Serum studies in man after administration of vitamin A acetate and vitamin A alcohol

II In subjects suffering from disturbances of absorption and digestion

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SYNOPSIS Vitamin A acetate and vitamin A alcohol, triolein $^{131}$, oleic acid $^{131}$, and fat balance tests have been assessed in studies on cases of coeliac disease, pancreatic insufficiency, and some disorders of the small intestinal wall.

In coeliac disease a very low serum carotene and flat vitamin A absorption curves have been noted. The contrast between vitamin A acetate and alcohol curves has been clearly shown in cases of pancreatic disorder showing maldigestion. The correlation between vitamin A and triolein $^{131}$ absorption (0.89) is closer than that between vitamin A and fat balance.

In assessing intestinal absorption serum carotene figures are of value only if very low figures are found.

Some of the many factors which may affect vitamin A absorption in the normal subject have already been noted (FitzGerald, Fennelly, and Hingerty, 1961). One might note in particular the effect of diet and exercise. In this paper the results of tests carried out on patients with coeliac disease, pancreatic disease, and other conditions involving the alimentary tract will be discussed. Where possible, the vitamin A tests will be compared with other absorption tests, such as fat balance, triolein $^{131}$ absorption, oleic acid $^{131}$ absorption and with serum carotene. The differential absorption of vitamin A acetate and vitamin A alcohol in pancreatic deficiency will also be discussed.

Low fasting plasma vitamin levels and flat absorption curves after ingestion of vitamin A are accepted findings in coeliac disease (Chesney and McCoord, 1934). Usually there is little difference in these cases between absorption of the vitamin from oily and aqueous phases, though Fox (1949) did find good absorption curves in coeliac patients after ingestion of emulsified vitamin A. Excellent absorption of vitamin A in an aqueous phase compared with the flat curves following tests with an oily preparation has been observed in cystic fibrosis of the pancreas (Lewis, Bodansky, Birmingham, and Cohlan, 1947). Moreover, pancreatin, administered during the test in these cases, has been shown to rectify a previously abnormal curve. Following gastrectomy some patients show subnormal absorption whereas others reveal earlier peaks in absorption than do normal subjects (Mendeloff, 1954). Other conditions studied in which poor absorption was found were tuberculosis (Breese, Watkins, and McCoord, 1942), bile duct atresia (May, Blackfan, McCreary, and Allen, 1940), and jejuno-ileitis (Adlersberg and Sobotka, 1943).

MATERIAL AND METHODS

The vitamin A absorption tests were carried out as described earlier (FitzGerald et al., 1961). Triolein $^{131}$ and oleic acid $^{131}$ absorption tests were carried out as described by Fennelly, FitzGerald, and Healy (1959).

For the evocative serum enzyme test the method of Howat, Duncan, Harper, Oleesky, Scott, Smith, and Varley (1955) and later described by Burton, Hammond, Harper, Howat, Scott, and Varley (1960) with minor modifications as regards time was used.

RESULTS

Normal absorption figures have already been noted, namely, a fasting level of 100 to 300 i.u. % rising to over 800 i.u. % after 250,000 i.u. % of vitamin A
taken orally, the figure being similar for vitamin A acetate and vitamin A alcohol preparations. Peak figures between 600 and 800 i.u. % are suggestive of malabsorption but need further evidence for definite diagnosis. Peak figures failing to rise over 600 i.u. % definitely indicate malabsorption. The normal fasting serum carotene level was taken as over 80 µg. % (FitzGerald et al., 1961).

Normal subjects showed peak absorption after ingesting triolein Í¹³¹ of over 12 % of the test dose. Faecal excretion should not exceed 4 % of the ingested dose in a 72 hours' collection. Fat balance results were expressed in g./day faecal excretion on a diet of 50 to 100 g./day. Less than 6 g. was excreted normally.

IN COELIAC DISEASE AND OTHER INTESTINAL DISORDERS The main conclusions which can be derived from Table I are that patients with coeliac disease showed poor absorption of both vitamin A acetate and vitamin A alcohol and also a low fasting serum carotene level.

Case I, an adult, had had steatorrhoea for many years; hypocalcaemia, fatty diarrhoea, abdominal distention, weight loss, and osteomalacia were also present. She responded well to a gluten-free diet and, as can be seen, vitamin A absorption and triolein Í¹³¹ absorption improved slightly during the first six weeks of treatment. The failure of serum tolerance tests to respond better is possibly due to the rapid tissue uptake of vitamin A and triolein Í¹³¹ in a patient with a long history of malabsorption.

Table II shows results in tests carried out on patients with other conditions involving the small intestine. Though classical ulcerative colitis does not involve the small intestine poor intestinal absorption may occur in this condition (Sandweiss and Levy, 1957). It can be seen that peak figures, while higher than those in coeliac disease, are still abnormal. There is a striking difference between the fasting serum carotene levels in Tables I and II. In only one member of this group (Table II) was the serum carotene level unusually low.

### Table I

<table>
<thead>
<tr>
<th>No.</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Age (yr.)</th>
<th>Sex</th>
<th>Vitamin A Acetate (i.u. %) (Peak)</th>
<th>Vitamin A Alcohol (i.u. %) (Peak)</th>
<th>Serum Carotene (µg. %)</th>
<th>Triolein Í¹³¹ Dose in Serum at Peak (%)</th>
<th>Fat Excretion (g./day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Coeliac disease (on treatment)</td>
<td>Gluten-free diet (1959)</td>
<td>50 F</td>
<td></td>
<td>100</td>
<td>115</td>
<td>10</td>
<td>2-9</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Coeliac disease</td>
<td>Gluten-free diet (1959)</td>
<td>8 M</td>
<td></td>
<td>141</td>
<td>400</td>
<td>20</td>
<td>3-9</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Coeliac disease (on treatment)</td>
<td>Gluten-free diet</td>
<td>10 F</td>
<td></td>
<td>200</td>
<td>149</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Coeliac disease (on treatment)</td>
<td>Gluten-free diet</td>
<td>7 M</td>
<td></td>
<td>73</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Coeliac disease (on treatment)</td>
<td>Gluten-free diet</td>
<td>14 F</td>
<td></td>
<td>158</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Coeliac disease (on treatment)</td>
<td>Gluten-free diet</td>
<td>8 M</td>
<td></td>
<td>284</td>
<td>39</td>
<td></td>
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### Table II

<table>
<thead>
<tr>
<th>No.</th>
<th>Diagnosis</th>
<th>Age (yr.)</th>
<th>Sex</th>
<th>Vitamin A Acetate (i.u. %) (Peak)</th>
<th>Vitamin A Alcohol (i.u. %) (Peak)</th>
<th>Serum Carotene (µg. %)</th>
<th>Triolein Í¹³¹ Dose in Serum at Peak (%)</th>
<th>Fat Excretion (g./day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Progressive systemic sclerosis</td>
<td>38 M</td>
<td></td>
<td>300</td>
<td>400</td>
<td>80</td>
<td>3-6</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Lymphosarcoma (intestinal)</td>
<td>36 F</td>
<td></td>
<td>480</td>
<td>520</td>
<td>128</td>
<td>16 faecal excretion</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>After massive resection of small intestine</td>
<td>58 M</td>
<td></td>
<td>278</td>
<td>800</td>
<td>128</td>
<td>16 faecal excretion</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Post-gastrectomy diarrhoea</td>
<td>50 M</td>
<td></td>
<td>634</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Post-gastrectomy diarrhoea</td>
<td>46 M</td>
<td></td>
<td>242</td>
<td>445</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Ulcerative colitis</td>
<td>30 M</td>
<td></td>
<td>640</td>
<td>*20</td>
<td>130</td>
<td></td>
<td></td>
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<tr>
<td>13</td>
<td>Intestinal moniliasis</td>
<td>14 F</td>
<td></td>
<td>80</td>
<td>600</td>
<td>36</td>
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<tr>
<td>14</td>
<td>Intestinal moniliasis</td>
<td>18 F</td>
<td></td>
<td>314</td>
<td>624</td>
<td>124</td>
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</table>
IN PANCREATIC DISEASE These tests were carried out on 27 patients with pancreatic disease of various types, namely, chronic relapsing, calcareous, post-gastrectomy, or hereditary pancreatitis and ampullary carcinoma. Tables III and IV show results in patients found to have normal and subnormal absorption respectively. Fig. 1 shows the contrast between the absorption of vitamin A acetate and vitamin A alcohol in pancreatic malabsorption.

It is worth noting that the mean absorption figures in normal subjects for vitamin A acetate are slightly higher than those of vitamin A alcohol.

For purposes of description results are divided into two groups, depending upon whether there is or is not any objective sign of a disturbance of digestion leading to an absorption defect (Tables III and IV).

In Table IV are shown results of tests in patients with pancreatic disease who showed malabsorption on fat balance studies or on the basis of poor serum lipid response, depressed triolein absorption, and often by steatorrhoea and loss of weight.

The absorption pattern was followed repeatedly over some years in five patients. Case 15 (Table IV) had stenosis of the sphincter of Oddi with evidence of malabsorption. After a sphincterotomy this absorption returned to normal. Case 21 developed pancreatitis following a partial gastrectomy and as the pancreatic disease progressed absorption deteriorated. Case 24 showed similar changes. Cases 22 and 23 (a father and daughter) had normal absorption curves in 1954 and 1955 at a time when both complained of symptoms referable to pancreatitis. With subsequent deterioration in the condition of both patients their curves became abnormal. At operation signs of pancreatic abnormality were present in both. Case 23 gained 30 lb. in weight following a sphincterotomy and excision of a polyp in the pancreatic duct.

### Table III

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr.)</th>
<th>Sex</th>
<th>Vitamin A Acetate (i.u.%)</th>
<th>Vitamin A Alcohol (i.u.%)</th>
<th>Serum Carotene (μg%)</th>
<th>Fat Balance as % Faecal Fat (50 g. fat diet)</th>
<th>Triolein 111 Dose in Serum at Peak (%)</th>
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<tr>
<td>1</td>
<td>40</td>
<td>F</td>
<td>1,250</td>
<td>1,040</td>
<td>292</td>
<td>2</td>
<td></td>
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<tr>
<td>2</td>
<td>36</td>
<td>F</td>
<td>3,500</td>
<td>900</td>
<td>350</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>M</td>
<td>1,550</td>
<td>1,850</td>
<td>223</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>F</td>
<td>1,850</td>
<td>1,000</td>
<td>225</td>
<td>2-5</td>
<td>19-5</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>M</td>
<td>1,973</td>
<td>1,952</td>
<td>207</td>
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<tr>
<td>6</td>
<td>44</td>
<td>F</td>
<td>1,100</td>
<td>1,960</td>
<td>188</td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>33</td>
<td>M</td>
<td>4,100</td>
<td>4,300</td>
<td>90</td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>F</td>
<td>2,620</td>
<td>830</td>
<td>74</td>
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<td></td>
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<tr>
<td>9</td>
<td>60</td>
<td>M</td>
<td>1,572</td>
<td>1,699</td>
<td>122</td>
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<tr>
<td>10</td>
<td>21</td>
<td>F</td>
<td>796</td>
<td>790</td>
<td>233</td>
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<tr>
<td>11</td>
<td>48</td>
<td>F</td>
<td>1,659</td>
<td>2,760</td>
<td>88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>64</td>
<td>F</td>
<td>2,522</td>
<td>2,506</td>
<td>195</td>
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<td></td>
</tr>
<tr>
<td>13</td>
<td>56</td>
<td>F</td>
<td>1,200</td>
<td>1,000</td>
<td>190</td>
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</table>

### Table IV

<table>
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<tr>
<th>Case No.</th>
<th>Diagnosis</th>
<th>Age (yr.)</th>
<th>Sex</th>
<th>Peak Serum Vitamin A Acetate (i.u.%)</th>
<th>Peak Serum Vitamin A Alcohol (i.u.%)</th>
<th>Fasting Serum Carotene (mg%)</th>
<th>Fat Balance (g./day)</th>
<th>Serum Peak Triolein 111 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Stenosis of sphincter of Oddi</td>
<td>48</td>
<td>M</td>
<td>458</td>
<td>956</td>
<td>120</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>16</td>
<td>Carcinoma of ampulla</td>
<td>64</td>
<td>F</td>
<td>110</td>
<td>320</td>
<td>40</td>
<td>6-8</td>
<td>6-8 (1959)</td>
</tr>
<tr>
<td>17</td>
<td>Chronic relapsing pancreatitis</td>
<td>37</td>
<td>F</td>
<td>750</td>
<td>1,150</td>
<td>328</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>18</td>
<td>Chronic relapsing pancreatitis</td>
<td>65</td>
<td>F</td>
<td>350</td>
<td>350</td>
<td>135</td>
<td>4-5</td>
<td>4-5</td>
</tr>
<tr>
<td>19</td>
<td>Chronic relapsing pancreatitis</td>
<td>58</td>
<td>F</td>
<td>550</td>
<td>820</td>
<td>140</td>
<td>3-5</td>
<td>3-5</td>
</tr>
<tr>
<td>20</td>
<td>Chronic relapsing pancreatitis</td>
<td>50</td>
<td>M</td>
<td>600</td>
<td>700</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Post-gastrectomy pancreatitis</td>
<td>55</td>
<td>M</td>
<td>450 (1956)</td>
<td>900 (1956)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Calcareous pancreatitis</td>
<td>58</td>
<td>M</td>
<td>435 (1959)</td>
<td>410 (1959)</td>
<td>73</td>
<td>9-3</td>
<td>6-6 (1959)</td>
</tr>
<tr>
<td>23</td>
<td>Stenosis of sphincter of Oddi</td>
<td>22</td>
<td>F</td>
<td>3,100 (1955)</td>
<td>2,270 (1955)</td>
<td>50</td>
<td>35% dried weight</td>
<td>6-8</td>
</tr>
<tr>
<td>24</td>
<td>Chronic relapsing pancreatitis</td>
<td>46</td>
<td>M</td>
<td>1,140 (1956)</td>
<td>1,650 (1956)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Calcareous pancreatitis</td>
<td>56</td>
<td>M</td>
<td>172</td>
<td>616</td>
<td>10</td>
<td>10</td>
<td>8-2</td>
</tr>
</tbody>
</table>
Serum studies in man after administration of vitamin A acetate and vitamin A alcohol

VITAMIN A ACETATE
20.800
1.450
1,150
986
820
700
616
504
400
300
200
100
0

FIG. 1. Contrast between absorption of vitamin A alcohol and vitamin A acetate in patients with pancreatogenous steatorrhoea.

- - - - Mean (normal)
- - - - Mean (malabsorption)

Range of peaks in pancreatic patients with malabsorption

FIG. 2. Percentage of triolein 131 dosage in total blood volume (7.7% body weight) at peak showing correlation between vitamin A and triolein absorption in 15 patients. Coefficient of correlation = 0.89 (P < 0.001).

The three absorption tests most widely used at present are fat balance studies, vitamin A absorption, and radioactive tagged fat absorption (triolein 131 and oleic acid 131). We have attempted to correlate these tests in patients who had more than one of them.

In Figs. 2 and 3 are shown comparisons between vitamin A absorption and triolein 131 and vitamin A absorption and fat balance tests. Shingleton, Baylin, Isley, Sanders, and Ruffin (1957) referred to the contrast in triolein and oleic acid absorption in four cases of pancreatic deficiency. In Fig. 2 both triolein 131 and vitamin A results are expressed as the percentage of the ingested test dose found in the total blood volume, the blood volume being taken as 7.7% body weight in kilograms.

There is a high degree of correlation between the vitamin A and triolein 131 absorption tests. The coefficient of correlation is 0.89 (P < 0.001). Study of the fat balance and vitamin A results in Fig. 3 indicates a lesser degree of correlation between these tests. There is much greater scatter of points around the lines representing the mean figures, the coefficient of correlation being only 0.61 in this case (P < 0.02). It has already been pointed out

FIG. 3. Correlation between vitamin A absorption and fat balance in 14 patients. Coefficient of correlation = 0.62 (P < 0.02).
that serum tolerance tests depend on factors other than absorption alone, so it is to be expected that there would be closer correlation between one serum tolerance test and another rather than between a serum tolerance test and a balance test.

**DISCUSSION**

Because of the variation in results obtained with vitamin A absorption tests in both normals and abnormalities noted by some authors (Mendeloff, 1954; Hillman and Becker, 1957) this test has been less frequently used than other absorption tests, such as fat balance or the more recently introduced $^{131}$I tagged fats, both of which have been much used (Shingleton et al., 1957; Beres, Wenger, and Kirsner, 1957; Duffy and Turner, 1958). Our experience with the vitamin A tests has led us to conclude that it is a satisfactory test and may have certain advantages over other tests for the following reasons:—It is less laborious than the commonly used fat balance test, both for patients and medical personnel. Results can be made available on the day of the test. The difference between normal peak figures (800 i.u.% and upwards) and abnormal figures (generally peak figures below 600 i.u.% ) is usually clear cut. Serial tests may be used if required, for example, in order to follow changing patterns of disease without hazard to the patient, such as might occur with $^{131}$I tagged fat; weekly repetition of vitamin A absorption tests is quite feasible. The differential absorption curves of vitamin A acetate and vitamin A alcohol preparations may give useful information in studying pancreatic disease.

Our use of this test has been restricted almost completely to adults, as repeated phlebotomy in children for 5 ml. of blood is difficult and may be hazardous if the external jugular veins have to be used. If the test is used in children it is essential to give doses calculated according to body weight (5,000 to 7,000 i.u./kg. body weight).

Patients with active coeliac disease usually show low serum carotene (mostly under 20 µg. %), subnormal fasting vitamin A levels and a poor serum response to oral administration of both acetate and alcohol preparations of vitamin A. All the subjects in Table I had these characteristics. In two cases it was possible to demonstrate the clinical improvement by the vitamin test after the use of a gluten-free diet.

As shown in Table II the figures in other intestinal disorders, though abnormal, were higher than those of patients with coeliac disease. Serum carotene was subnormal in only one of eight cases. The acetate and alcohol preparations were both poorly absorbed, vitamin A alcohol giving a slightly higher peak figure. Evidence of malabsorption was present biochemically in five of eight cases. In the other three the tests were carried out because of weight loss. These cases would appear to refute the belief that fasting serum carotene estimation alone is of value in studying malabsorption.

The contrast in absorption of vitamin A alcohol and vitamin A acetate was noted in patients with cystic fibrosis of the pancreas (Breese and McCoord, 1939). More recently Lewis et al. (1947) have pointed out a similar contrast using aqueous and oily preparations of the vitamin. In our studies on pancreatic disease we have been impressed with the contrast in absorption of the vitamin A alcohol and vitamin A acetate which appeared in 32% of the cases studied. Table IV and Fig. 1 show this fact quite clearly. Three patients (Cases 22, 23, and 24, Table IV), who had normal absorption capacity when they first presented with symptoms of pancreatitis, later developed characteristic defects due to the progress of the disease.

As vitamin A acetate also depends on pancreatic lipase for its proper absorption the disparity between triolein and oleic acid absorption curves should be similar to those of vitamin A acetate and vitamin A alcohol. In Table V we have shown the results of both tests carried out on three patients with pancreatic deficiency. It can be seen that the correlation is striking. There is definite similarity between the absorption ratio of vitamin A alcohol/vitamin A acetate and that between oleic acid $^{131}$I and triolein $^{131}$I. Fierst, Feldman, Solomon, and Langsam (1958) pointed out that correlation between fat balance tests and vitamin A absorption tests had not yet been proved, but they showed that absorption of

**TABLE V**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnosis</th>
<th>Serum Levels Vitamin A (i.u., %)</th>
<th>Percentage of Ingested Dose of $^{131}$I in Serum at Peak Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Acetate</td>
<td>Alcohol</td>
</tr>
<tr>
<td>21</td>
<td>Post-gastrectomy pancreatitis</td>
<td>435</td>
<td>410</td>
</tr>
<tr>
<td>23</td>
<td>Stenosis of sphincter of Oddi</td>
<td>384</td>
<td>2,161</td>
</tr>
<tr>
<td>25</td>
<td>Calcareous pancreatitis</td>
<td>172</td>
<td>616</td>
</tr>
</tbody>
</table>
triolein $^{131}$ and vitamin A acetate were related in 82.5% of cases.

Fasting serum carotene figures were normal in all cases of pancreatitis, except in Cases 16 and 22, both of which had reached that advanced stage of the condition when absorption of both forms of vitamin A may be abnormal.

The correlation between these tests, as shown in Figs. 2 and 3, indicates that the triolein $^{131}$ and vitamin A absorption tests are equally useful. There appears to be less correlation between fat balance and vitamin A absorption tests. As these tests were carried out in 20 subjects varying from normal to abnormal the figures are of some value.

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Serum studies in man after administration of vitamin A acetate and vitamin A alcohol: II In subjects suffering from disturbances of absorption and digestion

Oliver Fitzgerald, James J. Fennelly and Daniel J. Hingerty

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