and experience must therefore be necessarily limited, certain inescapable facts have come to light. Among the total of 133 cases so far accumulated there have been five maternal and nine foetal deaths. The majority of these patients fell into the unfavourable group (grades III and IV), and in most of them surgery was tolerated as well as in the non-pregnant state. They were able to continue the remainder of their pregnancy without undue limitation on their activities. In addition, Watt, Bigelow, and Greenwood (1959) followed up their series of 24 patients operated on during pregnancy, with neither maternal nor foetal mortality, for one to six years. They found that all had reverted to either grade I or II from a pre-operative grading of III or IV.

Our 10 patients were operated on by the transventricular route, using a mechanical dilator, the method we have employed exclusively since late 1956. In our unit 250 valvotomies have been performed with this instrument, and the uniformly satisfactory commissurotomy compares, we feel, very favourably with the uncertainty of the digital methods. The previous operations described in pregnancy appear to have been carried out through the atrium by the combination of finger and knife. In the series of 37 cases reported by Dogliotti *et al.* (1960) no mention is made of the actual technique, but as his cases date from 1953 the implication is that a conventional digital method has been used. Our experience is that instrumental valvotomy is tolerated equally well in the pregnant and non-pregnant state. In addition, we believe that the more certain relief of mitral obstruction obtained by the instrument is of double importance in the overburdened circulation of a pregnant woman suffering from mitral stenosis.

One of our patients (Case 10) died 18 hours post-operatively. At the beginning of pregnancy she was in grade II, but she progressed steadily to grade IV by the twentieth week. By this stage she was orthopnoeic, showed marked pulmonary congestion, and had bilateral pleural effusions. Operation was urgent if the mother's life was to be saved. During anaesthetic induction, cyanosis and peripheral circulatory collapse became rapidly obvious. Thoracotomy, promptly performed, revealed the heart in asystole. Expeditious valvotomy was carried out, and after cardiac massage for several minutes cardiac contractions returned, though the output was manifestly ineffective. She failed to regain consciousness and died next morning. Surgery at an earlier stage of this woman's pregnancy or prior to pregnancy might well have saved her life.

From the accumulated accounts of the surgical treatment of mitral stenosis in pregnancy and in the light of our own experience, we believe that operation is a safe and valuable procedure in those patients. In the absence of a reliable guide to the stability of functional grading in pregnant women with mitral stenosis, it seems reasonable to advocate operation if serial assessments indicate progressive cardiac disability. In grades III and IV the case for operation is even stronger. From the point of view of maternal safety, operation in the early months of pregnancy would avoid entirely the necessity for urgent intervention in the face of grave circulatory embarrassment.

Summary and Conclusions

The relevant literature on mitral valvotomy during pregnancy is briefly reviewed and a further 10 cases are described.

All patients were subjected to a transventricular operation, with very satisfactory short- and long-term results in all but one instance. A plea is made for the serious consideration of operative intervention in those patients, in view of their established tendencies to deteriorate clinically during the course of pregnancy.

We thank Mr. R. S. Barclay for his help and encouragement in the preparation of this paper and for his permission to have it published. We also thank the physicians and obstetricians who referred their patients for surgical treatment.

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TREATMENT OF SEVERE HYPERTENSION WITH BRETYLIUM TOSYLATE

BY

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Bretylium tosylate ("darenthin") is N-o-bromobenzyl-N-ethyl-N:N-dimethylammonium p-toluenesulphonate.

Pharmacology of Bretylium Tosylate

The pharmacology of this drug and the first clinical applications in the treatment of hypertension in man were described by Boura *et al.* (1959), in a joint paper from the Wellcome Foundation and University College, ten years after Arnold and Rosenheim (1949) first reported the use of the salts of hexamethonium in the treatment of hypertensive disease. A benzyl quaternary ammonium compound, it has no evident anticholinergic action, but selectively blocks the peripheral sympathetic (adrenergic) nerves, where its preferential accumulation has been demonstrated by radioactive techniques. Its action therefore differs in an important way from that of the earlier ganglioplegic agents, in which the concomitant parasympathetic block is a clinical disadvantage, and also from that of the secondary and tertiary amines, mecamylamine and pempidine, which enter the body cells and may, in addition, cause side-effects by their central action (Bennett *et al.*, 1957).

Adrenergic nerve blockade is not, it should be recalled, the same as adrenergic effect. On the contrary, just as denervated vessels become hypersensitive to the action of circulating adrenaline and noradrenaline, so

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the vasoconstrictor effects of these substances and their action on the nictitating membrane of the cat are increased after administration of bretylium tosylate. A very severe hypertensive crisis was observed in a patient with a pheochromocytoma after intravenous administration of bretylium (Boura *et al.*, 1959). This, however, is not a constant effect, as it did not occur in another similar case (Rosenheim, personal communication).

The chemical sympathectomy thus achieved by bretylium tosylate causes orthostatic hypotension in the experimental animal and in man, more conspicuously in the hypertensive subject, by release of vasoconstrictor tone, and the isolated nature of its action offers the clinician "a hypotensive agent of a new type" (Boura *et al.*, 1959).

The purpose of this paper is to describe our experiences with bretylium tosylate in the treatment of 75 cases of severe hypertension over a period of nine months. Of these, 65 have received the drug for more than six months continuously.

Method

Bretylium tosylate was used throughout by the oral route in tablets containing 200 mg. of the salt (112 mg. of the base). The tablets are scored in half so that doses of 100 mg. are given easily. The drug has been administered at approximately eight-hour intervals and always before meals, as this facilitates absorption. Every patient who had not previously been treated with ganglion-blocking agents was admitted to hospital for preliminary investigation and for the initial stages of treatment. The investigations were directed to assess the possible cause and severity of the hypertension, with special regard to cardiac and renal function. The fundal appearances were carefully noted.

A number of patients who had been treated over a period of time with mecamlamine and pempidine, whether or not in combination with reserpine, hydralazine, and oral diuretics, and who had been followed up at regular intervals at the hypertensive clinic, were switched, either gradually or suddenly, from the ganglion-blocking agent they were taking to bretylium tosylate without admission to hospital. At first the dose relation used was of one tablet of bretylium tosylate for each 5 mg. of mecamlamine or pempidine, but it was soon found wiser to substitute one tablet of bretylium tosylate for each 10 mg. of the other drugs.

In order to assess the action of bretylium tosylate, no other hypotensive agent was given in the initial stages of treatment to any patient. Later, the oral diuretic, hydroflumethiazide, was added in a number of cases. In previously untreated cases the initial dose of bretylium tosylate was 100 mg. eight-hourly, as it was soon found that even this small dose could give rise to marked postural hypotension. The dose was increased by 100 mg. t.i.d. every other day and in demonstrably less responsive cases by 200 mg. t.i.d. until the desired effect was obtained. While in hospital, blood-pressure was recorded in the lying and standing positions four hours after each dose and more frequently when required. In out-patients blood-pressure was also recorded in both postures and approximately four hours after the last dose of the drug. Fundal appearances were noted at monthly intervals, and the urine, blood urea, and, where necessary, the serum electrolytes, were periodically determined.

Classification of Cases

Table I shows the grouping of cases in our series.

By severe benign hypertension (group A) we mean uncomplicated hypertension with diastolic pressures of 120+ mm. Hg at rest.

TABLE I.—Grouping of Cases

Group	No. of Cases	Male	Female	Average Age in Years	No. of Cases Previously Treated with Ganglion-blocking Agents
A. Severe benign hypertension	7	6	1	49	4
B. Severe benign hypertension with cardiac involvement	39	19	20	50	18
C. Severe benign hypertension and blood urea greater than 50 mg./100 ml.	13	7	6	55	6
D. Malignant hypertension	13	6	7	53	7
E. Severe benign hypertension in pregnancy	3	0	3	30	0
Total	75	38	37	48	35

Group B (severe benign hypertension with cardiac involvement) comprises patients with hypertensive heart failure, both incipient and established, patients with associated coronary disease, and a few cases which, although symptomless, were found to have marked cardiac enlargement and T-wave inversion in the left ventricular surface leads of the electro-cardiogram.

Group C comprises all patients found to have albuminuria and renal failure (blood urea more than 50 mg./100 ml.) in the absence of congestive cardiac failure; aetiologically they are a heterogeneous group, as it was not always possible to establish with certainty whether renal failure was due to chronic glomerulonephritis, to chronic pyelonephritis, or to renal ischaemia which followed essential hypertension. This group does not include toxæmia of pregnancy and malignant hypertension.

Group D comprises all patients with severe diastolic hypertension and papilloedema irrespective of the aetiology of the hypertensive state and of the complications ensuing. They have been grouped separately because they are the obvious measuring-rod for assessing the results of hypotensive treatment (Harington *et al.*, 1959).

Group E (benign hypertension in pregnancy). Only three patients were thought to be suitable for treatment with bretylium tosylate. When toxæmia of pregnancy coexists or is the cause of the hypertensive state, bedrest is imperative, and bretylium tosylate was found to be an ineffective hypotensive in the supine position.

Results

The results of treatment in the various case groups are shown schematically in Table II. In general, a response was classified as satisfactory when, without interference with the patient's usual habits of work and leisure, the orthostatic diastolic blood-pressure could be maintained at about 90 mm. Hg. In the most severe and the malignant cases higher average diastolic pressures were accepted as satisfactory if they were accompanied by evidence or regression of the ocular and electrocardiographic signs and by a falling level of the blood urea.

TABLE II.—Response to Treatment in 75 Cases

Group:	A	B	C	D	E	Total
Satisfactory with a low dosage of bretylium tosylate. Less than 1,000 mg. a day...	2	9	2	0	1	14
Satisfactory with a high dosage of bretylium tosylate. More than 1,000 mg. a day...	3	20	9	7	0	39
Intolerance of optimum dosage	0	2	1	3	0	6
Poor response	0	0	1	2	2	5
Discontinued because of side-effects or some other contra-indication	2	8	0	1	0	11

The minimal effective dose for prolonged administration has varied from 100 to 1,800 mg. t.i.d. With a single exception, it has been found that some increase in dosage is necessary in order to maintain control after the patient has left hospital, and there has not infrequently been some anxiety about whether the ultimate effective dose will exceed the patient's capacity. Our upper limit of 1,800 mg. t.i.d. is low by some standards, but we have found that to give large numbers of the same tablets impairs the patient's confidence in the efficacy of the treatment, upsets his digestion, and makes him feel that his condition must be very serious. We have taken a total daily dose of 1 g. as an arbitrary level above which this difficulty may be encountered in some degree. We have found, as explained below, that the adjuvant effect of hydroflumethiazide has been most helpful in limiting the numbers of patients in whom the optimum dose cannot be attained.

Satisfactory control of blood-pressure in the orthostatic position does not, of course, necessarily mean satisfactory control of the disease process. Two of our patients have died, one of rapidly progressive cardio-renal failure and one of a cerebral haemorrhage. Another four, two with malignant hypertension and all with renal impairment at the onset of treatment, are deteriorating, and a second patient has had a massive cerebral haemorrhage evacuated surgically. In two cases the dose cannot be adequately raised, because profound orthostatic hypotension aggravates a pre-existing cerebral ischaemia and we have had to be content with more modest control over the blood-pressure. These are incidents and hazards which are always met in the treatment of any series of patients with severe hypertensive disease.

An unsatisfactory response was obtained in 2 of the 13 patients with malignant hypertension and in a third patient in whom polyarteritis nodosa is suspected. The other two failures were in pregnant women and were attributed to recumbency.

The drug has had to be discontinued in nine cases because of side-effects or the development of cardiac or cerebral complications. One patient returned to her previously well-established treatment with pentolinium and another to reserpine alone, with moderate control. Three patients have changed to trimethidinium and one to guanethidine. So far no patient has been reverted to mecamlamine or pempidine, although we still have a number who remain satisfactorily controlled with these drugs.

Side-effects

Postural Hypotension

Although the establishment of postural hypotension is the aim of treatment with this drug, a reduction of blood-pressure that is so sudden and profound as to cause a disabling cerebral anoxia must be regarded as an unwanted side-effect.

It was met with more frequently at the onset of treatment; and one patient, a woman of 40 with malignant hypertension, showed at first a "spirit-level" type of response to a single dose of 100 mg., but now requires 1,200 mg. t.i.d. with added hydroflumethiazide. In other cases the difficulty has persisted until the treatment has had to be abandoned. We agree with Turner and Lowther (1960) that giddiness is a difficult symptom to evaluate, as it is not necessarily linked with the severity of the hypotension. It appears that the individual response to the sudden fall in blood-pressure varies as widely as does the response to the fall in blood volume in the "dumping syndrome" as described by Le Quesne *et al.* (1960).

Some patients have particularly complained of giddiness or faintness on getting up at night to empty the bladder, causing a fall on one occasion, and there have also been several complaints of the same symptoms after exertion, such as climbing stairs, as Lowe and Rosenheim (1960) have observed.

In five cases pain in the nape has occurred at the height of the hypotensive effect, especially if the patient exercises at this time (Montuschi, 1957). In three of these patients the symptom, which had been noticed while they were previously under treatment with parenteral pentolinium, disappeared when change was made to mecamlamine and reappeared when bretylium tosylate was substituted for mecamlamine, presumably because of the sharper orthostatic hypotensive reaction induced by this drug.

General Tiredness

This side-effect is very common and is not simply linked with fall in blood-pressure, as it persists in the sitting posture and has been noticeable in patients who had been previously treated with ganglion-blocking drugs. Tiredness is both mental and physical, and on occasion patients have reported extreme fatigue in lifting the arms to shave or to do their hair. Neuromuscular block has been reported in experimental work (Boura and Green, 1959), but only with doses of the order of 30 times those required to reduce sympathetic tone. Extreme muscle fatigue led two patients to discontinue the treatment. The electromyogram showed a myopathic pattern in one case, and a similar finding has been reported to us by Evanson (personal communication).

Stiffness of Nose

Stiffness of the nose and puffiness of the eyes are in our experience uncommon side-effects. They are not usually troublesome. In one case, however, a dose of 1,800 mg. t.i.d., required in order to achieve satisfactory control over the blood-pressure, provoked an intolerable rhinorrhoea with lachrimation. The difficulty was overcome by reducing the dose of bretylium tosylate to 1,200 mg. t.i.d. and adding hydroflumethiazide. With this combination of drugs the blood-pressure was adequately controlled, and only moderate nasal congestion persisted.

Parotid Pain

Sharp transient pain in the parotid region at the very onset of mastication, relieved by continued eating, is a very common side-effect. Its incidence—not less than 25%—is difficult to estimate, as it is in great part a function of duration of treatment. It rarely occurs during the first month of treatment, and more commonly becomes manifest after three to six months. This may be the reason why only four cases were

reported in the Hammersmith series. Although alarming for some patients, it is mentioned by others only on direct questioning. In one case, not of this series (Caplan, personal communication), the severity of parotid pain led to discontinuation of treatment. It is noteworthy that pain continued for a whole week after treatment was withdrawn and long after any hypotensive effect of the drug was recorded. In one of our cases the symptom persisted for three months after cessation of treatment for other reasons. This, together with the delay in onset of the symptoms, strongly suggests a slow local preferential accumulation of the drug.

The mechanism of action of this side-effect is not known, but the symptomatology suggests a spasm of the orifice of the parotid duct with transient obstruction to salivary flow. One patient experienced pain simply at the sight of appetizing food.

Gastro-intestinal Intolerance

As the drug is administered on an empty stomach, nausea and vomiting may be troublesome at high dosage. The difficulty is often circumvented by diminishing the dose of bretylium tosylate and adding an oral diuretic of the benzothiadiazine series. When the dose of bretylium tosylate is raised rapidly diarrhoea may ensue, but this quickly passes on reducing the dose and building it up again more slowly. Transient looseness of the bowels is often met with—presumably as a release phenomenon—when patients are switched from ganglion-blocking agents to bretylium tosylate.

Disorders of Micturition

Frequency of micturition and a poor stream occur not uncommonly, but have never been very troublesome and have only been noticed at high dosage.

Failure of Ejaculation

Although systematic inquiries have not been made, two patients complained of failure of ejaculation, erection being normal. Married men who had been troubled by impotence during treatment with mecamlamine (with consequent periodic lapses from treatment) have spontaneously reported satisfactory conjugal relations when treated with bretylium tosylate.

Headache

One man experienced extremely violent headaches after a single dose of bretylium tosylate, and these occurred at two successive attempts to restart treatment. There was no evidence of pheochromocytoma and the patient is now well controlled by guanethidine. Another patient experienced throbbing headaches and palpitations—such as are more frequently met with under the action of hydrallazine—in the first two months of treatment with bretylium tosylate, but the side-effects were not severe and are becoming gradually less troublesome. They are presumably due to vasodilatation.

Shortness of Breath

Turner and Lowther (1960) mentioned shortness of breath as a possible side-effect of bretylium tosylate therapy. This is difficult to evaluate, as coexisting left ventricular failure is common in hypertensives, but we would confirm the impression that dyspnoea on effort would seem in a few cases to be unrelated to deterioration in cardiac function. We have never observed the radiological appearances of the "hexamethonium lung" nor the appearance of Kerley's subpleural lines which

might be expected in the long run if chronic pulmonary oedema ensued, as Turner and Lowther suggest.

Discussion

Since June, 1959, when the first results of treatment with bretylium tosylate were reported from University College (Boura *et al.*, 1959), further reports have appeared from Smirk and Hodge (1959), Dollery *et al.* (1960), Turner and Lowther (1960), and Evanson and Sears (1960), most of them embodying an experience of approximately six months' treatment. Our experience dates from June, 1959, when we received the first consignments of the drug from the Wellcome Foundation. On the whole we would agree with the findings of the other authors that bretylium tosylate is an important advance in the treatment of severe hypertension, but that it must be regarded as a drug not easy to handle with potential dangers. The dangers are mainly due to irregularity in absorption, clearly demonstrated by the labelled isotope studies from Hammersmith, and this may cause unpredictable sudden hypotensive crises, especially under the influence of physical effort, with consequent vascular occlusions in vital territories. The sharpness of orthostatic hypotension can be compared to that obtained with parenteral hexamethonium and pentolinium; we were therefore not surprised to find five patients who developed pain in the nape, three of whom had experienced similar symptoms while on parenteral pentolinium.

Because of this it is doubtful whether bretylium tosylate should ever be used in the presence of cerebral vascular disease. If recourse to powerful hypotensive agents is imperative in such cases, then the better-absorbed drugs with more predictable action, such as mecamlamine or pempidine, seem preferable. Bretylium tosylate has a very slight hypotensive action in the supine posture, and for this reason we have found it of little use in the treatment of patients confined to bed, such as in acute left ventricular failure, subarachnoid haemorrhage with severe hypertension, and severe toxæmia of pregnancy. In these cases we still favour the use of parenteral pentolinium. Uncomplicated essential hypertension in pregnancy can instead be successfully treated with bretylium tosylate, as the patient can be allowed to be ambulant.

We cannot agree with the Hammersmith and Edinburgh workers that the hypotensive response to bretylium tosylate is poor in malignant and severe hypertension with retinal exudates; in our experience the response is just as unpredictable as with ganglion-blocking agents, and in the first stages of treatment we found that orthostatic hypotension often ensued with doses of only 100 mg. t.i.d. We have found, however, that tolerance develops rather rapidly in these patients, so that the final stable dose is high.

Contrary to the experience of Dollery *et al.* (1960), we have found that the addition of an oral diuretic of the benzothiadiazine series will usually potentiate the hypotensive action of bretylium tosylate (Montuschi, 1959). We have used hydroflumethiazide for this purpose, and in 20 of our cases it has proved of great value in achieving control without the general inconvenience and liability to side-effects of the high dosage of bretylium that would otherwise have been needed. A morning dose of 100 mg. of the diuretic usually suffices.

With this exception we have little experience of the combined action of bretylium tosylate with other drugs. The addition of pempidine or of trimethidinium in a very few cases seemed to confirm the favourable findings of Smirk and Hodge (1959), and we feel that the whole question of combined treatment with modern hypotensive drugs requires further study. For example, as bretylium increases the sensitivity of the blood-vessels to circulating noradrenaline, it would be of great interest to observe whether the addition of an adrenalytic agent would help in the control or resistant cases.

The mechanism of the minor but annoying side-effects that interfere with the usefulness of this valuable drug also requires further investigation. Although Boura *et al.* (1959) claimed that it has no central action, a severe general asthenia with tremor of the limbs recalling the central effect of mecamlamine occurred in one of our patients one week after she had changed from pentolinium to bretylium tosylate, the symptoms ceasing immediately on reversion to the former treatment. Evanson (personal communication) reports dysarthria associated with severe general muscular weakness in another case.

So far there has been no evidence of a toxic action on the liver, kidneys, or the haemopoietic system, and none of our patients has developed a dissecting aneurysm (Beaven and Murphy, 1956).

The freedom from the more serious side-effects consequent on parasympathetic blockade and depressant central action of other drugs is a conspicuous advantage in the use of bretylium tosylate, and many patients, especially those on high dosage, were most grateful for this relief. As will be seen from Table II, satisfactory and uneventful control of the blood-pressure has been achieved in 71% of our cases, and it must be emphasized that no case of mild or moderate hypertension has been included. We feel, indeed, that bretylium tosylate, with its powerful and sometimes unpredictable action, is out of place in dealing with uncomplicated moderate benign hypertension, especially if the patient is leading an active life.

Judged by the yardstick of its effectiveness in malignant hypertension, this drug has given an encouraging success rate of just over 50% during a period of six to nine months. It is without doubt an important advance in the treatment of severe hypertension.

Summary and Conclusions

By its selective action in blocking the peripheral sympathetic nerves without interfering with parasympathetic transmission, bretylium tosylate offers a new type of treatment in hypertensive disease that is free from some of the serious disadvantages of its predecessors.

Using this drug in 75 cases of severe hypertension over a period of nine months, we have obtained successful control in 71%, including 7 out of 13 cases of malignant hypertension.

The main disadvantages in its clinical use appear to stem from a marked variability in its absorption from the digestive tract. This may lead on the one hand to severe postural hypotension on low dosage or on the other to the necessity for very large doses which expose the patient to a number of minor side-effects. This effect can be countered to some extent by the adjuvant action of hydroflumethiazide. The frequent occurrence

of postural hypotension after physical effort in patients taking this drug makes it unsuitable for the treatment of uncomplicated moderate benign hypertension in active subjects. Its mode of action also makes it ineffective in the recumbent patient.

Administration of bretylium tosylate requires careful supervision, as a collapse of the blood-pressure with fainting is not uncommon when the drug is first introduced, and may occur unexpectedly later. For this reason we do not recommend its use in patients with established coronary or cerebral vascular disease.

We thank Dr. David Long, of the Wellcome Foundation, for supplies of bretylium tosylate (darenthin).

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DRUG PROPHYLAXIS IN MIGRAINE

A CONTROLLED CLINICAL TRIAL

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Migraine, in common with other psychosomatic diseases, is subject to wide variation in severity during the patient's lifetime. The condition is exacerbated under the influence of adverse physical and psychological factors, and it is common experience that relief from these is sufficient in many patients to produce a remission. It follows, therefore, that assessment of any form of drug therapy aimed at the prevention or modification of attacks is beset with obvious practical difficulties: for not only is the disease influenced by many variable factors but also, as Graham (1956) has pointed out, it is "notorious for responding temporarily to any new and encouraging form of therapy."

It is therefore essential that any attempt to demonstrate the effect of drug treatment in migraine must be made with full statistical control by applying the technique of the double-blind trial.

Current Views

The idea that reserpine, an alkaloid contained in *Rauwolfia serpentina*, might be employed in the preventive treatment of migraine arose from light that has been shed on its pharmacology by recent research. Known and used in the Orient for centuries, and in recent years achieving universal use in the treatment of hypertension and a variety of psychiatric disorders, reserpine was thought to exert its effect on the central nervous system (Bein, 1953).