explain all our cases of seminal reflux except the case in which a return of ejaculatory power occurred after a six-months interval. This patient had noticed a post-coital cloudiness of the urine at first—a sign common to the other cases which showed reflux—although there was no actual emission. Later, with the return of emission, the cloudiness had become less obvious. A further point of extreme interest was the fact that he believed the return of seminal emission coincided with a much more virile erection. He was one of the few patients who thought he had not been quite normal in this respect after operation.

This case raises the point of production of urethral obstruction by erection. Apart from the narrowing produced by the erect corpus spongiosum, it is obvious that if the erectile verumontanum enlarges proportionately it would help to block the posterior urethra. This would account for the well-known difficulty of micturition in full erection, and is beautifully illustrated, for example, by a case reported by Swift Joly (1929).

This unfortunate patient suffered from continuous priapism due to vesical calculus, and although constantly driven to attempted micturition was prevented from obtaining relief until the erection had sufficiently subsided.

The attachment of the trigonal muscle to the base of the verumontanum has suggested—and this theory is put forward purely as a possibility—that during normal ejaculation the trigonal muscle, now acting synergistically through the

FIG. 4.—(a) Tight internal sphincter. The dotted line represents shortened trigonal muscle, and the verumontanum is pulled up to plug the internal meatus. (b) Lax internal sphincter. The dotted line represents straightened-out trigonal muscle with open bladder-neck. The verumontanum is not pulled up.

unyielding ring of a spastic internal sphincter, expends its energy in shortening its fibres as it is prevented from straightening itself out. It therefore pulls up the erect colliculus, thereby shortening the posterior urethra and plugging the bladder-neck (Fig. 4, a). This renders doubly secure the closure of the internal meatus, and possibly even opens the ejaculatory ducts. If this theory is correct it is easy to visualize how the denervated internal sphincter now yields to the contracting trigonal muscle, so that shortening of its fibres fails to occur. The verumontanum is not elevated, therefore, and seminal reflux occurs into the bladder (Fig. 4, b).

This hypothesis postulates that in normal ejaculation the internal sphincter is of predominant importance, thoroughly able to resist the antagonistic attempt of the trigonal muscle to open it, and indeed assisting in the action of this muscle to elevate the verumontanum. The combined tight spasm of the internal sphincter aided by the obstructive effect of the erect colliculus seminalis serves to prevent seminal reflux. If, however, the sympathetic denervation of these muscles occurs, the internal sphincter, although it may recover sufficient tone to remain closed under normal conditions, cannot undergo the accentuated spasm which normally occurs at ejaculation and therefore fails to resist even the weakened attempts of the trigonal muscle to open it. The resulting incompetence is aggravated by failure of the plugging action of the verumontanum secondary to the shift in the balance of muscular power.

Summary

Thirty cases of bilateral lumbar ganglionectomy in which the first, second, and third lumbar ganglia had been removed have been followed up with regard to post-operative sterility (seminal anorrhoea). Only three of this series were found to be sterile.

Eight cases of extensive sympathectomy for hypertension were followed up, and seven were found to be sterile.

The sterility in 11 of the above 38 cases was due in seven cases to complete failure of ejaculation to occur, while four cases showed that there was reflux into the bladder. There was no obvious reason for the difference in these two groups.

The mechanism of sterility in these cases is discussed and a theory of normal ejaculation is advanced.

This paper is regarded as a report on work that is as yet incomplete, and further investigation is in progress. I am grateful to Professor A. M. Boyd for his constant stimulation and advice and for his original idea which initiated this investigation.

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COMBINED USE OF HEXAMETHONIUM BROMIDE AND PROCAINE AMIDE IN CONTROLLED HYPOTENSION

A PRELIMINARY REPORT

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Despite increased experience in the use of hexamethonium bromide it was felt that this drug was not of itself wholly satisfactory, and there still remained the small percentage of patients in whom it seemed impossible to produce a blood pressure low enough to achieve the required ischaemia for relatively "bloodless field" surgery. Successes had risen from 50% (Enderby, 1950) to 85% (Enderby and Pelmore, 1951). Failures were almost always in the younger age group of patients, and it was observed that such patients often responded to the administration of hexamethonium bromide by an increased pulse rate (up to 120–140 a minute) and a small and often inadequate fall in blood pressure.

A constant search has been maintained for a drug which would either replace or enhance the action of hexamethonium bromide. Procaine amide appeared likely to achieve the latter for two reasons: (1) its vaso-

dilatory action would enhance the similar vasodilatory action of hexamethonium bromide; and (2) its effect in increasing the refractory period of the heart muscle might prevent the tachycardia which usually occurred and which may well be the cause of failure when using hexamethonium bromide.

Pharmacology of Procaine Amide

Procaine amide hydrochloride is *p*-amino-N-(2-diethyl-aminoethyl) benzamide hydrochloride, with the empirical formula $C_{13}H_{21}N_3O.HCl$, and the molecular weight of 271.79. Its structural formula is:

It differs from procaine only by the substitution of the amide group for the ester group. The structural formula of procaine is:

Procaine is a more potent local analgesic than its amide (Newman and Clark, 1950), but it causes much more central stimulation (Kayden, Steele, *et al.*, 1951). Both drugs are slight respiratory depressants, procaine having the greater effect. Both drugs produce hypotension when administered intravenously, but in conscious patients this is only a temporary effect.

Bradycardia is a feature of the action of both drugs, with depression of the T wave and QRS complex. Such production of bradycardia may well be one of its important features in its power to enhance the action of hexamethonium bromide.

Joseph *et al.* (1951) studied the mechanism by which procaine amide is believed to influence ventricular arrhythmias, and suggested that by some means, not yet satisfactorily determined, it depressed ventricular irritability—specifically the refractory period, as measured by the Q-T interval.

Whether the effect of procaine amide was due to the direct action of the circulating drug, or whether its effect was mediated through either the nervous system or some humoral mechanism, or both, has not yet been clarified. In view of the observation at operations, that inadequate ventilation was associated with most of the ventricular arrhythmias encountered, it was thought possible that the efficacy of procaine amide lay in the diminution of the oxygen requirement of the ventricular musculature, and the cardiac conduction mechanism. Conversely, perhaps, procaine amide participated in the intracellular oxidative processes to increase the oxygen utilization of the tissues (Kayden, Steele, *et al.*, 1951).

Procaine amide is absorbed rapidly and completely from the gastro-intestinal tract, permitting oral dosage when such is desirable. It is excreted in the urine, approximately 60% being recovered unchanged (Mark *et al.*, 1951). Plasma levels decline slowly, approximately 10–20% an hour after intravenous administration (Mark *et al.*, 1951). The amide of procaine is not hydrolysed by the enzyme which affects procaine, and hence is relatively stable *in vivo* (Brodie *et al.*, 1948).

Procaine has been used for the correction of cyclopropane-induced cardiac arrhythmias during anaesthesia (Burstein, 1949). He claimed satisfactory results in 50 cases. Joseph and Rovenstine (1951) and Joseph *et al.* (1951) had similar results with procaine amide. No toxic effects of procaine amide have been produced, as evidenced by haematological, renal, and hepatic studies in dogs (Mark *et al.*, 1951).

Effect on Ventricular Arrhythmias

Ventricular fibrillation is usually rapidly fatal, and search has long been made for a drug which will prevent its onset. Among the drugs that have been used are diethylamino-ethanol, potassium chloride, quinine, "dibenamine," procaine, and procaine amide. Intravenous procaine has been the most widely used during anaesthesia, and has provided the best results (Burstein, 1949).

Ventricular arrhythmias leading to fibrillation may occur under the following conditions: (1) If the patient has pre-existing ventricular extrasystoles, which may be occasional or paroxysmal. (2) With direct mechanical stimulation of the ventricle such as occurs in cardiac catheterization, or operations on the heart itself. (3) The administration of drugs which have a tendency to produce ventricular irregularities—for example, chloroform, cyclopropane, trilene, and adrenaline. (4) Ventricular arrhythmias are sometimes produced for no apparent reason. Stimulation of the larynx, peritoneum, or pleura, and section of the vagi have all been implicated.

Effect on Supraventricular Arrhythmias

Kayden, Steele, *et al.* (1951) stated that the effectiveness of procaine amide in auricular arrhythmias may be influenced by the duration of the arrhythmia. Chronic auricular flutter (10 cases) and chronic auricular fibrillation (14 cases) failed to respond, whereas auricular fibrillation of recent origin (4 cases) responded and reverted to normal rhythm (Kayden, Brodie, and Steele, 1951). Auricular premature contractions were eliminated by procaine amide, although its effect was of shorter duration than in ventricular premature contractions.

Schaffer *et al.* (1951) treated 14 patients with procaine amide and found the drug clinically effective in the treatment of auricular extrasystoles, tachycardia, flutter, and fibrillation. They observed that procaine amide had a depressant influence on abnormal auricular stimulus formation and on normal conduction, as well as having an atropine-like action.

Procaine amide, while protecting the heart from arrhythmias, has been shown to be less toxic than procaine (Mark *et al.*, 1951). It is therefore the drug of choice when treating arrhythmias from any of the above causes. One side-effect of both procaine and its amide is the production of hypotension. In view of the increasing use of hexamethonium bromide for the deliberate production of hypotension in all branches of surgery, the possibility of a series of conditions occurring which necessitate the use of both these drugs in the same patient is becoming more likely—for example, one of us (A. A. M.) was recently faced with the problem of anaesthetizing a patient who showed pronounced irregularity of the pulse. Ventricular extrasystoles were diagnosed, and the control of these with procaine amide during operation was thought advisable. The operation was for removal of a retrobulbar tumour, and because of the ease with which these tumours are removed under the hypotensive technique the surgeon requested that if possible hexamethonium bromide should be used.

It was not known whether the hypotensive action of hexamethonium bromide would be further potentiated by the previous or simultaneous use of procaine amide. The result of this first case encouraged us to study a series of cases using hexamethonium bromide following the previous administration of procaine amide.

We have compared this series with figures taken from 50 unselected cases in which hexamethonium bromide alone was used. Anaesthesia in the two series was exactly the same—namely, induction was with a mixture of thiopentone and gallamine triethiodide, and maintenance was with nitrous oxide and oxygen (2:1), in a semi-closed absorber system, together with intermittent thiopentone or pethidine.

Present Series

Table I shows plainly that after the previous administration of procaine amide a blood-pressure fall to below 60 mm. Hg occurs in more than twice the number of cases

TABLE I.—*The Blood-pressure Levels in 50 Unselected Cases Using Hexamethonium Bromide Alone, Compared with the Levels Achieved when Hexamethonium Bromide is Given After 1 g. of Procaine Amide*

Control Series : Hexamethonium Bromide Alone ; Average Dose, 95 mg.		Hexamethonium Bromide; Average Dose, 65 mg., after Procaine Amide, 1 g. Given in Two Divided Doses of 500 mg.	
Average Blood-pressure Level during Operation	No. of Cases	Average Blood-pressure Level during Operation	No. of Cases
80 and over	16	80 and over	5
70-80	21	70-80	15
60-70	10	60-70	23
50-60	3	50-60	7
	50		50

(30 against 13 in the control series) in which hexamethonium bromide alone was used. It is also evident that the dose of hexamethonium bromide needed to produce a similar fall in blood pressure is reduced by about 30 mg. after the administration of procaine amide. From this we may conclude that the drugs show a true potentiation of each other's hypotensive effects.

In the case of retrobulbar tumour mentioned both procaine amide and hexamethonium bromide were used in the following manner.

Case A.—A woman aged 42 had a neurofibroma of the left orbit. Her general condition was good. "Omnopon," $\frac{1}{2}$ gr. (22 mg.), and scopolamine, 1/150 gr. (0.43 mg.), were given one hour pre-operatively. Her pulse was 84 and irregularly irregular; and blood pressure 130. Anaesthesia was established with a mixture of 0.9 g. of thiopentone and 80 mg. of gallamine triethiodide. An oral tube was passed and anaesthesia was maintained with N_2O+O_2 (2:1) and intermittent thiopentone. The table was then tipped to a 35-degree foot-down position. Her blood pressure was 110, pulse 86 and irregular. Procaine amide was injected intravenously as two doses of 500 mg. each. The pulse became regular two minutes after this and remained so throughout the remainder of the operation. The blood pressure fell to 80 and the pulse rate to 82. Surgery was begun and after only three minutes the blood pressure began to rise, reaching 100 mm. in six minutes. Hexamethonium bromide was then administered intravenously, 20 mg. at a time. After 60 mg. had been injected the blood pressure fell to 60 mm. and remained steady at this level until the operation finished 35 minutes later. The colour remained excellent throughout, the surgical field was clear of blood except for the merest ooze, three swabs only being used. Respirations were unlaboured at 24 a minute. Post-operatively the patient was levelled to a 5-degree foot-down tilt. The blood pressure rose to 100 mm. and the pulse rate was 86. She was transferred at this tilt to her bed. Recovery was uneventful.

It may also be said that cases with a blood pressure of over 80 mm. Hg are often unsatisfactory from an ischaemic point of view. The number of such cases was reduced from 16 with hexamethonium bromide alone to 5 when procaine amide had first been administered. We did not, however, find that all cases with a blood pressure of 80 or over were necessarily unsatisfactory. In fact, many were relatively bloodless, and did not require the pressure to be taken any lower in order to facilitate surgery.

It must be emphasized that the primary object of the anaesthetist is to produce a field which is satisfactory to the surgeon, and not necessarily to produce a particular level of blood pressure. The optimum blood pressure for any particular case varies enormously with the age of the patient, the site of operation, the state of the blood vessels, the pulse rate, and probably many other variables which have not yet been fully assessed. Many cases—for example, excision of a rodent ulcer of the face in a patient of over

70—are virtually bloodless with a pressure of 80–85 mm. Hg, while a young patient may bleed profusely from any site with a blood pressure as low as 65 mm. Hg.

It is estimated that in approximately 85% of all cases in which hexamethonium bromide is used alone a satisfactory surgical result is achieved. That being so, it would be unnecessarily wasteful and troublesome to administer procaine amide to every case, in an attempt to avoid the small number of failures (15%) (Enderby and Pelmore, 1951) which occur when hexamethonium bromide is used alone.

It was therefore decided to restrict the use of procaine amide to cases in which the use of hexamethonium bromide alone had failed to produce adequate ischaemia. A series of 17 such cases were subsequently treated with 1 g. of procaine amide. It will be seen (Table II) that in all except one of these cases a satisfactory operative level was achieved. In no case was any toxic effect seen, and in no case was the blood-pressure fall so severe as to cause concern. The maximum fall occurred within five minutes of administration.

TABLE II.—*Blood Pressure in Cases of Failure with Hexamethonium Bromide (H.M.B.), Showing Subsequent Levels Following the Use of Procaine Amide (P.A.)*

Case	Age	Dose of H.M.B.	B.P. after H.M.B.	B.P. after Addition of P.A.	Dose of P.A.
1	34	200 mg.	120	65	1 g.
2	25	100	90	60	1 "
3	23	200 "	100	60	1 "
4	10	100	105	70	1 "
5	18	100 "	90	65	1 "
6	16	200 "	90	55	1 "
7	32	80	80	65	800 mg.
8	46	100 "	85	65	700 "
9	14	100 "	80	70	1 g.
10	27	100 "	70	50	1 "
11	40	100 "	95	45	1 "
12	26	100 "	90	65	1 "
13	24	160 "	100	80	1 "
14	25	100 "	80	60	600 mg.
15	22	100 "	120	120	1 g.
16	23	95 "	80	60	1 "
17	23	95 "	100	85	1 "

Cases Illustrating Response to Procaine Amide

Two case histories show the type of response to procaine amide.

Case B.—A boy aged 10 had an operation for the removal of a neurofibroma of the orbit. Premedication was with omnopon, $\frac{1}{2}$ gr. (11 mg.), and scopolamine, 1/300 gr. (0.22 mg.). Induction was with 3 ml. of thiopentone (0.15 g.) and maintenance was with N_2O+O_2 and ether, using an Ayre's T-piece. An endotracheal tube was passed and the table tipped to a 35-degree foot-down position. The systolic blood pressure was 110 mm. Hg, and pulse 120. Hexamethonium bromide, 100 mg., was injected intravenously. After five minutes the pulse rate had risen to 140, and the blood pressure had dropped only 5 mm. Hg. Positive pressure could not be used because of the Ayre T-piece. Procaine amide, 800 mg., was given intravenously. The blood pressure fell in five minutes to 60 mm. Hg and the pulse rate resumed its original level of 120. Operation was begun and the field was virtually bloodless. Four swabs only were used during the entire operation, and these only to mop the merest ooze. The pulse remained steady up to the completion of the operation 50 minutes later, and the blood pressure climbed slowly to 80 mm. Hg. On levelling the patient the blood pressure rose to 95 mm. Hg and subsequently recovery was uneventful.

Case C.—A girl aged 18 had an operation for nasal reduction. Premedication was with omnopon, $\frac{1}{2}$ gr. (22 mg.), and scopolamine 1/150 gr. (0.43 mg.). The pre-operative blood pressure was 120 mm. Hg, pulse 84. Induction was with 0.9 g. of thiopentone and 80 mg. of gallamine triethiodide. The blood pressure was then 110 and the pulse 80. An oral tube was passed and anaesthesia maintained with N_2O+O_2 in a semi-closed circle system. Intermittent thiopentone was used. The patient was tipped to a 35-degree foot-down tilt, and hexamethonium bromide, 100 mg., was injected intravenously. After five minutes the blood pressure became 110 and the pulse 116. A second dose of hexamethonium bromide, 100 mg., was then injected and positive pressure respiration began. After five minutes the blood pressure became 85 and the pulse 118. The operation was started and after ten minutes the bleeding was brisk. The blood pressure was 100

and pulse rate 124. Procaine amide, 1 g., was injected intravenously. Within five minutes the blood pressure became 65 and pulse fell to 90. The bleeding stopped. The operation was continued uneventfully, there being only three swabs used, and the sucker was discontinued completely once the blood pressure had fallen to 65 mm. The blood pressure gradually rose to 75 mm. after 70 minutes, but no further bleeding occurred. The pulse was 92. On levelling, the blood pressure rose to 100 mm. Hg. Recovery was uneventful.

Discussion

Cases B and C show an interesting relationship between pulse rate and blood pressure. On the administration of hexamethonium bromide the pulse rate is seen to rise, and the fall in blood pressure is only slight. The injection of procaine amide causes both the blood pressure and the pulse rate to fall. It seems highly probable that the main action of the procaine amide is on the pulse rate, and that the fall in blood pressure is secondary and due to the prevention of this tachycardia.

It would seem reasonable to suppose that the rise in pulse rate following hexamethonium bromide is an effort by the body to compensate for the fall in blood pressure, and occurs possibly through the secretion of adrenaline. The prevention of this compensatory tachycardia seems to be a necessary concomitant of a successful hypotensive anaesthetic, for it has long been observed that almost all the unsuccessful cases have an elevated pulse rate.

It may well be that the omission of gallamine triethiodide, with its tendency to produce tachycardia, will further increase the success rate. This substance was used in our first hexamethonium bromide/procaine amide series so as to make it strictly comparable with the 50 control cases using hexamethonium bromide alone. Enderby has omitted the use of gallamine triethiodide recently, but continues to get a percentage of cases in which a compensatory tachycardia detracts from a good ischaemic result.

Another point of interest is the age group of the 17 cases in which the addition of procaine amide was deemed advisable. Thirteen of the total were under 30 years of age, and this strengthens our previous view that the failures were mostly in the younger age group of patients. Thus the anaesthetist who deals more with the older age group will have greater success with hexamethonium bromide alone and less need for an adjuvant in order to achieve hypotension.

Conclusions

If it is deemed advisable to use hexamethonium bromide and procaine amide together—for example, with ventricular arrhythmias and maxillo-facial operations—no toxic effects occur. The blood pressure, however, does fall more than with either one of these used separately, and also with smaller doses. The drugs show a true potentiation of each other's hypotensive effects. The anaesthetist must use supreme caution and vigilance when using them together.

If hexamethonium bromide fails to bring the blood pressure down to a level in which bleeding is negligible the result will almost always be safely and quickly achieved by the subsequent addition of 1 g. of procaine amide intravenously.

Failure of hexamethonium bromide alone seems to occur with the greatest frequency in patients under the age of 30, and it may be anticipated that procaine will be required most often in this age group.

Summary

A series of 50 cases is reported in which procaine amide was used before the administration of hexamethonium bromide, and the results are compared with a control series.

A further series of 17 cases is reported in which hexamethonium bromide failed to produce a sufficient fall in blood pressure, and which responded after the administration of procaine amide.

The effect on the pulse rate and its relationship to the hypotensive effect of these two drugs are clearly demonstrated.

We wish to thank our colleagues for their encouragement and assistance with these investigations and their permission to use some of their records, and Messrs. Squibb for generously supplying procaine amide ("pronestyl"). We are also indebted to Dr. D. A. Robertson, cardiologist at this unit, for his help and advice.

[ADDENDUM.—Since completing the foregoing article in February, 1952, work has gone forward with procaine amide, and 150 additional cases have received this drug. Careful observations have been made and records kept. So far no cases of allergy or untoward side-effects have been noticed. The pulse rate has almost invariably been reduced, with resulting benefit. The drug is being used by us in doses of 0.5 to 1 g. in those cases in which the pulse rate remains higher than 110. An additional paper is being produced on this series.

We are indebted to Messrs. May and Baker Ltd. for supplying the entire requirements of this later series of cases.]

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TREATMENT OF ACUTE MALARIA WITH PYRIMETHAMINE

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Pyrimethamine, which is 2:4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine, is the latest of the new synthetic anti-malarial drugs to be tested by us in the Malaria Research Division of this institute. This compound is produced by Burroughs Wellcome & Co. under the trade name "daraprim," and was formerly known by the experimental number B.W. 50-63.

Falco *et al.* (1951) found that pyrimethamine was active in very small doses against *Plasmodium gallinaceum*, *P. berghei*, and *P. cynomolgi*, and its toxicity was slight. Rollo (1951) reported that proguanil-resistant strains of *P. gallinaceum* and *P. berghei* were susceptible to pyrimethamine, and found that *P. gallinaceum* could not readily be made resistant to pyrimethamine by the usual methods. Archibald (1951) gave the first account of the effect of pyrimethamine in human malaria. Single doses of as little as 5 mg. cleared *P. falciparum* trophozoites from the blood of Nigerian schoolchildren; his patients, however, seem to have been parasite carriers rather than sufferers from acute malaria.

Through the kindness of Brigadier J. S. K. Boyd, Director of the Wellcome Laboratories of Tropical