no further trouble. Chemotherapy was continued for over a year, during which she had a segmental resection of the residual disease.

Summary of Case 3.—A female patient aged 23 developed a high temperature and a morbilliform rash after 22 days on streptomycin and P.A.S. Test doses proved she had become sensitive to both drugs. The daily dose of P.A.S. was gradually increased from 0.5 g. to 15 g. over 11 days; 10 days later it was raised to 17.5 g. Streptomycin doses were increased from 0.1 to 1 g. daily over 12 days. Subsequently she continued both drugs for over a year without incident.

Summary

Desensitization of streptomycin-handlers who have become hypersensitive to the drug is difficult but quite feasible. Two cases are reported.

By contrast, patients who acquire hypersensitivity to streptomycin or P.A.S. during treatment are usually readily desensitized. As an example a case is described of a patient hypersensitive to both drugs.

My thanks are due to the residents and nursing staff at Hammersmith Hospital, London, the Northern General Hospital, and Southfield Hospital, Edinburgh, who carried out the day-to-day treatment of these patients.

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EFFECT OF HEXAMETHONIUM BROMIDE ON THE CEREBRAL CIRCULATION IN HYPERTENSION

BY

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The fall in total peripheral resistance which occurs after the administration of the ganglion-blocking agent hexamethonium bromide is not distributed equally between the vascular areas of the body; there follows, therefore, a redistribution of peripheral blood flow. Thus the flow to the foot and toes is greatly increased, while that to the calf segment of the leg muscles is diminished; vascular resistance in the liver decreases enough to maintain the blood flow at its previous level (Freis *et al.*, 1952). The more complex changes in the kidneys have been described by these and other authors (Kirkendall and Culbertson, 1952; Mackinnon, 1952; Miles *et al.*, 1952; Moyer *et al.*, 1952). The effects upon the cerebral and coronary circulations are of particular importance, considering how serious might be the risk of impairment of the blood supply to heart or brain in hypertensive patients. Crumpton and Murphy (1952) have shown that in dogs with experimental renal hypertension the vascular resistance in the coronary system is slightly re-

duced by hexamethonium and that the mean coronary blood flow is maintained. These authors have further outlined the results of their studies of the cerebral circulation in six patients with hypertension and grade III to IV retinopathy before and after blood-pressure reduction with hexamethonium bromide. The present investigation covers the same field in a series of hypertensive patients, in all of whom the changes in the fundi were classified as grade II (Keith-Wagener-Barker) with the exception of one case of malignant hypertension and grade IV retinopathy (Patient 2).

Methods

The studies were carried out on six patients with arterial hypertension who had been admitted to hospital for treatment with subcutaneous hexamethonium bromide. The nitrous oxide technique of Kety and Schmidt (1945, 1948) as modified by Scheinberg and Stead (1949) was employed, constant-rate samples over the ten-minute periods being withdrawn by means of an electrical device (Dewar *et al.*, 1953). In three cases cerebral venous blood was sampled through a needle introduced direct into the superior jugular bulb (Myerson *et al.*, 1927; Gibbs *et al.*, 1945); in the remainder cerebral venous blood was obtained through a cardiac catheter inserted into the left antecubital vein, the technique of which has been described elsewhere (Dewar *et al.*, 1953). Mean cerebral blood flow (C.B.F.) was calculated according to the formula:

$$\text{C.B.F. in ml. per 100 g. brain per minute} = \frac{CV_{10} \times S \times 10}{\int_0^{10} (A-V) dt}$$

where CV_{10} is the concentration of nitrous oxide in the cerebral venous blood in volumes % at the end of the ten-minute period, S is the partition coefficient of nitrous oxide between brain tissue and blood (known to be unity), and $\int_0^{10} (A-V) dt$ is the integral of the arterial-cerebral venous nitrous oxide difference for the period as determined from the difference between the nitrous oxide concentrations of the integrated arterial and cerebral venous samples.

Blood-pressure readings were made by the auscultatory method in the arm held at heart level, and the mean arterial blood pressure (M.A.B.P.) for each ten-minute period was calculated by adding one-third of the average pulse pressure to the average diastolic reading. The cerebral vascular resistance (C.V.R.) was taken as the quotient of M.A.B.P. divided by the mean C.B.F. In four cases analyses for oxygen content were made on the integrated arterial and cerebral venous samples and the cerebral oxygen consumption ($CMRO_2$) calculated by dividing the product of the mean arterio-venous oxygen difference ($A-VO_2$) and mean C.B.F. by 100. The gas analyses were made in a Van Slyke-Neill manometric apparatus, and were all performed by one of us (A. R. J.). Two estimations of blood flow were made on each patient, separated by at least 25 minutes. The conditions of the second were identical with those of the first except for the prior administration of hexamethonium bromide by intravenous or subcutaneous injection in a dose sufficient to cause significant blood-pressure reduction. The second estimation was not begun until the blood pressure had stabilized at its new level. The results of the studies are shown in the Table.

Hexamethonium bromide produced an average fall in the M.A.B.P. of 30% ($t = 4.7$, $P < 0.01$). This was accompanied by a 28% decrease in the C.V.R. ($t = 3.7$, $P < 0.05$), which in four instances fell to a value within the normal range (Kety and Schmidt, 1948). No significant change occurred in the mean C.B.F. during the period of blood-pressure reduction, successive estimations showing close agreement. (In each pair this was in fact within the range of twice the theoretical standard error of the method as performed by us—Dewar *et al.*, 1953.) In the four cases in which this was estimated, no essential alteration occurred in the $A-VO_2$ difference, nor in the rate of $CMRO_2$. These results agree with those obtained by Crumpton and Murphy

Effect of Hexamethonium Bromide on the Cerebral Circulation in Hypertension

Patient	Sex	Age	Fundi	Cerebral Venous Sampling Technique	Hexamethonium Bromide	M.A.B.P.		C.B.F.		C.V.R.		A-VO ₂		CMRO ₂	
						C	E	C	E	C	E	C	E	C	E
1	F	62	Grade II	Percutaneous	48 mg i.v.	168	103	37	38	4.5	2.7	—	—	—	—
2	F	32	.. IV	..	50	169	127	60	57	2.7	2.2	—	—	—	—
3	F	48	.. II	..	45 .. subcut.	137	91	48	46	2.8	2.0	6.7	7.1	3.2	3.3
4	M	56	.. II	Cardiac catheter	45	191	109	55	51	3.5	2.2	7.6	7.5	4.2	3.8
5	M	49	.. II	..	10	127	111	38	38	3.3	3.0	9.6	9.2	3.7	3.4
6	M	57	.. II	..	15	132	100	59	58	2.2	1.7	4.8	5.7	2.9	3.3
Mean age		51		Mean values		153	107	50	48	3.2	2.3	7.2	7.4	3.5	3.5

C = Control observations.

E = Observations following the administration of hexamethonium bromide.

M.A.B.P. = Mean arterial blood pressure (mm. of mercury) over ten-minute period.

C.B.F. = Mean cerebral blood flow (ml. blood per 100 g. brain per minute) over ten-minute period.

C.V.R. = Mean cerebral vascular resistance (mm. mercury per ml. blood per 100 g. brain per minute) over ten-minute period.

A-VO₂ = Mean arterial-cerebral venous oxygen difference (ml. O₂ per 100 ml. blood) over ten-minute period.CMRO₂ = Mean cerebral oxygen consumption (ml. O₂ per 100 g. brain per minute) over ten-minute period.

(1952) in their group of six hypertensive patients with grade III to IV retinopathy; they found no significant alteration in the C.B.F., A-VO₂, and CMRO₂ values after reduction of the M.A.B.P. and C.V.R. with hexamethonium by 29% and 30% respectively.

It seems unlikely that hexamethonium lowers the abnormal cerebral vascular tone in hypertension by blocking sympathetic impulses to the cerebral vessels, since it has been shown that, while unilateral and bilateral procaine injections of the stellate ganglion produce no alteration in C.V.R. in hypertensive conditions (Harmel *et al.*, 1949; Scheinberg, 1950), such relaxation follows various procedures which result in decrease in the systemic arterial pressure—namely, the administration of dihydroergocornine, thoraco-lumbar sympathectomy, and differential spinal sympathetic block (Hafkenschiel *et al.*, 1950; Shenkin *et al.*, 1950; Kety *et al.*, 1950). The nature of the mechanism by which increased cerebral vascular resistance is maintained in hypertensive states, and by which it falls when the arterial pressure head is reduced, is not fully understood, but it appears to be a homeostatic response on the part of the cerebral circulation, which tends to maintain the cerebral blood flow and metabolism within normal limits.

These findings imply that cerebral nutrition and metabolism will not ordinarily be impaired by the treatment of hypertensive patients with hexamethonium bromide, since cerebral vascular relaxation to a degree sufficient to maintain adequate cerebral blood flow and oxygen consumption accompanies blood-pressure reduction of the order obtained above. Whether this mechanism is able to compensate for the more drastic and sudden hypotension which may sometimes follow the administration of this drug in sensitive patients is less certain, since it has been shown that the acute hypotension consequent upon differential spinal sympathetic block diminishes mean C.B.F. values (Kety *et al.*, 1950). Further, the possibility of an increased likelihood of cerebral thrombosis in patients in whom arterial disease favours the occurrence of such a complication cannot be considered to be eliminated by the present findings; a decrease in C.V.R., assuming blood viscosity and intracranial tension to remain constant, implies increased vessel calibre and increased blood volume per unit weight of tissue. This, if the mean C.B.F. does not alter, will cause slowing of the linear flow rate and prolongation of the local circulation time. It remains possible that such a result would contribute to the development of intravascular thrombosis.

Summary

The cerebral blood flow has been estimated by a modification of the nitrous oxide method in six patients suffering from arterial hypertension before and after administration of hexamethonium bromide. The mean arterial blood pressure fell by an average of 30%, but no significant change occurred in mean cerebral blood flow. The rate of cerebral oxygen utilization was

measured in four of these patients and showed no essential alteration. The practical implications of these findings is briefly discussed.

We wish to acknowledge our indebtedness to Mr. H. Campbell, of the Department of Industrial Health, King's College, Durham University, for help with the statistical analysis, and to Mr. T. Copeland for much technical assistance.

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The Royal Medico-Psychological Association's journal, the *Journal of Mental Science*, celebrates its centenary this month. It was in 1852 that the Association of Medical Officers of Asylums and Hospitals for the Insane decided at a meeting held in Oxford to establish a special asylum journal; and in November, 1853, the first issue of the *Asylum Journal*, as the *Journal of Mental Science* was then called, was published. Its aim was to "afford a medium of intercommunication between men engaged in the construction and management of asylums, in the treatment of the insane, and in all subsidiary operations. . . . It will be a record of improvements and experiments in psychotherapeutics." An editorial article in this issue was devoted to "The Headdress of Pauper Lunatic Men." A stone-coloured fustian forage cap was recommended as peculiarly well suited for the use of the insane—"Its weight is 4½ oz., its cost, home made, 7d." (only a penny more than the *Asylum Journal*). It was admitted that the cap's appearance became "perhaps a little odd" when the fustian washed out white. "By no means an ill-looking cap," however, it was strongly advocated for epileptics subject to frequent and heavy falls. This was a modification of the old-fashioned epileptic ring, which "certainly had a somewhat uncouth appearance and suggested . . . the belt of Saturn or the halo of a Saint," and was a chamois leather ring, stuffed with curled horsehair, somewhat in the shape of a narrow quoit and covered with grey serge—evidently an early type of crash helmet.