number of years, and particularly to Dr. I. Todd, Dr. J. Tallack, and Dr. I. Gray. I am grateful to my secretary, Mrs. E. O. Price, without whose help in keeping records this work could not be done. Not least of all, I wish to thank my colleagues for referring these cases to me, and particularly our genito-urinary surgeon, Mr. F. J. Foster.

REFERENCES

- Adamson, D. W., Billingham, J. W., Green, A. F., and Locket, S. (1956). *Nature (Lond.)*, 177, 523.
 Bennett, G., Tyler, C., and Zaimis, E. (1957). *Lancet*, 2, 218.
 Billingham, J. W. (1956). In M. Harington's *Hypotensive Drugs*, p. 35. Pergamon Press, London.
 Freis, E. D., and Wilson, I. M. (1957). *Med. Ann. D.C.*, 26, 468.
 Green, A. F. (1956). In M. Harington's *Hypotensive Drugs*, p. 95. Pergamon Press, London.
 Hollander, W., and Wilkins, R. W. (1957). *Boston med. Quart.*, 8, 69.
 Locket, S. (1951). *Brit. med. J.*, 1, 1331.
 — (1956a). *Ibid.*, 2, 116.
 — (1956b). In M. Harington's *Hypotensive Drugs*, p. 142. Pergamon Press, London.
 McKendrick, C. S., and Jones, P. O. (1958). *Lancet*, 1, 340.
 Tapia, F. A., Dustan, H. P., Schneckloth, R. A., Corcoran, A. C., and Page, I. H. (1957). *Ibid.*, 2, 831.

EFFECTS OF PENTACYNIIUM METHYL-SULPHATE ON RENAL CIRCULATION IN HYPERTENSION

BY

J. R. COX, M.B., Ch.B.
Senior House Officer

AND

J. J. DALY, M.R.C.P.
Research Assistant

The Medical Professorial Unit, Sheffield Royal Hospital

One of the disadvantages of some of the ganglion-blocking drugs used in the treatment of hypertension is the fall in renal blood flow that follows their systemic administration. Reports of the new ganglion-blocking drug pentacynium methylsulphate (139c55; "presidal") claim (Locket, 1956) that it is not associated with gross changes in renal blood flow or glomerular filtration rate and produces a prolonged fall in blood pressure with few side-effects. We have therefore studied the effect of pentacynium on the renal circulation in a number of patients with hypertension.

Present Investigation

Nine patients (seven women and two men), whose ages ranged between 50 and 70 years, were studied (Table I). The minimum basal blood-pressure reading was 230/130, and all showed clinical and electrocardiographic evidence of left ventricular hypertrophy. Cases 6 and 7 had been in heart failure some months previously but had responded

to digitalis and diuretics and were free of this complication at the time of study. Hypertensive retinopathy of varying degree was present in all cases; six showed retinal haemorrhages, and exudates and papilloedema were present in Case 8. In six cases there was a trace of albumin in the urine, but with the exception of Case 8 there were no red cells or casts in the urinary deposits. The blood urea, in the absence of vomiting and heart failure, was above 40 mg. per 100 ml. in seven subjects. Seven patients had been treated for between 6 and 18 months with either pentolinium tartrate or hexamethonium bromide in combination with one of the reserpine alkaloids. Treatment was stopped because with the increasing dosage necessary to control blood pressure side-effects became intolerable. Case 8 presented with malignant hypertension and Case 3 had not been previously treated.

Methods

Each subject lay at rest in bed with the head raised to 30 degrees. Renal blood flow and glomerular filtration rate were measured by a technique previously described (Smith *et al.*, 1938) and inulin and para-aminohippuric acid (P.A.H.) were estimated, using a method as reported by Dick and Davies (1949). Mean blood pressure was calculated as the diastolic plus one-third of the pulse pressure.

Renal-clearance periods lasted 20 minutes. Each value for effective renal blood flow (E.R.B.F.) and glomerular filtration rate (G.F.R.) in Table II is the average of two consecutive measurements. Following the drug two clearance periods were estimated during the period of falling blood pressure. Two further estimations were carried out in six subjects when their blood pressure had remained at or near normal levels for an average of 30 minutes. Percentage changes of blood pressure E.R.B.F. and G.F.R. in Table II are related in all cases to control values. Blood pressures were recorded every two minutes during the study and then six-hourly for 24 hours in both lying and standing positions. Pentacynium was given subcutaneously; Cases 8 and 9 received 12.5 mg. and the remainder 25 mg.

Results

Blood Pressure.—A fall in blood pressure occurred in all subjects between 9 and 20 minutes after the drug. In six the figure was approximately 120/80 by 30 minutes. The diastolic pressure fell to 100 mm. Hg in Cases 1 and 9 by 50 minutes, while Case 4 showed little change in blood pressures at this stage. The average reduction in mean blood pressure for the whole group was 49% at 50 minutes. Diastolic blood-pressure readings in all patients had reached levels below 100 mm. Hg by 120 minutes and remained so for a further 16 to 24 hours.

E.R.B.F.—A mean reduction in E.R.B.F. of 53% occurred by 50 minutes, and the individual changes were closely related in time and magnitude to the alteration in blood pressure. Subsequent clearance values obtained between 30 and 110 minutes in Cases 2, 5, 6, 7, 8, and 9 reveal a mean percentage increase in E.R.B.F. of 28 above mean control value. This figure is largely accounted for by a rise in renal blood flow to above control levels in Cases 8 and 9. The remaining four cases show a rising E.R.B.F., but individually these were still well below control values.

G.F.R.—Changes in G.F.R. showed a similar trend to those of E.R.B.F. but were proportionately greater in amount, producing a fall in the filtration fraction. The reduction in G.F.R. occurred *pari passu* with the fall in blood pressure. Case 4 showed little initial change in blood pressure and a correspondingly small alteration in G.F.R. The initial mean reduction in G.F.R. for the nine patients occurred between 10 and 30 minutes, and was approximately 71%. Subsequent values for G.F.R. obtained between 30 and 110 minutes in six subjects reveal a mean rise of 9%. As with E.R.B.F., this striking rise in G.F.R. for the group is produced largely by the increase in Cases 8 and 9 to above control values. Cases 2, 5, 6, and 7

TABLE I

Case No.	Age and Sex	Basal B.P.	Retino-pathy Grade	Left Ventricular Hypertrophy	Blood Urea mg./100ml.	Previous Therapy
1	50 F	250/160	I	+	41	Pentolinium
2	51 F	260/160	I	+	42	Hexamethonium bromide
3	58 F	270/150	III	+	55	Nil
4	51 M	230/130	II	+	180	Hexamethonium bromide
5	52 M	240/130	I	+	62	Pentolinium
6	52 F	260/140	III	+ with heart failure	31	Hexamethonium bromide
7	70 F	300/140	II	+ with heart failure	35	" "
8	51 F	260/150	IV	+	200	Nil
9	53 F	250/140	III	+	49	Hexamethonium bromide, pentolinium, and mecamlamine

reveal a rising G.F.R. between 30 and 80 minutes, but individual levels are still well below control values.

Side-effects.—Bradycardia and dryness of the mouth occurred in all subjects by 15 minutes. Three complained of blurred vision; six developed nausea, and three of these vomited at 30 minutes. Moderate to marked drowsiness was a prominent feature in all nine subjects, occurring approximately 20 minutes following the drug.

Discussion

The changes in renal haemodynamics following pentacynium are similar in nature to those observed with other ganglion-blocking drugs. Pentamethonium iodide is associated with a reduction in E.R.B.F. and G.F.R. in hypertensive subjects when the blood pressure fall is minimal (Mackinnon, 1952), but observations of changes occurring up to 110 minutes after the drug are not available in all reports. Case selection introduces the difficulty of comparing results in this type of study.

The doses of pentacynium given were on average higher than those subsequently necessary to control blood pressure in the same group of patients, and this fact, with the high incidence of impaired renal function, may explain the degree of reduction in E.R.B.F. and G.F.R. observed. Following the initial fall, E.R.B.F. and G.F.R. had risen in Cases 2, 5, 6, and 7 to approximately 50% of their control values by 30 to 110 minutes. Data for Case 8 with malignant hypertension and Case 9 at 60 minutes showed that E.R.B.F. and G.F.R. had risen above their control values. Mackinnon reported a rise in renal blood flow, following an initial fall, in a patient with malignant hypertension given a small dose of pentamethonium iodide; the blood pressure at this stage had not reached normal levels.

These observations lend support to the view that the changes in E.R.B.F. are to some extent independent of changes in blood pressure. A rise in renal blood flow with fall in blood pressure has been observed following hydralazine hydrochloride ("apresoline"). However, use of this compound produces a high incidence of toxic effects, and no advantage appears to be gained by its combination with other hypotensive drugs. The increase in renal blood flow which immediately follows hydralazine hydrochloride may be due to renal vasodilatation; a similar mechanism may account for the unexpected rise in E.R.B.F. and G.F.R. in Cases 8 and 9. However, a partial redistribution of blood volume has been demonstrated following some of the ganglion-blocking drugs, and experimental evidence supports the view that this factor may produce the initial fall in renal blood flow (Combes *et al.*, 1957). It is possible that later changes are due to compensatory mechanisms dependent on vascular tone, so that E.R.B.F. is restored to its original level in spite of a persisting reduction in blood pressure.

We cannot state precisely when E.R.B.F. had returned to control level in all our subjects, but the rapid rise observed indicates that it probably had done so within three to four hours of giving a therapeutic dose of pentacynium. The effective blood-pressure reduction with a single daily dose of pentacynium is an advantage compared with other systemically given ganglion-blocking drugs, where presumably repeated injection is followed on each occasion by a fall in both G.F.R. and E.R.B.F. There is little evidence that prolonged administration of these compounds produces renal damage *per se* or hastens that already present. A blood urea of 60 mg. per 100 ml. has been quoted (Harrington, 1956) as the upper limit desirable when using the more powerful hypotensive drugs. In this respect Cases 8 and 9 are worthy of further comment.

TABLE II.—Details of Cases

Case No.	Time (mins.)	Dose (mg.)	B.P.	Mean B.P. (mm. Hg.)	B.P. % Change from Control	G.F.R. (ml./min.)	G.F.R. % Change from Control	*E.R.P.F. (ml./min.)	E.R.B.F. (ml./min.)	E.R.B.F. % Change from Control
1	0	25	260/150	187	-39.5	105	-84.3	210	412	-22.3
	50		140/100	113		27		163	320	
2	0	25	250/100	183	-46.9 -49.1	75	-77.3 -34.6	169	291	-76.3 -14.4
	30		130/80	97		17		40	69	
	50		120/80	93		39		157	249	
3	0	25	260/140	180	-46	175	-66.8	650	1,180	-67.3
	40		110/90	97		58		212	386	
4	0	25	240/150	180	-74.4	27	-51.8	68	115	+3.4
	50		180/130	46		13		70	119	
5	0	25	250/150	183	-49.1 -57.9	120	-90.8 -88.3	212	451	-81.2 -64.5
	30		140/70	93		11		40	85	
	80		110/60	77		14		75	159	
6	0	25	240/140	173	-47.9 -52.1	35	-74.3 -60	123	222	-72.5 -43.6
	30		110/80	90		9		33	61	
	70		110/70	83		14		70	125	
7	0	25	260/150	186	-51.6 -55.3	110	-83.6 -65.4	400	701	-72.5 -64.7
	10		110/80	90		28		110	193	
	30		110/70	83		38		141	247	
8	0	12.5	230/130	163	-40.4 -38.0	1.8	-27.7 +177.7	4.9	7	-18.6 +265.7
	30		130/80	97		1.3		4.0	5.7	
	110		140/80	100		5		17.9	25.6	
9	0	12.5	260/150	187	-35.8 -42.7	105	-81.9 +14.2	242	493	-74.3 +91.4
	50		160/100	120		19		62	126.6	
	70		140/90	107		120		462	944	
% changes immediately following drug					-49%	Mean change	-71.2%	Mean change		-53.5%
Calculated from later clearance periods up to 110 mins. in six subjects					-49%	Mean =	+9.4%	Mean =		+28.3%

* Effective renal plasma flow.

Case 8.—This patient was suffering from malignant hypertension. The initial blood urea was 200 mg. per 100 ml. Following 12.5 mg. of pentacynium the patient complained of drowsiness and a dry mouth. Thirty minutes later she became unconscious, with a systolic pressure of 95 mm. Hg. Elevation of the foot of the bed raised the blood pressure to 130/95. Over the next 12 hours, with a constant pressure reading, consciousness returned. At the end of 18 hours after the injection the blood pressure had reached 250/140. Subsequent doses of 1.25 mg. of pentacynium subcutaneously reduced the B.P. to 140/110. The blood urea, however, rose to 419 mg. per 100 ml. and the patient died in coma three weeks later. Permission for necropsy was not obtained.

Case 9.—This patient, who had severe essential hypertension, cardiac enlargement, and a left-sided hemiplegia, had received a low-protein and low-salt diet for 18 months before admission. His blood pressure had not been controlled by large doses of parenteral pentolinium or mecamlamine by mouth. The initial blood urea was 180 mg. per 100 ml. A satisfactory fall in blood pressure occurred initially with 25 mg. of pentacynium subcutaneously, and normal blood pressure was later achieved with 6.25 mg. subcutaneously each morning. The patient's general condition improved over the next two weeks, and before discharge his blood urea was 80 mg. per 100 ml. He had not experienced any side-effects, and was back at light work.

The incidence of side-effects in our series appears high, and may be partially explained by the dose of drug used and the incidence of renal damage. Nausea and vomiting were probably aggravated by the water drunk in an attempt to maintain urinary flow. The fall in urine flow was marked in all instances and water intoxication might be precipitated under these circumstances.

Drowsiness occurred in all nine subjects, and does not seem to have been commented on previously. It appeared earlier than the maximum fall in blood pressure. This effect, which was not associated with hypotension, has not been recorded with other ganglion-blocking drugs, and may be due to a central action, possibly on the hypothalamus.

Eight patients of this series have been followed up for six months after the study. Blood pressures were still well controlled with 6.25–12.5 mg. of pentacynium once daily, combined with a reserpine preparation three times a day.

Summary

The effect of pentacynium methylsulphate (presidal) on the renal circulation in nine subjects with hypertension has been studied.

A fall in blood pressure to normal levels occurred in all subjects and persisted for at least 16 hours.

Reduction in E.R.B.F. and G.F.R. occurred initially in all subjects by 30 minutes. In four subjects the mean E.R.B.F. and G.F.R. had risen to 50% of the mean control value by 60 to 110 minutes. In two subjects with severe renal damage the values for E.R.B.F. and G.F.R. had risen to greater than their control values by 110 minutes.

The significance of these findings is discussed, and it is noted that satisfactory control of blood pressure may be obtained with a single daily injection of pentacynium.

We thank Professor C. H. Stuart-Harris for his help and advice, and Mrs. S. Bradford for technical assistance.

BIBLIOGRAPHY

- Adamson, D. W., Billingham, J. W., Green, A. F., and Locket, S. (1956). *Nature (Lond.)*, 177, 523.
Combes, B., Preedy, J. R. K., Wheeler, H. O., Hays, R. M., and Bradley, S. E. (1957). *J. clin. Invest.*, 36, 860.
Dick, A., and Davies, C. E. (1949). *J. clin. Path.*, 2, 67.
Harington, M. (1956). *Hypotensive Drugs*. Pergamon Press, London.
Lauson, H. D., Bradley, S. E., and Courmand, A. (1944). *J. clin. Invest.*, 23, 381.
Locket, S. (1956). *Brit. med. J.*, 2, 116.
— (1957). *Postgrad. med. J.*, 33, 105.
Mackinnon, J. (1952). *Lancet*, 2, 12.
Smith, H. W. (1943). *Lectures on the Kidney*. Lawrence, Kansas.
— Goldring, W., and Chasis, H. (1938). *J. clin. Invest.*, 17, 263.

FOLIC-ACID STUDIES IN MEGALOBlastic ANAEMIA DUE TO PRIMIDONE

BY

I. CHANARIN, M.D., D.C.P.

P. C. ELMES, B.M., M.R.C.P.

AND

D. L. MOLLIN,* M.B., B.Sc.

*Departments of Haematology and Medicine, Postgraduate
Medical School of London, W.12*

It is well known that a megaloblastic anaemia may develop in patients being treated with barbiturate-like anticonvulsants such as phenytoin sodium (Badenoch, 1954; Hawkins and Meynell, 1954), primidone (Fuld and Moorhouse, 1956), and, very occasionally, other barbiturates (Hobson, Selwyn, and Mollin, 1956). The cause of the anaemia is uncertain. The patients resemble patients with folic-acid deficiency in that their serum vitamin B₁₂ concentrations are normal, and they fail to respond, or they respond suboptimally, to treatment with vitamin B₁₂, while responding excellently to treatment with folic acid. However, as there is no evidence of malabsorption of folic acid in these patients it has been generally assumed that the drugs act by interfering with the metabolism of folic acid. In this paper we report studies made on the utilization of folic acid in a patient who developed severe megaloblastic anaemia while receiving primidone ("mysoline").

Case Report

An Anglo-Indian woman aged 44 was admitted to Hammersmith Hospital on May 28, 1957, under the care of Dr. J. G. Scadding. She had lived in India until August, 1956, when she was brought to England. She had a bilateral hemiplegia, probably due to a birth injury, and at 13 years of age began to have major and minor epileptic fits. She was looked after at home, and until two years before admission had been given bromides and various barbiturates for her fits. Two years before admission treatment with primidone (1 to 2 g. daily) was started and treatment with other barbiturates was stopped. Until six months before admission she was reasonably well and took a well-balanced diet. Shortly after arriving in England she became lethargic, lost interest in her surroundings and refused food, and from this time until the time of admission she ate only tea, bread, biscuits, Horlicks' milk, and an occasional banana. She became progressively weaker and paler, had episodes of diarrhoea, and shortly before admission became incontinent of urine and faeces.

Examination.—The patient was a well-nourished Anglo-Indian, crying out incomprehensibly but able to respond to simple commands. Her mucous membranes were very pale, but there were no skin lesions, purpura, or haemorrhages, and her gums were normal. The lymph nodes were not enlarged and the spleen was not palpable. Her temperature was 97° F. (36.1° C.), she was slightly dyspnoeic, the jugular venous pressure was 10 cm. above the sternal angle, but there was no oedema. Her pulse rate was 120 a minute and blood pressure 110/30. Her heart was not grossly enlarged, but there was a soft apical systolic murmur. Signs of a bilateral hemiplegia were present, more marked on the left than on the right side. There were scars around the left eye, and the left retina appeared disorganized.

* In receipt of a grant from the Medical Research Council.