Some aspects of the long-term treatment of severe hypertension with methyldopa

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EARLY reports demonstrated the value of methyldopa in the control, and short-term treatment, of hypertension (Irvine, O’Brien & North, 1962; Dollery & Harrington, 1962; Bayliss & Harvey-Smith, 1962), including the malignant phase (Hamilton & Kopelman, 1963). Subsequently, Johnson et al. (1966) convincingly demonstrated its value in the control of blood pressure of 100 hypertensive subjects over periods of up to 36 months, similar results being obtained by Dawson & Palmer (1966).

In this paper, I present the results obtained in the treatment of 222 patients (104 female and 118 male) with severe hypertension, maintained on methyldopa for periods of up to 5 years. Thirty-four had hypertension in the malignant phase, fifty-two showed grade III retinal change, and the remainder had no retinopathy. The details of age, blood pressure, and duration of treatment, for both sexes, are shown in Table 1.

All patients were subjected to the conventional investigations in order to determine the aetiology of the raised blood pressure. In forty, this was attributed to chronic pyelonephritis, in eleven, to renal artery stenosis, in six, to chronic glomerulonephritis, in six, to polycystic kidneys, and in one, to disseminated lupus erythematosus. The remainder were considered to be suffering from essential hypertension.

Only the minority received methyldopa alone; in 158, this was combined with a thiazide diuretic and in seven, with guanethidine; the dose of drugs given being that which maintained the best control of blood pressure with the fewest side-effects of treatment. The control of blood pressure has been considered to be good, when the diastolic pressure has been consistently maintained below 100 mmHg, to be fair, when the diastolic pressure has been consistently below 110 mmHg, and to be poor, in those cases in whom the diastolic pressure has been repeatedly over 110 mmHg.

Results
Only two patients have left the district since the start of this survey. The remainder have all remained under supervision of the clinic.

Mortality
Thirteen patients died, the causes of death being coronary thrombosis in four, subarachnoid haemorrhage in one, cerebral haemorrhage in two, bronchopneumonia in two, and renal failure in four. Of those dying from renal failure, the

<table>
<thead>
<tr>
<th>Sex, and grade of retinopathy</th>
<th>No.</th>
<th>Age (years)</th>
<th>Blood pressure (mmHg)</th>
<th>Dose of methyl-dopa (g)</th>
<th>Duration of treatment (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade IV</td>
<td>11</td>
<td>53 ± 9-9</td>
<td>246 ± 21-6</td>
<td>145 ± 15-1</td>
<td>1-75 ± 1-17</td>
</tr>
<tr>
<td>Grade III</td>
<td>23</td>
<td>55 ± 9-6</td>
<td>236 ± 30-1</td>
<td>138 ± 15-3</td>
<td>1-51 ± 0-79</td>
</tr>
<tr>
<td>Total</td>
<td>104</td>
<td>50 ± 10-6</td>
<td>220 ± 29-1</td>
<td>132 ± 14-4</td>
<td>1-43 ± 0-75</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade IV</td>
<td>23</td>
<td>52 ± 12-4</td>
<td>230 ± 27-7</td>
<td>143 ± 15-3</td>
<td>2-07 ± 1-09</td>
</tr>
<tr>
<td>Grade III</td>
<td>29</td>
<td>50 ± 9-6</td>
<td>212 ± 19-7</td>
<td>135 ± 11-6</td>
<td>1-81 ± 2-70</td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
<td>51 ± 10-1</td>
<td>217 ± 26-8</td>
<td>134 ± 13-9</td>
<td>1-76 ± 0-87</td>
</tr>
</tbody>
</table>
hypothesis was secondary to chronic glomerulonephritis in two, and chronic pyelonephritis in two.

*Conversion to other treatments*

In twenty-seven patients, it has been necessary to convert the regime from methyldopa to some alternative therapy—the indications for conversion being:

- Escaped control: 15
- Mental depression: 8
- Haemolytic anaemia: 3
- Diarrhoea: 1

Four of the eight patients in whom conversion was undertaken on account of mental depression and apathy, showed features resulting from cerebral vascular disease: the remaining four were all employed in exacting work, demanding a high intellectual standard which they could not maintain whilst taking the drug.

Nineteen of these twenty-seven patients had essential hypertension, five chronic pyelonephritis, two renal artery stenosis, and one disseminated lupus.

The duration of treatment, before conversion became necessary, is shown in Table 2.

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Less than 12</th>
<th>12-23</th>
<th>24-35</th>
<th>36-47</th>
<th>Over 48</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>5</td>
<td>9</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>27</td>
</tr>
</tbody>
</table>

In addition to these twenty-seven patients in whom treatment could not be maintained, there were many in whom the dose had to be altered after the treatment had become established. Variations in the dose are commonplace in the first 6 months of treatment, but, thereafter, seventy-four patients required an alteration in the daily dose of methyldopa, by 750 mg or more, as shown in Table 3. Although most of these changes occurred during the first 18 months after starting treatment, in five the alteration was needed after 48 months, in eight, after 36 months, and in twenty, after 24 months of therapy. In none of these in whom the dose was decreased, could any cause, e.g. coronary thrombosis, be demonstrated as being responsible for the reduced demand.

Of the remainder, control of the hypertension was judged to be good in all except thirteen, who remained on the drug, in whom the control was considered only fair.

The side-effects otherwise encountered, which have not demanded conversion of therapy, do not differ from those fully recorded by Smirk (1963), and by Johnson et al. (1966).

**Table 3**

<table>
<thead>
<tr>
<th>Aetiology of hypertension</th>
<th>No. requiring increased dose</th>
<th>No. requiring reduced dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential hypertension</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Renal vascular</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Chronic nephritis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Polycystic kidneys</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>D.L.E.</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>28</td>
</tr>
</tbody>
</table>

**Haemolysis**

In 1966, Carstairs et al. first drew attention to the development of Coombs-positive haemolytic anaemia in patients undergoing treatment with methyldopa. Further cases were reported by Hamilton, Jenkins & Turnbull (1966) and by Worledge, Carstairs & Dacie (1966), and this same group (Carstairs et al., 1966) described 20% of 202 unselected hypertensive patients treated with methyldopa who were shown to give a positive direct Coombs' test of the IgG type; these findings being recently confirmed by Lo-Buglio & Jandl (1967).

Of the 222 patients here reported, Coombs' tests have been performed on 145, of whom nineteen have proved positive, i.e. an incidence of 13%, which conforms to the now accepted incidence of 10–20% of patients treated with methyldopa who develop this reaction.

However, the occurrence of three cases of frank haemolytic anaemia is a far higher incidence than that usually accepted. The details of the first of these cases have already been given (Hamilton et al., 1966); the second, a man of 46 years, suffering from benign pyelonephritic hypertension, had been under treatment with methyldopa for 36 months, when a positive Coombs' test was demonstrated. Six months later the haemoglobin had fallen from 91% to 70% and this was accompanied by a 6% reticulocytosis, an increased urinary urobilinogen excretion, and positive Coombs' reaction. On withdrawal of the methyldopa all these features reverted to normal. The third case, a woman of 66 years, with benign essential hypertension showed a negative Coombs' reaction 3 months after start-
ing treatment. However, 9 months later, she presented to the follow-up clinic with splenomegaly, anaemia and slight jaundice. Her haemoglobin was 70% with a reticulocytosis of 14%; the urine contained an excess urobinogen; the serum haptoglobin level was reduced. The direct antiglobulin test was positive and the cells sensitized with an antibody of the IgG type; the red cell survival was reduced. Following withdrawal of the methyldopa, and substitution of an alternative regime, all abnormal physical signs regressed and the blood count has reverted to normal, although the Coombs' reaction remained positive 2 months later.

Pregnancy
Methyldopa has been successfully used for the control of hypertension in pregnancy (Hans & Kopelman, 1964; Kincaid-Smith, Bullen & Mills, 1966). I have previously described seven patients with severe hypertension, successfully maintained throughout pregnancy, who gave birth to normal infants of average birth-weight (Hamilton, 1966). Since that time, I have treated a further three women, all with substantial manometric hypertension (two essential: one pyelonephritis) with blood pressure levels of 190/120, 160/110 and 170/110 respectively at the start of pregnancy. In all, blood pressure was easily controlled throughout pregnancy: in all, labour was induced between the 36th to 38th week of pregnancy; all gave birth to normal infants of birth weight 6 lb 14 oz, 5 lb 12 oz and 6 lb 11 oz, respectively.

Discussion
In the majority of these 222 patients, the blood pressure has been easily controlled with methyldopa, and good control maintained over many years without major alteration in the dose. However, in fifteen, after a considerable period during which the blood pressure was well controlled, the treatment failed to control the pressure and an alternative regime established; in a further forty-six patients the dose of methyldopa had to be increased by 750 mg or more per day, after a long period of control on a smaller dose. To offset this, in twenty-eight, the dose could be reduced by a similar amount. I feel sure that these alterations in requirement are due to changes in the disease, rather than change in the effect of treatment.

As a result of a recent double-blind trial, Vejlsgaard, Christensen & Clausen (1966) conclude methyldopa to be the first treatment of choice when thiazides alone prove inadequate for the control of hypertension, and with this opinion I am in wholehearted agreement.

It now appears that methyldopa is the ideal anti-hypertensive agent for use in pregnancy, controlling the blood pressure level without imposing hazard of foetal abnormality, although the number of infants yet delivered of such pregnancies is probably too small to be dogmatic on this issue.

In the majority of patients treated, the side-effects are less troublesome than those resulting from administration of ganglion-blocking agents, and no more troublesome than those resulting from sympatholytic agents. However, the development of haemolysis is disturbing; there is as yet no clear evidence of dose-dependence, even though the incidence in the females of this series is suggestive the numbers are too small to form any definite conclusion. However, the advantages of this drug are so great, and the risks of onset of haemolysis so small, that I consider the risks of administration do not yet justify relegating methyldopa from its present role as the first choice of anti-hypertensive therapy for those cases in which thiazides alone prove incapable of maintaining adequate control of the blood pressure.

Acknowledgments
It is a pleasure to record my gratitude to my registrars and house physicians for their interest and assistance in the care of these patients; to Dr J. J. Merry and Dr F. G. Clayton, and Mr R. Davies of Messrs Merck Sharp and Dohme for assistance and advice, particularly statistical, and to Mrs B. Freiseis for secretarial help.

Postscript
Since this paper was completed, a further case of frank haemolysis due to methyldopa has been admitted. This is a 54-year-old man with benign essential hypertension well controlled by methyldopa 2 g daily. Five and a half months after starting treatment, he was admitted with haemolysis giving a 2 weeks history of increasing tiredness and breathlessness. His haemoglobin was 50% with 16% reticulocytes. Four days after stopping methyldopa the haemoglobin had fallen to 29% and the reticulocyte count risen to 42%. He was therefore started on steroids and transfused.

The incidence of haemolysis, in this series, is far higher than that reported elsewhere—at almost 2% of the total cases treated. If this in fact represents the overall incidence of hae-

molytic anaemia complicating treatment with this drug, the use of the drug in routine management of hypertension will have to be seriously reconsidered.
The information provided by metabolic balance studies enables us to determine the minimal requirements of foodstuffs, their availability to the body after ingestion, their routes of excretion, and the modifications of all of these which may arise as a result of disease or administration of other substances. For some nutrients such as fat and nitrogen, balance studies may be readily carried out in man as the quantities involved are easily measured and intake easily controlled. In the case of iodine, however, one must deal with minute quantities which are mixed with large amounts of interfering substances, for example in the faeces where about 1 part of iodine per 10 million by weight is present, together with relatively vast amounts of organic material that must be removed before iodine can be measured. To the technical difficulties of measuring such small amounts are added the risks of contamination of specimens from extraneous sources and unintentional administration of iodine to the individuals during the balance period. These difficulties have prevented large-scale investigation of iodine balance in man, and most of our knowledge of iodine metabolism has been derived from studies with radioactive isotopes of iodine, particularly $^{131}$I. These studies have added enormously to our knowledge of thyroid function, but due to the transient radioactivity of these isotopes they are of greatest value in short-term studies, and their use is limited in balance studies and others in which a longer period of observation is desired.

We have attempted to study stable iodine metabolism in men and women with normal thyroid function under different conditions and in others with thyroid disorders. Balance studies have been carried out in a metabolic ward under conditions of controlled intake of iodine with precautions to prevent access of unwanted iodine either to the individuals being studied or their excreta. Urine and faeces were collected over periods of several weeks, the urine daily and faeces in pooled collections averaging 6 days. Details of the collection methods and measurements of iodine have been reported previously (Harrison et al., 1965a).

The effects of varying the intake of iodine in normal people were first studied. Iodine balances were carried out during two levels of iodine intake, a low level of approximately 100 µg/day, which is near the minimal level at which equilibrium can be maintained (Wayne, Koutras & Alexander, 1964), and a level of approximately
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