering from minor surgical disorders. According to the responses of the diastolic pressure to the test, the hypertensives can be divided into three groups (see Table).

Group A.—Eighteen patients in whom there was an appreciable fall of diastolic pressure (exceeding 14 mm. Hg.) to 90 mm. Hg or below. The mean fall in diastolic pressure was 28 mm. Hg (range 16–58) and the mean minimal diastolic pressure was 82 mm. Hg with a mean effective hypotensive dose of 25.8 mg. of H.M.B.

Group B.—Nine patients in whom the fall in diastolic pressure was at least 14 mm. Hg but remained above 90 mm. Hg. The mean fall was 28 mm. Hg (range 16–48) and the mean minimal diastolic pressure 104 mm. Hg with a mean effective dose of 37.7 mg. of H.M.B.

Group C.—Nineteen patients in whom the pressure remained within 14 mm. Hg of the initial level. To exclude the possibility that variations in sensitivity might account for the absence of response, repeated doses were continued in this group until an average dose of 110 mg. had been given. At these doses there was sometimes the slight fall in pressure already described, and this has been disregarded.

Throughout the entire series the reduction in the blood pressure was not related to the initial systolic, diastolic, or pulse pressures (Fig. 1). The initial resting blood pressures recorded show that the pulse pressure is related to the diastolic pressure and not to the age of the patient. The degree of response to the test was not determined by the clinical severity, as is illustrated by Fig. 2, in which the results of two similar cases are recorded. Group A contained the greatest proportion of cases of uncomplicated essential hypertension, while the nine cases of Group B appear to be more severe.

The average age in Group A was 53.1 years (only four being below 50 years) and in Group C it was 35.6 years.

Data of Controls and of Hypertensive Patients Divided into Three Groups According to Responses to Tests with Hexamethonium Bromide

	No. of Cases	Mean Age	Sex	Clinical Type of Hypertension	Mean Initial Blood Pressure	Mean Minimal Diastolic Pressure	Mean Fall in Diastolic Pressure	Mean Effective Dose	
								B.P.	Pupils
Controls ..	12	46.1 yrs. (s.d. 14.0)	M 4 F 8	None	118/64 mm. Hg	60 mm. Hg	4 mm. Hg		77 mg.
Group A ..	18	53.1 yrs. (s.d. 7.2)	M 5 F 13	Essential 13 Malignant essential 1 Renal 3 Malignant renal 1	186/110	82	28 (s.d. 11.1)	25.8 mg	76.7 ..
Group B ..	9	43.6 yrs. (s.d. 10.3)	M 6 F 3	Essential 2 Malignant essential 5 Renal 1 Malignant renal 1	206/132	104	28 (s.d. 8.2)	37.7 ..	83 ..
Group C ..	19	35.6 yrs. (s.d. 11.6)	M 9 F 10	Essential 10 Malignant essential 3 Renal 2 Malignant renal 3 Coarct. aorta 1	188/112	107	5		82.6 ..

FIG. 1.—Initial status of 46 patients with hypertension, divided according to their responses to tests with hexamethonium. Group A—fall in diastolic pressure exceeds 14 mm. Hg and reduces it to 90 mm. Hg or below. Group B—fall in diastolic pressure at least 14 mm. Hg but remains above 90 mm. Hg. Group C—fall in diastolic pressure is less than 14 mm. Hg.

This difference was highly significant ($P < 0.001$), and was still valid when all cases of renal hypertension were excluded and essential hypertension was considered alone. The sensitivity of the blood pressure was not associated with that of the pupils. The effective pupillary dose in all groups was approximately the same (76.7–83 mg.).

Controls.—The control series of 12 patients showed an insignificant fall in diastolic pressure. There were no differences in the response of older and younger subjects. The average age of the group was 46.1 years. The effective pupillary dose was approximately the same as that of the hypertensive patients.

Repeatability.—To establish the value of the test 15 patients were given two or more tests, and in these the minimal diastolic pressure remained within 10 mm. Hg. Five patients had repeated tests over a period exceeding 12 months, the minimal diastolic pressure remaining at the same level in all except one, in whom it rose as the clinical state deteriorated. The effect of treatment with H.M.B. is found in general to follow that of the tests, a response being obtained in the blood pressure of patients in Groups A and B, but not in Group C. Prolonged treatment, however, with hexamethonium, or by sympathectomy, has not been found to affect the minimal diastolic pressure. In one patient, however, a strict rice diet which had been maintained for

two months had a considerable effect on the minimal diastolic pressure, reducing it from 88 to 64 mm. Hg. A similar effect has been reported by Stead *et al.* (1948) using T.E.A.B.

Discussion

Hypertension is a single physical sign of what is known to be a large group of diseases. The separation of these from one another is sometimes difficult because the raised blood pressure itself in time produces changes, particularly in the arteries, and treatment is usually required for these effects of the raised pressure and not for the cause. The test described offers a method of identification of those cases of hypertension in which the nervous system plays an important part. It is only by the separation of types that order can be introduced into this bewildering subject.

The appreciation of the part played by nervous factors in elevation of the blood pressure has been maintained in spite of evidence to the contrary (Pickering, 1936; Prinzmetal and Wilson, 1936), from the study of the variability of the blood pressure (Ayman, 1931; Alam and Smirk, 1943) and its response to rest in bed (Watkin *et al.*, 1950) and sedatives (Cady *et al.*, 1936). More recently this has been reinforced by the markedly depressor response sometimes obtained to drugs which block the activity of the autonomic nervous system—T.E.A.B. (Lyons *et al.*, 1948; Frisk *et al.*, 1948) and more recently hexamethonium. This drug, like T.E.A.B., reduces the blood pressure by causing arteriolar dilatation and has little effect on the cardiac output in the recumbent subject (Gilmore *et al.*, 1952). Evidence of the overactivity of sympathetic ganglia controlling the blood vessels is demonstrated by their marked sensitivity to blockade in contrast with the ciliary ganglion. The main effect on the blood pressure is achieved by a small dose (10–35 mg.) before transmission through the sympathetic ganglia is completely blocked, and at approximately one-third of the dose required to paralyse the pupils. Response to hexamethonium is therefore similar to experimental neurogenic hypertension, which is the only type of experimental hypertension responding to autonomic blockade by T.E.A.B. (Page, 1949; Page and McCubbin, 1951).

As the degree of vasoconstriction is represented by the fall in blood pressure it is inevitably somewhat exaggerated in these tests, since the neurogenic component is always removed at the highest initial pressure. The same degree of vasodilatation at a lower initial pressure would give a smaller reduction in pressure. Nevertheless a great fall in pressure, particularly if it then comes within the normal range, must indicate that the nervous system is the dominant though not necessarily the only aetiological factor.

The responses in clinically similar cases were found to be quite unpredictable, as there was no correlation with the signs by which the severity is assessed, and each group contained both mild and severe cases. The depression of blood pressure was compared with that of amylobarbitone sedation, and in 12 patients it was also compared with the response to T.E.A.B. Although the trend of the three tests was often the same, there were considerable quantitative differences between them, and each test would have resulted in a somewhat different classification in this series. There is likewise a broad correlation between results of the H.M.B. test and those of Frew and Rosenheim (1949) using T.E.A.B., and also of Frisk *et al.* (1948) and Lyons *et al.* (1948), with the difference that Frisk *et al.* and Lyons *et al.* both report a correlation between the response and the initial level of diastolic blood pressure.

The variability of the minimal pressure in a particular patient reported by Levinson *et al.* (1948) and Ferris *et al.*

FIG. 2.—Response to hexamethonium test of two clinically similar patients, EV and PK, with malignant hypertension.

(1948) using T.E.A.B. was not found. Stability of the minimal diastolic pressure suggests the relative independence of the nervous and humoral factors in hypertension. The striking difference in the ages of Groups A and C is the only factor with which the response to H.M.B. could be correlated, and it suggests the separation of elderly hypertensives into a distinct aetiological group.

Collateral evidence for this is found in the well-known differences in mortality of hypertension below and above 50 years (Bechgaard, 1946; Burgess, 1948), particularly as the incidence of hypertension increases so strikingly with age, rising from 5% in young adults to 30–40% after the age of 40, and thereafter increasing progressively with age (Master *et al.*, 1943). In contrast to the severity and frequency of changes in the renal arteries of young hypertensives, in elderly hypertensives the lesions have been shown to be mild, and only a little more severe than those seen in subjects of the same age without hypertension (Perera and Krane, 1951).

In the group which failed to respond to hexamethonium it is clear that the autonomic nervous system can play little part in the elevation of the blood pressure at rest, and in this they behave in the same way as experimental renal hypertension. It is concluded that the absence of a response in the case of coarctation of the aorta is evidence that a humoral mechanism is present in this condition.

The evolution of early labile hypertension into a sustained humoral one is not supported by the present findings, but the reverse seems possible. Subjects in the intermediate Group B and those with renal hypertension in Group A may tentatively be said to have had a nervous mechanism superimposed upon a humoral one.

Summary

Hexamethonium was used to investigate a group of 46 cases of hypertension. It was given in repeated doses to produce the maximal fall in diastolic pressure. The results show that the neurogenic component is present in elderly hypertensives and is very uncommon below the age of 50 years.

I acknowledge the co-operation of the staff of Charing Cross Hospital, Drs. R. A. Hickling, K. Shirley Smith, and E. C. Warner, who allowed me access to their cases of hypertension, and to Mr. E. A. Crook and Mr. L. A. Broster for allowing certain of their cases to act as controls. I also thank Dr. A. A. Osman for facilities to investigate cases of hypertension at the Renal Unit, Pembury Hospital, Kent, and Mr. K. Browne for checking the statistical material.

REFERENCES

- Alam, G. M., and Smirk, F. H. (1943). *Brit. Heart J.*, 5, 156.
 Ayman, D. (1931). *Arch. intern. Med.*, 48, 89.
 Bechgaard, P. (1946). *Acta med. scand.*, Suppl. 172.
 Burgess, A. M. (1948). *New Engl. J. Med.*, 239, 75.
 Cady, J. B., Horton, B. T., and Adson, A. W. (1936). *Proc. Mayo Clin.*, 11, 825.
 Ferris, E. B., Reiser, M. F., Stead, W. W., and Brust, A. A. (1948). *Trans. Ass. Amer. Phys.*, 61, 97.
 Frew, J. L., and Rosenheim, M. L. (1949). *Clin. Sci.*, 7, 217.
 Frisk, A. R., Hammarström, S., Lagerlöf, H., Werkö, L., Björkenheim, G., Holmgren, A., and Larsson, Y. (1948). *Amer. J. Med.*, 5, 807.
 Gilmore, H. L., Kopelman, H., McMichael, J., and Milne, I. G. (1952). *Lancet*, 2, 898.
 Levinson, J. E., Reiser, M. F., and Ferris, E. B. (1948). *J. clin. Invest.*, 27, 154.
 Lyons, R. H., Hoobler, S. W., Neligh, R. B., Moe, G. K., and Peet, M. M. (1948). *J. Amer. med. Ass.*, 136, 608.
 Master, A. M., Marks, H. H., and Dack, S. (1943). *Ibid.*, 121, 1251.
 Page, I. H. (1949). *Amer. J. Physiol.*, 158, 403.
 — and McCubbin, J. (1951). *Circulation*, 4, 70.
 Paton, W. D. M., and Zaimis, E. J. (1949). *Brit. J. Pharmacol.*, 4, 381.
 — (1951). *Ibid.*, 6, 155.
 Perera, G. A., and Krane, S. M. (1951). *Ann. intern. Med.*, 34, 1017.
 Pickering, G. W. (1936). *Clin. Sci.*, 2, 209.
 Prinzmetal, M., and Wilson, C. (1936). *J. clin. Invest.*, 15, 63.
 Stead, W. W., Reiser, M. F., Rapoport, S., and Ferris, E. B. (1948). *Ibid.*, 27, 766.
 Watkin, D. M., Froeh, H. F., Hatch, F. T., and Gutman, A. B. (1950). *Amer. J. Med.*, 9, 428.
 White, P. D. (1944). *Heart Disease*, 3rd ed., p. 441. New York.

TERRAMYCIN IN THE TREATMENT OF ACUTE OTITIS MEDIA IN CHILDREN

BY

STUART MAWSON, F.R.C.S.

Surgeon to the Ear, Nose, and Throat Department,
 King's College Hospital and the Belgrave Hospital for Children

J. D. GRAY, M.D.

Pathologist, the Belgrave Hospital for Children

AND

A. B. HEWLETT, M.R.C.S., L.R.C.P.

Clinical Assistant, the Ear, Nose, and Throat Department,
 King's College Hospital and the Belgrave Hospital for Children

It is generally agreed that procaine penicillin, in single daily injections of not less than 300,000 units, is the most reliable means of controlling acute otitis media in children with a minimum degree of supervision. Larger doses of crystalline penicillin at more frequent intervals increase the margin of certainty. Oral penicillin and sulphonamides are less reliable, but they offer advantages of administration which favour their use in certain cases. Lewis *et al.* (1952) assessed the value of chloramphenicol and aureomycin in this disease, but concluded that they were unsuitable for domiciliary treatment because, although as effective as penicillin against the organisms commonly found in acute otitis media, some children took such a strong aversion to them that it was impossible to maintain an adequate dosage.

With the advent of terramycin it was decided to review the position, as this compound appeared to offer certain advantages that might answer the need for an oral antibiotic effective in this disease. Terramycin has a wide range of antibacterial activity, and so far has been reported free from toxicity. It is reasonably stable in flavoured solutions, not unduly bitter to the taste, and can also be given in the form of sugar-coated tablets or capsules. In the absence of any published studies of the action of terramycin in otitis media and of an exact precedent for dosage, a clinical trial was made using 50 mg. of terramycin per kg. of body weight per twenty-four hours, against a control series of cases receiving penicillin.

Method

A two-page form was prepared, the first page containing the history, results of examination, type of treatment, and notes on the bacteriological investigation. The second page showed the patient's name only and a summary of daily progress. When a case of acute otitis media was accepted the necessary parts of the form were completed and the pages separated: the first was retained in the laboratory and the second in the out-patient folder. This was to ensure that the clinical observers (S. M. and A. B. H.), who saw each case from the second day onwards, had no knowledge of which antibiotic was being used for treatment and could therefore rely on the impartiality of their judgment.

All cases were first seen by the same casualty officer, well experienced in the recognition of the disease, who allocated the cases to their respective antibiotic in strict alternation. Myringotomy was performed, regardless of