Great progress has been made in the control of hypertension since the introduction of the first ganglion blocking agent, hexamethonium, by Paton and Zaimis in 1948. We can look, with some degree of satisfaction, at the rather impressive list of drugs introduced during the past decade which have enabled us to treat severe hypertension with better results and less upsetting side-effects for our patients. Milestones in this development include the synthesis of pentolinium, chlorisondamine, mecamylamine and pempidine and the recognition of the potentiating effects of saluretic agents such as chlorothiazide and its newer derivatives.

Nevertheless the overall results by no means justify any great degree of complacency and especially those at the receiving end, our patients, fully realised the shortcomings of these compounds. Most of the complaints arose from the apparently unavoidable parasympathetic blocking effects resulting in blurred eye sight, dryness of the mouth, severe gastro-intestinal upsets including abdominal cramps, constipation and even ileus, difficulty in micturition, impotence etc., as well as more specific toxic reactions attributable to some of these drugs, such as the neurological effects of mecamylamine. It was therefore not surprising that the encouraging report of Boura et al (1959) of a new selective adrenergic blocking agent attracted a great deal of attention and raised great hopes in the minds of clinicians and patients. This new compound, bretylium tosylate, was reported to be completely free from parasympathetic blocking effects and appeared to go a long way towards the goal of a perfect, potent, hypotensive agent. Further experience published by Dollery et al (1960), Turner and Lowther (1960), Hayden and Boake (1960) and Mackie (1960) pointed out new difficulties and problems, which, together with our experiences published below, make it doubtful whether this drug will find a permanent place in our therapeutic hypotensive regime.

Pharmacology

Bretyllium tosylate is the p-toluene sulphonate salt of a benzyl quaternary ammonium compound with the following formula:

\[
\begin{align*}
&\text{CH}_2 \\
&\text{CH}_2 - \text{N}^+ - \text{C}_6\text{H}_5 \\
&\text{CH}_3 \\
&\text{SO}_3^- \\
&\text{Br} \\
&\text{CH}_3
\end{align*}
\]

It has been shown in animal experiments to block selectively transmission in the post-ganglionic adrenergic sympathetic nervous system and to prevent the release of adrenaline and nor-adrenaline at the nerve endings. This block is unaccompanied by any inhibition of the parasympathetic system and by central depression. It does not prevent the release of catecholamines from the adrenal medulla, whose nerve supply is cholinergic, nor does it reduce the effects of injected adrenaline or nor-

* This paper was read in part on the 2nd June, 1960 in Melbourne during the Second Asian-Pacific Congress in Cardiology.
adrenaline in a way characteristic of phentolamine. There is some pharmacological evidence that in high concentrations the drug exerts a blocking effect at the neuro-muscular junction, not unlike the curare-like effect previously reported with mecamylamine.

Gastro-intestinal absorption appears to be incomplete. Studies reported by Dollery et al (1960) using isotope labelled bretylium, revealed a urinary twenty-four excretion of only 5% to 18%, with a mean of 13%, following an oral dose, compared with a mean twenty-four hour excretion of 71% in four subjects following an intravenous dose. Excretion rates are significantly diminished by impaired renal function.

The hypotensive effects of bretylium depend largely on postural drops, even with big doses the fall in the supine blood pressure is only slight compared with the marked hypotensive response on standing. We have measured intermediate degrees of blood pressure reduction in the sitting and semi-reclining postures. The therapeutic implications of this phenomenon have been fully utilised in the practical management of our patients.

**Clinical Trial**

Twenty-seven patients, fourteen males and thirteen females, suffering from severe hypertensive cardio-vascular disease, were treated with bretylium for periods of up to seven months. Their ages ranged from twenty-three to fifty-seven years. They were all fully investigated from the aetiological point of view, as well as to determine the extent of cardiac, renal and vascular damage. In addition to full history and clinical examination, all patients, as part of their routine investigations, had ophtalmoscopic inspection supplemented by retinal photography, electrocardiogram, chest X-ray, full urinalysis and blood urea nitrogen estimation. In addition, many patients had further renal function tests including intravenous pyelography, renal aortography and full urological consultation. Whenever indicated patients were screened to exclude a phaeochromocytoma.

Twelve of the twenty-seven patients were in the malignant phase of hypertension with retinal haemorrhages, exudates or papilloedema. All but four patients had repeated diastolic blood pressure readings, measured to disappearance of sound, of 130 mm of mercury or more, in ten patients the diastolic blood pressure exceeded 150 mm of mercury. Only two patients had normal electrocardiograms, the others showed varying degrees of left-sided cardiac enlargement. In twelve the changes were classified, according to our criteria, as grade 111 left ventricular hypertrophy with tall R waves, ST segment depression and T wave inversion in left ventricular surface leads. Renal impairment was obvious in fifteen patients with persistent proteinuria or non-protein nitrogen retention. Nine patients had a significantly raised blood urea, three patients had a blood urea nitrogen of over 60 mgm %, one patient with an initial blood urea nitrogen of 107 mgm % has been on treatment for four months. Two patients had previously suffered from major cerebro-vascular accidents, four patients had cardiac complications including myocardial infarction, ischaemic effort pain and hypertensive heart failure.

Fifteen patients were thought to suffer from renal hypertension. Eleven were diagnosed from history and investigations as chronic pyelonephritis, including four patients with recurrent renal calculi. Three patients suffered from chronic glomerulo-nephritis, one of them gave a clear-cut history of acute nephritis some years earlier. One patient was found on aortography to have a renal artery stenosis and whilst awaiting definitive surgery, has temporarily been treated with hypotensive agents. Eight of the fifteen patients suffering from renal hypertension were in the malignant phase.

Twelve patients, including four with malignant eye-ground changes, were thought to suffer from essential hypertension. A definite family history of hypertensive or other vascular disease was obtained in half the patients, but such a family history was surprisingly enough even more common in patients with renal hypertension. One female patient with diabetes and hirsutism was suspected to suffer from Cushing's syndrome, but this was not confirmed.

Twenty-one patients had previously been
treated with ganglion blocking agents, such as pentolinium, chlorisondamine, mecaminylamine and pempidine. In the majority a change-over to brettylum was attempted because of excessive side-effects. Later in the trial a number of patients were stabilised on brettylum de novo.

In accordance with the practice at the Cardio-Vascular Clinic, Sydney Hospital, the majority of patients were admitted to hospital during the initial period of treatment. Blood pressure reduction was usually commenced, after a preliminary period of observation, with a dose of 100 mgm brettylum three times a day. Instructions were given to crush the tablets and not to take them together with meals in order to minimise irregular gastro-intestinal absorption. Patients with renal failure were started on a smaller dose and special care was taken to avoid prolonged hypotensive episodes. Patients were encouraged to be up and about as much as possible and to sleep propped up. The effect of any given dose was judged by hourly standing blood pressure estimations with frequent checks on the amount of postural drop. It became customary to increase the dose when necessary every second or third day by 100 mgm up to 600 mgm and then to increase by 200 mgm to 1000 mgm. If the response to 1000 mgm three times a day was inadequate, especially with the addition of chlorothiazide and reserpine, the patient was considered relatively resistant to the drug and a change to some other form of treatment was advised.

Once a pharmacologically active dose was reached a significant drop in systolic and diastolic blood pressure was recorded one to two hours after the ingestion of brettylum, with a gradual, if somewhat irregular, climb to previous readings in four to six hours. More persistent drops in standing blood pressure were observed in patients with renal failure who had occasionally adequate blood pressure control with a single daily dose and in whom it has been possible to demonstrate some postural drug effect for as long as forty-eight to seventy-two hours. After the blood pressure was considered adequately reduced the patient was observed at frequent intervals as an out-patient where further adjustments of dosage were carried out after assessment of hourly run-through figures.

A number of patients, either because of previous difficulty with ganglion blocking stabilisation, or because of an inadequate initial response to brettylum, were concomitantly treated with chlorothiazide or one of its derivatives and occasionally with reserpine. In these instances we have found it advisable to commence with the diuretic agent and gradually add brettylum, or alternatively to half the dose of the adrenergic blocking agent whilst introducing chlorothiazide, in order to avoid excessive hypotensive reactions.

RESULTS OF TREATMENT

Of the twenty-seven patients treated with brettylum tosylate, sixteen are at present continuing with some, but varying, degree of blood pressure control. Two patients whilst still taking the drug are uncontrolled and are awaiting change-over to a more suitable regime. Treatment was terminated in nine patients.

Three patients included in this series died. Two, with preexisting advanced renal failure, who were treated on account of malignant hypertension, died from uraemia, all hypotensive treatment having been suspended some weeks before the final event. One patient with gross cardiomegaly, previous myocardial infarction and atrial fibrillation, died in his sleep. In none of these three instances was the drug thought to be in any way a contributory factor.

In two patients with malignant hypertension there was no sustained hypotensive response with doses as large as 3000 mgm per day and treatment was abandoned. The drug, supplied in 200 mgm tablets, has a bitter taste, and when exceeding fifteen tablets a day often causes anorexia and nausea. Concern was also felt at the increased risk of sudden unpredictable hypotensive responses from such large oral doses.

Two patients complained of severe tiredness, shakiness, abdominal pain and vomiting necessitating interruption of treatment. In one patient with malignant hypertension these symptoms persisted after suspension of brettylum and were therefore thought unlikely to be due to the drug. The other patient was difficult to assess having experienced great discomfort with other ganglion blocking agents.

Japanese Circulation Journal  Vol. 25, May 1961
and being generally not a very cooperative patient.

Treatment was suspended in one patient because of intercurrent gastro-intestinal haemorrhage and one patient had to interrupt treatment for geographical reasons finding it difficult to attend the clinic.

Of the sixteen patients who continue to take bretylum, seven suffered from malignant hypertension and five had severe degrees of renal impairment. Of the nine patients with non-malignant hypertension and normal renal function who were started on treatment, six patients have good blood pressure control and continue with therapy. Whilst more patients with milder forms of hypertension, as judged by diastolic blood pressure, eye ground changes, left ventricular hypertrophy and extent of renal damage, continue on bretylum, there are some in the accelerated phase of hypertension who are able to carry on.

In ten of the sixteen patients regarded as having some degree of blood pressure reduction, moderate to substantial increases in dosage were necessary following their initial stabilisation in hospital. This development of tolerance has been much more noticeable with bretylum than with the ganglion blocking agents previously studied. Successive increases in dosage in some patients have been necessary over the entire seven months period of observation. This phenomenon is one of the main drawbacks of bretylum requiring repeated follow-up observations at frequent intervals.

Final daily dosages in the sixteen patients continuing on adequate treatment range from 100 mgm, in a patient with advanced renal failure, to 2400 mgm. In nine patients the daily maintenance dose lies between 600 mgm and 1500 mgm, usually administered in three equal doses. The great variation in the maintenance dose once again underlines the need for careful initial stabilisation and strict follow-up supervision. Patients with renal failure required, and indeed only tolerated, significantly smaller quantities of bretylum.

SIDE EFFECTS

Bretylum was by no means as free from unpleasant side-effects as preliminary reports had led us to hope. First of all by virtue of its irregular and unpredictable gastro-intestinal absorption and its marked postural effect on blood pressure, hypotensive symptoms, ranging from a mere complaint of fatigue, tiredness and dizziness to constrictive chest pain, transient neurological disturbance and syncope, were more frequent than with other ganglion blocking agents. These hypotensive episodes may not only produce unpleasant symptoms but in the presence of renal impairment and cardiac or cerebral ischaemia could prove potentially hazardous. The incidence of hypotensive side-effects depends on such variables as marked diuresis, excessive perspiration, physical exercise and gastro-intestinal upsets, it also depends on the time and care taken during initial stabilisation.

 Eleven patients, including eight continuing with treatment, were free from all side-effects during the period of observation. This is in marked and favorable contrast with previously available ganglion blocking agents in whom the effects of parasympathetic inhibition were an unavoidable by-product of pharmacologically effective hypotensive therapy.

Six patients complained of nasal stuffiness, three patients of dryness of the mouth and two patients were quite severely, but transiently, inconvenienced by parotid pain, a side effect which in the first patient led to a tentative diagnosis of mumps.

Seven patients complained of abdominal symptoms, especially nausea and vomiting. In some this was suspected of being due to some associated condition such as migraine or progressive renal failure, in others it may have been due to transient hypotension or some direct effect of the drug. Four patients felt unduly restless and irritable after starting bretylum, reminiscent of the nuerological effects sometimes observed during mecamylamine treatment. One young man, who had been impotent whilst taking pentolinium and pemipidine, regained potency whilst taking bretylum but complained of failure of ejaculation.

DISCUSSION

We have previously published our experiences with ganglion blocking agents in the

treatment of hypertension (Bauer 1955, Bauer et al 1957, Bauer et al 1959) and have also reported on the potentiating effects of chlorothiazide and some of its newer derivatives (Bauer 1960). The introduction of bretylium marks a further mile-stone in this pharmacological and therapeutic development. It is the first benzyl quaternary ammonium compound with selective adrenergic blocking effects unaccompanied by parasympathetic suppression and central inhibition. Following their preliminary trial on thirty-six hypertensive patients, Boura et al (1959) reported that the hypotensive action of the drug was largely postural and also mentioned the onset of tolerance in the course of prolonged treatment. Smirk and Hodge (1959) confirmed the great promise of this new compound but were the first to point out that the bulk and bitter taste might be a disadvantage to some patients. Dollery et al (1960) stressed the variability of the degree of blood pressure drop and their studies with isotope labelled bretylium confirmed the incomplete gastro-intestinal absorption of the drug. Only nine of their twenty-two patients with severe hypertension and high-grade retinopathy were satisfactorily controlled and the majority had to be transferred to another ganglion blocking drug. Further reports by Turner and Lowther (1960) and Evanston and Sears (1960) were less encouraging. Increasing length of observation showed that more and more patients were inadequately controlled and required steady increments in dosage with the appearance of new and varied side-effects. Hayden and Boake (1960) and Mackie (1960) published the first experiences from this country and were in general favourably impressed. The Melbourne workers stated that some patients requiring very large doses were probably unsuitable for prolonged treatment, whilst patients with renal damage sometimes had further rises in blood urea. Mackie stressed the augmenting effect of chlorothiazide and advised the routine combination of this drug with bretylium.

After seven months experience we feel that the main advantage of bretylium lies in the absence of parasympathetic blocking effects. All patients previously treated with pentolinium, chlorisondamine, mecamylamine and pempidine were initially delighted with the apparent freedom from side-effects, absence of visual disturbances, normal bowel and bladder functions and normal potency.

The disadvantages of bretylium however are not inconsiderable. First of all with increasing length of observation drug tolerance has been seen to be a common and disturbing problem demanding careful follow-up examinations. The necessity for frequent visits to the clinic or the physician’s consulting rooms resulting in increasing loss of time from work and domestic duties often leads to excessive economic burdens, as well as placing a greater strain on the medical staff. The second disadvantage concerns the incomplete and irregular gastro-intestinal absorption of the drug, which together with the marked postural effects frequently lead to transient hypotensive episodes not unlike those seen in the early days of oral hexamethonium treatment. Thirdly bretylium causes its own side-effects and although they are not nearly as severe as those of the older ganglion blocking agents, they are nonetheless unpleasant. Nasal stuffiness, dryness of the mouth, parotid pain, abdominal discomfort and vague weakness and tiredness are most commonly complained of. Fourthly the bitter taste and large bulk of the tablets has been objected to by patients requiring larger doses, especially as we try to encourage patients to crush the tablets in order to reduce irregularity of absorption. Fifthly a not inconsiderable problem is presented by the high price of this drug. In some cases the cost of maintenance treatment is so great as to be entirely impracticable for patients on high dosage especially when considering prolonged treatment for an indefinite period of time.

It is largely on account of such considerations that we are doubtful whether this drug will find a permanent place amongst our hypotensive drugs. At present, from the practical point of view, it shows greatest promise in the less severe and non-malignant forms of hypertension, especially in the patient who does not develop marked tolerance to the drug and who obtains an adequate fall in blood pressure with moderate doses, less than 600 mgm three times a day. We trust that bretylium will
soon be followed by further compounds of even greater promise which will bring us nearer yet to the goal of the ideal hypotensive drug.

SUMMARY

A seven months trial involving twenty-seven patients with the new hypotensive agent bretylium is described. This drug selectively blocks adrenergic nerve transmission and leads to marked postural falls in blood pressure. It is free from parasympathetic blocking effects such as blurred vision, constipation and bladder atony, but other, generally milder side effects have been noted. The drug is incompletely absorbed when given by mouth. Advantages and disadvantages of this new compound are discussed and its likely future place in the hypotensive drug regime has been considered.

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