some sort during their lifetime. Approximately one person in eight having a fit will go on to become a chronic epileptic, and about one in every 160 will become completely disabled by the disease.

Some 74% of all chronic epileptics were fully employed, 12% were in sheltered employment, 6% were unemployed for reasons other than epilepsy, and 8% were unemployed because of their fits or because of social difficulties arising from epilepsy. Some 3.5% of the patients received treatment of some sort in hospitals during the survey year. 16% of the cases presented a social problem. Fits were completely controlled in 42% of cases. A similar proportion had more than one fit in the year.

Phenobarbitone was the anticonvulsant most often used, with phenytoin sodium next and methoin third.

Consultants probably did not see more than 75% of the epileptics in the community, and an even smaller proportion of first fits.

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ACKNOWLEDGMENTS

Members of the working party would like to express their thanks to all the general practitioners who helped in the survey and made it possible, and especially to Dr. Denis Williams and Dr. Peter M. Jeavons, who gave invaluable help both in the planning stages and during the survey. They are most grateful to the Department of Medical Statistics of Birmingham University, which produced the various tables on which the paper is based. The recorder would like to thank the Medical Research Council for a grant made to cover clerical expenses; Mrs. B. L. Gretton, who carried out so much of the clerical work; and Mr. Knox Matthews, who helped with the Tables and Figures.

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England and Wales.—S. C. Alcock, June Alexander, G. A. Ames, J. Atkinson, M. P. Atkinson, P. J. Atkinson, C. A. M. Aitken, S. M. Binson-Cooke, O. Birkett, N. G. Blackwell, H. J. Bliss, K. W. Bolt, M. H. B. Borthwick, G. F. Bradbury, J. C. Brown, W. A. Brown, Sheila G. S. Burnie, Ruth Cammock, W. Cammock, H. F. Cantwell, P. A. L. Chapple, G. C. H. Chase, H. S. Cheetham, N. Conley, E. Conway, D. L. Crombie, G. H. Curnock, J. A. Currie, J. A. Dale, P. T. Davies, R. Davies, G. W. Dryland, R. A. K. Elliott, D. I. Evans, J. H. Fairweather, E. K. A. Firth, A. M. M. Fitzgerald, D. Ford, M. M. Frais, D. G. French, J. Fry, H. W. C. Fuller, L. S. Gathergood, C. H. Gattie, J. S. Gilmore, H. Goldie, J. C. Graves, C. Green, E. J. Guest, S. G. Hamilton, H. N. W. Harley, D. C. Harris, F. E. Hobbs, L. R. Holt, R. E. Hope-Simpson, P. Hopkins, R. Horn, D. M. Hughes, J. H. Hughes, Helen Jessler, J. V. Jessler, E. Joffe, A. K. Johnstone, R. G. M. Keeling, Mimi Keidan, Agnes Kennie, R. W. Kennon, D. Kyle, A. J. Laidlaw, B. W. Laithwaite, M. Lampard, D. M. Lees, J. Lenton, J. W. Logan, J. B. Longmore, T. S. M. Low, I. G. McGregor, J. McMaster, G. E. Malloy, H. R. Marker, G. Martin, J. J. Medalia, W. J. Meldrum, N. E. Melling, G. H. Miles, A. B. Milligan, E. H. Milner, B. R. Mitchell, A. Model, Margaret Morgan, W. D. Oliver, P. J. Olney, R. S. Parker, W. Parker, T. C. L. Parry, J. A. Paterson, T. Pemberton, R. J. F. H. Pinsent, A. M. Porteous, R. A. Ratcliffe, G. A. Readett, J. H. T. Rees, E. J. Roche-Kelly, C. Royle, L. C. Rutter, R. W. Rutter, K. D. Salzmann, J. Saperia, R. H. Scott, K. L. Skene, J. D. W. Shedden, R. M. Soloman, J. Squire, C. J. H. Starey, J. F. Stent, E. L. Stout, J. M. Stuart, G. Swift, W. G. Tait, G. W. Taylor, E. C. Till, Lorna Torrance, A. Torrance, T. R. Trounce, E. Tuckman, B. E. Wall, G. L. Ward, G. I. Watson, C. A. H. Watts, I. L. Wilkinson, Margaret Wilkinson, P. K. Wilson, J. Woodall, K. A. A. Wray.

EFFECTS OF BRETYLIUM TOSYLATE ON BLOOD-PRESSURE, CARDIAC OUTPUT, AND RENAL FUNCTION IN HYPERTENSION

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Although there is general agreement that ganglion-blocking drugs produce clinical improvement in hypertensive patients, their effective use may be limited by the occurrence of side-effects due to block of the parasympathetic ganglia. The severity and frequency of such side-effects have been diminished by combining other hypotensive drugs with smaller doses of ganglion-blocking drugs, but in spite of such measures, some patients have side-effects which are at best a nuisance and at worst may be intolerable. While such patients are now comparatively few, the report of Boura *et al.* (1959) that a new type of hypotensive agent, bretylium tosylate ("darenthin"), produced no block of the parasympathetic system suggested that this substance might prove to be better tolerated by many hypertensive patients.

We report here the effects of bretylium tosylate in 25 hypertensive patients treated for periods of up to nine months, and some observations on its effects on the cardiac output and renal function.

Methods

Clinical Observations

The 25 patients selected for treatment had been attending the hypertensive clinic at the Royal Melbourne Hospital, and had experienced troublesome side-effects while taking mecamylamine or pempidine. Most had also been taking 0.5 g. of chlorothiazide and 0.25 mg. of reserpine twice daily.

Initially the patients attended daily. The first oral dose of bretylium tosylate was 200 mg. twice daily; subsequently this was increased by increments of 100 mg. until a dose was reached which reduced the systolic blood-pressure to about 140 mm. Hg, with the patient standing. The blood-pressure was recorded at frequent

*In receipt of a grant from the Life Insurance Medical Research Fund of Australia and New Zealand.

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intervals for seven hours, both in the supine and in the standing positions. Subsequently the patients were seen at regular frequent intervals in the hypertensive clinic.

Cardiac Output

In seven patients the cardiac output was measured by the dye-dilution method, using continuous sampling from an intra-arterial Cournand needle. Weighed samples of 2.5% solutions of cardiogreen (" indocyanine green ") were injected into the right median basilic vein, and arterial blood was collected through a photo-electric cuvette in two timed samples, the first before and the second during passage of the dye. The current from the cuvette was amplified and recorded. The blood concentrations of cardiogreen were estimated by the following technique: 1 ml. of the stirred blood sample was added to 0.5 ml. of 12.5% saponin, and 3 ml. of distilled water was then added; after shaking, the mixture was centrifuged for 10 minutes and the concentration of dye measured in a Unicam S.P. 600 spectrophotometer at a wavelength of 800 Å. Calibration curves were obtained by measuring the absorption of known concentrations of dye in the blood. Each dye-dilution curve was then calibrated by comparing the dye concentration of the appropriate blood sample with the mean deflection during the period of collection (McNeely and Gravallese, 1954), and the cardiac output was derived from the whole dye curve by the method of Hamilton *et al.* (1932).

Blood-pressure was recorded continuously except during the measurements of cardiac output, by connecting the arterial needle to a Sanborn electromanometer through a three-way tap. Before and after each measurement of cardiac output, the mean blood-pressure was recorded by electrical damping, to permit calculation of total peripheral resistance (T.P.R.).

Measurements were made with the patient resting on a tilting couch at a room temperature of 70° F. (21.1° C.). After the needles had been inserted the patient was allowed to rest for 10 minutes. A sham cardiac output was then performed, using saline instead of indicator. Measurements of cardiac output and blood-pressure were obtained with the patient supine and again after being tilted 60 degrees, feet down.

Bretylium tosylate, 50–150 mg., was injected intravenously over a period of three to five minutes. The patient then rested quietly, the blood-pressure being recorded continuously for 40–60 minutes or until a significant fall had occurred. Measurements of cardiac output and blood-pressure were then repeated in both postures.

Renal Function

This was estimated by measuring the clearance of sucrose (Steinitz, 1940), creatinine, and para-aminohippuric acid (P.A.H.). Five patients with severe hypertension were studied.

Observations were made with the patient in a cardiac bed, with the feet down, to avoid postural variations. All studies were carried out with the patient fasting. Loading doses of 4 ml. of a 20% solution of P.A.H. and 20 ml. of a 50% solution of sucrose were given intravenously, and an intravenous infusion containing 16 ml. of 20% P.A.H. and 50 ml. of 50% sucrose in 500 ml. of saline was then begun. 500 ml. of this solution was infused in five hours.

Samples of venous blood were taken during each clearance period from a thin-walled 18-gauge B.D. needle, left *in situ* in the other arm. Urine samples were obtained with an indwelling catheter.

The first clearance period began 90 minutes after the loading dose. Clearances were then measured in a 30-minute control period. 75 mg. of bretylium tosylate was given intravenously, and clearances were measured one hour, two hours, two and a half hours, and three hours afterwards. Blood-pressure was recorded at intervals by the auscultatory method. Blood and urine levels of sucrose, creatinine, and P.A.H. were estimated in duplicate.

Results

All but four of the 25 patients selected for trials with bretylium tosylate had previously been treated with mecamylamine or pempidine, and with chlorothiazide and reserpine, and had experienced parasympathetic side-effects of moderate or severe degree. In 10 the side-effects had not been severe enough to make control of the blood-pressure difficult, but in 11 the severity of side-effects had prevented fully effective doses being used. In addition, four previously untreated patients were given bretylium tosylate.

In all 25 the initial dose used was 200 mg. thrice daily. The dose ultimately required to achieve a therapeutically satisfactory fall of blood-pressure varied from 200 to 1,200 mg. t.d.s. The average dose required was 600 mg. t.d.s. In four patients, after an initial response had occurred, tolerance appeared to develop. In these the initially effective dose had to be doubled in three and increased threefold in one. In the remainder of the patients little or no tolerance was noted.

Effect on Blood-pressure

The blood-pressure rarely began to fall for two hours after an oral dose, and even with intravenous administration no effect was demonstrable before 30–60 minutes. The fall in blood-pressure reached a maximum at about three to five hours after an oral dose and had usually disappeared within six to eight hours. The postural fall of blood-pressure after bretylium tosylate was very conspicuous, often more so than when mecamylamine or pempidine was used; there was usually little or no fall of blood-pressure when the patient was supine, certainly in doses which were therapeutically tolerable. The concurrent use of chlorothiazide and reserpine often reduced the supine blood-pressure.

Unlike mecamylamine and pempidine, bretylium tosylate appeared to be only partly absorbed from the gastro-intestinal tract, for the effective intravenous dose was from one-fifth to one-tenth of the effective oral dose. Presumably because of variation in absorption, the effects on the blood-pressure varied somewhat from day to day. To some extent the variation in response could be reduced by the dose being taken before rather than after food, but even when this was done the effects were less predictable than the effects of mecamylamine or pempidine. Variation in response from day to day makes control of the blood-pressure difficult to achieve, as patients may experience episodes of hypotension and hypertension. Moreover, casual blood-pressures at clinic attendances tend to be higher in patients taking bretylium tosylate than in those taking mecamylamine or pempidine, which adds to the difficulty of management.

In all, the blood-pressure has been reduced to a moderately satisfactory degree in 19, but in six the control has been distinctly poor.

Side-effects

Side-effects due to parasympathetic blockade have not been reported by patients taking bretylium tosylate. In particular, patients who had previously had impotence, urinary retention, and severe constipation all claimed relief from these symptoms. However, side-effects attributable to sympathetic block have been noted. Bilateral Horner's syndrome and nasal stuffiness often occurred during the initial day or two of treatment, but have not persisted.

Bretylium tosylate seems to give rise to a group of side-effects apparently unrelated to autonomic block. The most conspicuous symptom has been pain in the region of the parotid glands, not usually accompanied by any swelling or by disturbance of salivation. The glands were often tender. This symptom was reported by 11 patients. Other symptoms included tremor in two, and mental depression, ceasing with withdrawal of bretylium tosylate, in the same two. Headache not apparently related to the height of the blood-pressure occurred in four. Two patients have discontinued bretylium tosylate because of the side-effects, preferring the discomforts of parasympathetic blockade.

General Assessment

Of the 25 patients treated two have died, both of cerebral haemorrhage. While their death cannot be confidently attributed to the change to bretylium tosylate, they were not as well controlled as when they were taking pempidine. Of the remaining 23, 11 have moderately well controlled blood-pressures with few or no side-effects. Six of the remainder have side-effects of moderate severity but prefer bretylium tosylate to other drugs. In most of them the main symptomatic improvement is relief of impotence. Bretylium tosylate was stopped in two because of the side-effects, and in the remaining four because ganglion-blocking drugs gave a much better control of blood-pressure.

Acute Circulatory Effects

Seven patients were studied. The results are shown in Table I. In six the mean blood-pressure fell by 15–51 mm. Hg in the horizontal position after bretylium tosylate, there being no change in the seventh. Further falls of blood-pressure occurred in all of the six patients who were tilted after taking the drug: this contrasts with the effects of tilting before taking it, when the mean blood-pressure rose in all seven patients.

In the horizontal position the cardiac output fell after bretylium tosylate in three patients, rose in two, and was substantially unaltered in two. The calculated T.P.R. fell in three, rose in one, and was unchanged in three.

On tilting before bretylium tosylate the cardiac output fell in all but one. After the drug the cardiac output fell on tilting in all six patients studied. In four the output was lower after bretylium tosylate than before, in one it was higher, and in one the same.

Before bretylium tosylate, the T.P.R. rose substantially on tilting in three. After bretylium tosylate it was substantially unaltered in the six patients studied.

It thus appears that bretylium tosylate produces falls of blood-pressure in the horizontal position which are the result primarily of a fall in cardiac output, with variable small changes in T.P.R. On tilting, the usual fall in cardiac output occurs, often to a greater degree and usually without the compensatory vasoconstriction which ordinarily occurs.

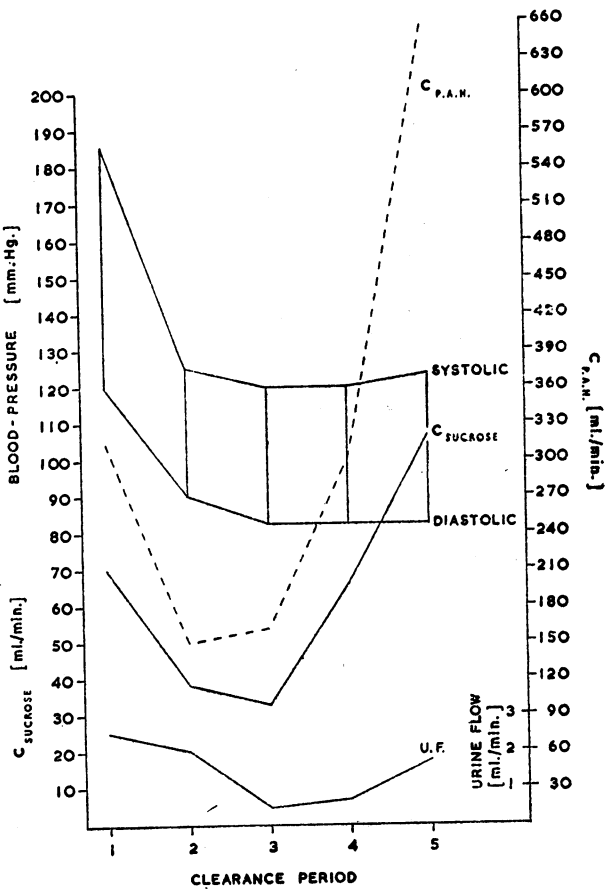
TABLE I.—*Changes in Mean Arterial Pressure, Cardiac Output, and Peripheral Resistance Induced by an Intravenous Dose of Bretylium Tosylate*

Patient	I.V. Bretylium Tosylate mg.	Posture	Mean Arterial Pressure (mm. Hg)		Cardiac Output (litres per min.)		Peripheral Resistance*	
			Before	After	Before	After	Before	After
			Bretylium Tosylate		Bretylium Tosylate		Bretylium Tosylate	
A	125	Supine	160	145	7·07	5·97	22·6	24·3
		60° tilt	169	134	6·14	4·62	27·5	29·0
B	150	Supine	130	130	6·49	6·97	20·0	18·7
		60° tilt	135	97	5·95	4·79	22·7	20·3
C	100	Supine	155	130	6·92	7·79	22·4	16·7
		60° tilt	165	60	4·66	4·07	35·4	14·7
D	125	Supine	170	119	8·71	5·37	19·5	22·2
		60° tilt	186	—	7·87		23·6	—
E	75	Supine	164	144	7·66	7·84	21·4	18·4
		60° tilt	172	122	4·61	6·82	37·3	17·9
F	50	Supine	165	130	6·24	4·61	26·4	28·2
		60° tilt	172	90	2·61	2·70	65·9	33·3
G	50	Supine	155	125	5·83	6·59	26·6	19·0
			170	85	6·86	4·07	24·8	20·9

* Calculated thus: $\frac{\text{Mean arterial pressure (mm. Hg)}}{\text{Cardiac output (litres per min.)}}$ and expressed in arbitrary units.

Effects on Renal Function

The responses in the five severely hypertensive patients studied were very similar. The reductions of blood-pressure and changes in urine volume and clearances are shown in Table II. It is evident that while the blood-pressure was falling both the glomerular filtration rate (G.F.R.) and the effective renal plasma flow



The mean changes in Csuc, CP.A.H., urine volume, and blood-pressure in five hypertensive subjects after an intravenous dose of bretylium tosylate. Clearance periods are those detailed in Table II.

TABLE II.—*Changes in Renal Clearance Values and Blood-pressure in Five Hypertensive Subjects. Period 1 is the Control Period Before, Period 2 One Hour, Period 3 Two Hours, Period 4 Two and a Half Hours, and Period 5 Three Hours After*

Observation	Subject 1. F. aged 45					Subject 2. F. aged 57					Subject 3. F. aged 53					Subject 4. M. aged 46					Subject 5. M. aged 50				
	Period					Period					Period					Period					Period				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Blood-pressure mm.Hg	170/130	145/105	120/90	130/90	130/90	185/120	130/100	130/90	130/90	140/80	180/110	90/60	110/80	100/70	100/80	190/120	155/105	130/90	130/90	125/90	200/120	100/60	110/60	110/70	110/70
$C_{suc.}$ ml./min. ..	63	49	27	73	84	92	53	27	39	140	42	15	22	75	123	74	36	66	78	77	81	19	18	—	50
$C_{P.A.H.}$ ml./min. ..	209	173	108	266	380	396	203	135	115	770	153	88	153	463	670	368	151	309	373	396	434	128	112	—	1160
C_{CR} ml./min. ..	96	60	39	122	127	86	65	8	32	170	47	3	—	89	150	93	62	88	98	146	126	27	23	—	250
U/P% suc. ..	11	11·5	64	86	84	13	19	89	85	80	8	15	22	73	91	58	62	83	113	105	10	11	23	—	
UV ml./min. ..	2·75	4·17	0·25	0·57	0·35	2·84	2·34	0·21	0·20	1·17	3·46	0·05		0·04	1·86	0·80	0·80	0·80	0·47	0·71	2·9	2·0	0·76	—	4·0

U/P = Urinary concentration/plasma concentration. UV = Urinary volume.

(E.R.P.F.) fell to between 25% and 60% of the control levels. However, although the blood-pressure remained low two and a half hours and three hours after the injection, the G.F.R. and E.R.P.F. had risen to values well above the initial levels. The urinary volume fell sharply as the blood-pressure fell and usually remained low for the remainder of the experiment, with a resulting rise in the U/P ratio. The mean changes are shown in the Chart.

Discussion

In the past 10 years the means available for treating high blood-pressure have progressed from the intermittent hypotensive effects of parenterally administered hexamethonium to the very effective combination of chlorothiazide, reserpine, and mecamylamine or pempidine. With a combination of the latter drugs for the treatment of 70 severely hypertensive patients in the hypertensive clinic excellent control of blood-pressure has been achieved with few or no side-effects in 49 out of 70 patients. In 10 of the remainder side-effects were only moderately severe, but in 11 they were severe enough to cause difficulty in management.

Thus in 21 of the 70 there was reason for attempting to improve the existing regime. In all but two of them side-effects have almost completely disappeared with bretylium tosylate, but in almost all the degree of control of blood-pressure is not as good with bretylium tosylate as in those still taking ganglion-blocking drugs. For this reason we still regard mecamylamine or pempidine rather than bretylium tosylate as the drug of choice in the treatment of severe hypertension. All are best used in combination with chlorothiazide and reserpine. When parasympathetic side-effects cause symptoms, bretylium tosylate seems to be a useful alternative to mecamylamine; in young men who are likely to experience impotence bretylium tosylate is the drug of choice. In some patients control of blood-pressure may be improved without severe side-effects by using bretylium tosylate, chlorothiazide, and reserpine, with a small dose of mecamylamine.

From our observations of the acute effects of bretylium tosylate on cardiac output it seems that this drug, like the ganglion-blocking drugs, prevents compensatory vasoconstriction in the erect posture and may have little effect on the total peripheral resistance or blood-pressure when the patient is supine. Indeed, when the supine blood-pressure is reduced it seems to be usually the result of a fall in cardiac output, although occasionally a small fall in total peripheral resistance may occur.

However, the effects of bretylium tosylate on renal function and blood flow seem to differ from those of other hypotensive drugs, for though both the G.F.R. and the E.R.P.F. fall when the blood-pressure falls, both recover and usually exceed the resting levels, even though the blood-pressure remains low. Reports of the effects of ganglion-blocking drugs have all shown that the G.F.R. and E.R.P.F. fall in proportion to the fall in blood-pressure (Mills and Moyer, 1953; Hershberger, 1955); while these values may sometimes return towards normal when the blood-pressure is still low, no reports of a rise in G.F.R. and E.R.P.F. occurring during the hypotensive phase seem to have been made. The only drug which has been reported to raise the E.R.P.F. is hydrallazine, but with this drug the G.F.R. remains low (Mackinnon, 1952). It seems from this unique action that bretylium tosylate may be worthy of trial in patients with severe hypertension and diminished renal function.

Summary

Bretylium tosylate, a new hypotensive drug, enables the blood-pressure to be reduced with no parasympathetic side-effects, but the falls in blood-pressure produced are less predictable than those produced by mecamylamine.

For most patients with severe hypertension the treatment of choice is chlorothiazide and reserpine, with mecamylamine. When side-effects of the latter are severe bretylium tosylate should be used.

The acute effects of bretylium tosylate on the circulation have been studied. A fall in cardiac output occurs as the blood-pressure falls, with an absence of compensating vasoconstriction.

Though bretylium tosylate produces a transient fall in renal clearance values, these usually rise subsequently to levels greater than the control values although the hypotensive effect persists.

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