BP, LABORATORY RESULTS, AND BODY WEIGHT, BEFORE, DURING, AND AFTER TREATMENT OF DRUG-RESISTANT SEVERE ESSENTIAL HYPERTENSION WITH FRUSEMIDE

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP, lying (mm Hg)</td>
<td>205/122±27/7</td>
<td>177/109±37/11</td>
<td>200/118±36/13</td>
</tr>
<tr>
<td>BP, standing (mm Hg)</td>
<td>183/118±22/7</td>
<td>151/100±40/14</td>
<td>182/114±35/9</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>3.67±0.34</td>
<td>3.26±0.37</td>
<td>3.81±0.46</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>138±1</td>
<td>138±1</td>
<td>138±2</td>
</tr>
<tr>
<td>Uric acid (µmol/l)</td>
<td>358±80</td>
<td>456±170</td>
<td>336±94</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>97±2</td>
<td>124±35</td>
<td>106±27</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>45±2</td>
<td>45±2</td>
<td>44±2</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>75±11</td>
<td>74±11</td>
<td>75±11</td>
</tr>
</tbody>
</table>

Results as means±SD. * BPs were lowered significantly during frusemide therapy (systolic, p<0.001; diastolic, p<0.003) for lying BP and p<0.02 and p<0.005 standing. Serum potassium levels fell (p<0.01) while uric acid (p<0.02) and creatinine (p<0.005) rose. 1 µmol/l uric acid=0.017 mg/dl; 1 µmol/l creatinine=0.0113 mg/dl.

(<160/100 mm Hg) was achieved or side-effects occurred. The study was evaluated when the last patient had been treated with frusemide for 4 weeks, which gave a mean treatment period of 12 weeks (range 4–27) and a mean frusemide dose of 75 mg/day (range 40–120). At that time frusemide was discontinued in all the patients and measurements were repeated 2 weeks later.

During frusemide treatment the BP, particularly the standing pressure, fell strikingly (see table). The serum-potassium fell 11%, despite potassium supplements in six patients; serum creatinine and uric acid values rose by 27% and 28%, respectively; serum sodium and albumin and body weight remained unchanged. 2 weeks after frusemide, none of these measurements differed significantly from pre-frusemide values.

In mild and severe hypertension frusemide lowers the blood pressure, and our data suggest that the BP reduction in drug-resistant hypertension can be ascribed to frusemide, which seemingly is what White et al. observed also. The benefit of combining frusemide and captopril seems to be that which seemingly is what White et al. observed also. The drug-resistant hypertension can be ascribed to frusemide, and they wonder if this might have been the major component of the blood pressure reduction in our patients.

Neither of our studies was a formal controlled trial. We did not examine the ability of other drugs (such as beta-adrenergic blockers or methyldopa) to lower plasma angiotensin II in combination with diuretics although, a priori, captopril seems likely to be more effective. Moreover, we did not add captopril after starting frusemide because of the danger of inducing severe hypertension.

There is little doubt, however, from our studies, that the combination of frusemide with captopril is markedly and consistently effective in resistant hypertension, in cases where a loop diuretic given with other drugs has been unsuccessful.

In SEARCH OF THE SOMOGYI EFFECT

Sir,—Dr Gale and colleagues (Aug. 9, p. 279) have studied the response to nocturnal hypoglycaemia in two groups of insulin-treated diabetics. One group reacted with a rebound hyperglycaemia (Somogyi) whilst the other remained hyperglycaemic. Their conclusion—that the endocrine response to hypoglycaemia is not the major cause of the Somogyi phenomenon—is open to debate. We would like to submit alternative interpretations to their findings.

(1) Both groups had a mean rise in plasma cortisol, growth hormone, and glucagon levels, following the hypoglycaemia, results which are consistent with other reports. There is a significant difference in plasma levels of free insulin (expressed in µU/ml rather than mU/ml) between the two groups. Gale et al. attribute the apparent rebound hypoglycaemia to the lack of free insulin. One can equally take the converse view. If the counter-regulatory hormones do indeed have a significant effect, then the group that failed to raise their morning blood sugar can be said to have remained hyperglycaemic because of higher levels of circulating insulin.


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* ** The Glasgow and Oxford groups' reply follows.—Ed L

Sir,—Dr Kristensen and Dr Skov, in an elegant study, have confirmed the powerful hypotensive action of large doses of frusemide, and they wonder if this might have been the major component of the blood pressure reduction in our patients.

6 of the 11 patients in the Glasgow series and 5 of the 10 in the Oxford series had, before starting captopril, received frusemide in doses at least as big as those used subsequently with captopril, but in combination with other drugs. 1 Other Glasgow patient received similar doses of thiazide throughout. In none of these was blood pressure reduction as effective without captopril. This is not surprising; besides the workers we cited, others have provided good evidence that the hypotensive action of diuretics is limited by the consequent rise in renin and hence in angiotensin II. This was, as we stated, a major theoretical reason for using captopril together with frusemide. We further showed that, despite large doses of frusemide, captopril effectively suppressed plasma angiotensin II in the long term.

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levels that has suppressed the tendency to hyperglycaemia. This would explain why only one patient exhibited the Somogyi effect when the insulin dosage was reduced. 

(2) Catecholamines rise in response to hypoglycaemia,9,10 and adrenaline infusion causes an elevation in blood sugar.11 Furthermore, beta-adrenergic blockade has been claimed to have a stabilising effect on blood sugar levels in poorly controlled diabetics.12 Although it can be argued (as in your Aug. 9 editorial) that these observations do not directly determine the extent of involvement of catecholamines in the pathogenesis of the Somogyi effect, their potential importance may have been insufficiently emphasised. 

(3) Peak hormonal levels may not be the ideal index for separating the two groups: perhaps total hormonal secretion, such as measurement of urinary hormonal excretion13 or the area under the curve of serial plasma estimations,14 might be better. 

(4) Hormonal interactions could have an effect on blood sugar in excess of each hormone alone.15 None of the above explanations is claimed to be necessarily correct, nor are they mutually exclusive. But if, as is argued, the Somogyi effect is due to low plasma levels of free insulin, it is difficult to understand why a reduction in insulin secretion can sometimes abolish or ameliorate this effect.

Kenneth R. Lyen
David Finegold
Lester Baker

David Finegold and his colleagues found the so-called Somogyi effect to be caused by insulin deficiency due to deficient insulin delivery after the hypoglycaemic event, rather than by an excess of counter-regulatory hormones such as cortisol, growth hormone, and glucagon.1

This conclusion accords with our findings from a study of six insulin-treated patients in whom we measured insulin disappearance from subcutaneous tissue on the thigh during 12 consecutive days.2 Hypoglycaemia followed by hyperglycaemia was seen only in patients who had an increased insulin absorption during the hours preceding hypoglycaemia followed by a decreased insulin absorption. This indicates that the blood glucose rebound was associated with deficient insulin delivery. The fluctuations in insulin absorption rate were unrelated to the dose of insulin, but rather related to the unpredictable and substantial intraindividual variation in insulin absorption rate seen in some subjects.3 The same blood glucose pattern may, however, also be seen in patients with only minor day-to-day variation in insulin absorption rate. These patients seem to be very sensitive to insulin. The variability in insulin absorption rate remains to be explained. Recent studies indicate that the local subcutaneous blood flow may be an important determinant.4 These findings imply that not all episodes of rebound hyperglycaemia are due to excess insulin dosage and that reduction of insulin dosage will not always produce clinical benefit.

Intravenous Stopcocks and Injection Ports

Sir,—We have already pointed out that the design of the ‘Venflon’ intravenous cannula (British Viggo; B.O.C.) can cause unnecessary complications for patients.5 The risk of intermittent intravenous bacterial inoculation exists whenever stopcocks and injection ports are incorporated into cannule, junctions, or extension tubes. High incidences of bacterial contamination in the interstices of three-way taps have already been reported.6,7 An editorial in the British Medical Journal also warned of the risks of sepsis from monitoring devices.8 Minute air emboli can be seen to enter via side-ports at each injection and, no doubt, these favour the entry of bacteria. Also, accidental omission of the silicone membrane protecting these ports in the manufacturing plant in Sweden could lead to air embolism in a hypovolaemic or tachyphylactic patient. The Viggo intravenous cannula marketed in the U.S.A. ('Vasculon') differs from that sold in the U.K. ('Venflon'). The vasculon is radio-opaque and the side-port is firmly and permanently occluded by a plastic stopper, so that it cannot be used for injection purposes (see figure). Why do the manufacturers operate to a double standard?

Viggo vasculon and venflon cannule showing open and closed side-ports.