The measurement of albumin leak into the gastrointestinal tract using $^{131}$I-albumin and ion exchange resin by mouth

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EDITORIAL SYNOPSIS These studies cast doubt on the validity of the technique of the use of an ion exchange resin by mouth together with $^{131}$iodine-labelled albumin intravenously as a method of measuring albumin loss in the alimentary tract.

The use of an ion exchange resin by mouth together with $^{131}$I-labelled albumin intravenously has been advocated (Jeejeebhoy and Coghll, 1961; Jeejeebhoy, 1962) as a method for measuring the amount of albumin passing across the intestinal wall into the lumen both in normal and pathological conditions. For the amount of radioactive iodine found in the faeces to be significant as a quantitative measure of albumin leakage, it has to be assumed that the intestinal enzymes are able to liberate all the $^{131}$I-iodide from the albumin, and that the resin in the gut is able to adsorb and retain all the radioactivity thus liberated. Investigations were therefore made both in normal humans and in rats, although it is appreciated that intestinal excretion of iodide in rats differs from that in humans (Pastan, 1957).

The first series of experiments involved the intravenous injection of $^{131}$I-albumin and $^{131}$I-sodium iodide into both humans and rats. If the method of Jeejeebhoy and Coghll (1961) can be relied upon and a measurable amount of $^{131}$I-albumin was passing into the gut, then the ratio of $^{131}$I to $^{125}$I accumulating in the faeces should be higher than the ratio of non-protein $^{131}$I over non-protein $^{125}$I in the plasma at any given time. In practice it is not possible to relate particular faecal samples to the plasma at the time of formation of the faeces because of lack of knowledge of the time between formation and collection. To get over this difficulty faecal and urine radioactivities have been measured over a long enough period to allow for excretion of all but a small percentage of the $^{125}$I. Approximately 25% of the $^{131}$I is liberated by catabolism during the period of the experiment. Under these circumstances passage of $^{131}$I albumin into the gut at any time during the experiment would be expected to raise the $^{131}$:125 ratio above that found for the urine accumulated over the same period.

EXPERIMENTAL

Two iodine isotopes having sufficiently different physical characteristics to permit independent estimation in a mixed sample (Cohen and Freeman, 1960) were used in these experiments. $^{131}$Iodine was used to label normal human albumin and rat albumin (McFarlane, 1958). Ion exchange resin (Amberlite IRA 400 C1) was fed by mouth; in human experiments 10 g. (damp weight) was taken every four hours except for the 2 a.m. dose which was omitted. Resin was taken for 24 hours before the injection of radioactivity, and continued for the duration of the experiment. In rats the ion exchange resin was mixed with the diet and fed in the normal manner, so the precise dose was not known; however, resin loading per gram body weight was estimated to be about three times the human dose. Non-radioactive sodium iodide was given by mouth before and during the experiment to block thyroid uptake; because of the presence of resin an increased amount (200 mg. per day) was given in divided doses between intakes of resin. External counting indicated that about 1% of the dose of radioactivity had been taken up by the thyroid.

In the human experiments, 24 hours after the first dose of resin by mouth about 60 $\mu$g. of $^{131}$I-albumin mixed with about 20 $\mu$g. of Na $^{125}$I was injected intravenously. All urine and faeces were collected, and the activity measured by scintillation counting in a well-type detector. Faecal samples were emulsified with a minimum volume of water to a thick slurry; if the resin tended to sediment, either potato starch or Sephadex G 75 was added to thicken the mixture. In order to recover samples of resin from the faeces, washing with water was used instead of adding starch. The rats, after the intravenous injection of radioactive material, were kept in a metabolism cage placed over a rapidly spinning disc covered with filter paper. This caused the faeces to be
thrown off sideways so that contamination with urine was minimal. Blood samples were taken daily in the human experiments, and gave values for the catabolism of albumin consistent with those previously reported (Cohen, Freeman, and McFarlane, 1961).

RESULTS

As shown in the table, after intravenous injection of 131I-albumin plus 125I-sodium iodide, the average ratios of 125I to 131I in the faeces were 1.86 compared with 0.81 in the urine for the human cases and 1.21 (faeces) compared with 0.77 (urine) for the rats. In other experiments it was shown that: 1 Resin reclaimed from the faeces after a human experiment was still capable of binding additional iodide. 2 When 125I-sodium iodide was given by mouth to humans between doses of resin only 35% was bound to the resin, the remainder being absorbed and excreted in the urine. 3 When rats were fed with resin on to which a small amount of 131I had been firmly bound, 70% appeared in the faeces, the remaining 30% appearing in the urine. 4 In two human cases when 131I-albumin (60 μc. and 1.0 g. albumin) was given by mouth between doses of resin, only 34% of the radioactivity was bound to the resin in the faeces, the remaining 66% appearing in the urine. 5 Monoiodotyrosine was taken up by the resin in vitro, but could be partially eluted with N acetic acid.

DISCUSSION

In all four experiments (Table I) in which 131I-albumin and 125I-sodium iodide were injected intravenously a slightly greater proportion of the 131I than of the 125I activity was found in the urine. If, however, 131I albumin passed into the gut as such, was catabolized there by intestinal or microbial enzymes and the 131I iodide thus formed was taken up and retained by the resin, then the proportion of 131I iodide on the resin should be greater than that of 125I iodide. Two possibilities need to be considered, namely, either no significant quantity of albumin passes into the gut, or the resin is unable to absorb and retain even part of the non-protein 131I radioactivity formed from it.

Although the resin has been shown to lose a considerable part of any 131I iodide originally bound to it during passage through the gut the latter possibility still appears unlikely, especially as resin recovered from the faeces was shown to have retained some capacity for trapping iodide. If some part of the 131I iodide which would certainly be formed from any 131I albumin passing into the gut would in fact be retained in the faeces, and also because it has been shown with certainty that the resin is unable to retain all previously adsorbed 131I iodide, it seems safe to conclude that the method of Jeejeebhoy and Coghill (1961) cannot be used to measure passage of albumin into the gut or to show whether it occurs in a particular case.

The only aspect of the present experiments which is difficult to interpret is the finding of rather higher ratios of 125I to 131I in the faeces as compared with the same ratio in the urine. Just possibly the higher ratio in the faeces might be due to uneven distribution of resin in the gut resulting from its intermittent administration by mouth. In these circumstances the passage of sufficient 131I albumin into the gut to equalize the ratio with that in the urine would have been missed if in fact it had occurred. On the other hand, if albumin does not pass into the gut then the observed faecal and urine 125I:131I ratios may be the result of the catabolism of a part of the albumin in the kidneys. However this problem may ultimately be resolved, unless substantial catabolism of albumin by the kidneys can be established the present evidence must tend to invalidate any theory involving passage of more than very small amounts of albumin into the gut. Above all it should be noted that whether or not albumin passes into the gut in normals is strictly irrelevant to the main purpose of this investigation which was to examine the validity of the method of Jeejeebhoy and Coghill (1961).

Finally it may be noted that the increased proportion of activity found on the resin in patients where an increased leak of albumin (Jeejeebhoy and Coghill, 1961) is postulated could be explained by altered conditions (of bulk, mobility, and pH) inside the bowel which favoured retention of activity by the resin. Alternatively there may in fact be a large leakage of albumin into the gut in these cases.

TABLE I

RESULTS OF EXPERIMENTS WITH INTRAVENOUS 131I-ALBUMIN AND 125I-SODIUM IODIDE

<table>
<thead>
<tr>
<th>Subject</th>
<th>Length of Experiment (days)</th>
<th>Percentage Total Excreted Activity Found in Faeces</th>
<th>Percentage Total Excreted Activity Found in Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without Resin</td>
<td>With Resin</td>
<td>131I</td>
</tr>
<tr>
<td>A.H.</td>
<td>8</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>S.H.</td>
<td>8</td>
<td>28</td>
<td>17</td>
</tr>
<tr>
<td>Rat 1</td>
<td>5</td>
<td>61</td>
<td>58</td>
</tr>
<tr>
<td>Rat 2</td>
<td>5</td>
<td>67</td>
<td>48</td>
</tr>
<tr>
<td>Rat 3</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

All figures are the sum of all the radioactivity excreted over the whole period of the experiment, despite the fact that most of the Na 125I was excreted in the first 48 hours.

AVERAGE OF SEVEN CASES

GIVEN AS Na 125I ONLY
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The technique described here using sodium $^{125}I$ iodide, which for optimum results should be infused for several days, should differentiate clearly between these hypotheses.

CONCLUSIONS

In normal subjects and in rats experiments with $^{131}$iodine-labelled albumin given intravenously and amberlite IRA 400 by mouth provide no evidence in favour of leakage of albumin into the gut; however, because of the inefficiency of the resin as a trap for iodide this does not prove conclusively that some leakage may not occur.

The faecal recovery of radioactivity after injection of labelled albumin only does not provide the basis for a quantitative estimation of the amount of albumin which may pass into the gut in certain pathological conditions.

REFERENCES