

## Progress report

# Intestinal malabsorption in the experimental animal

The study of human malabsorption syndromes has fascinated gastroenterologists for many years, but only recently has any understanding of the basic mechanisms underlying these conditions become available. This lack of knowledge was partially due to the inability of investigators to reproduce the same symptoms in the experimental animal. Much progress in 'experimental gastroenterology' has been made in the last few years, which should eventually assist clinical gastroenterologists in their understanding of human diseases. This review, which condenses and updates an earlier article,<sup>1</sup> presents some of the experimental work of the last decade which has helped us in our comprehension of some of the malabsorption syndromes.

Perhaps the most studied malabsorption syndrome in man is coeliac sprue, a disease characterized by a pathological sensitivity to gluten and by the appearance in the intestine of flattened villi, elongated crypts, and an increased cell turnover<sup>2-4</sup>. Large numbers of histochemical studies have been performed on biopsy samples from patients with sprue, and a generalized decrease in enzyme activity within the epithelium has been demonstrated.<sup>2,3,5-8</sup> On the other hand, a specific diffuse reaction for lysosomal hydrolases within the surface cells has also been observed, and it has been suggested that this is the primary cellular change responsible for the characteristic reaction of the tissue.<sup>3</sup> For as the surface cells are destroyed by autolysis by the lysosomal hydrolases, the mitotic patterns of the crypts are accelerated in an attempt at compensation for the increased cell loss. This hypothesis received strong support when it was demonstrated that the diffuse activity of lysosomal enzymes in the affected cells could be reduced by corticosteroid administration,<sup>9</sup> since such drugs are known to be stabilizers of the lysosomal membrane.<sup>10</sup> What is not yet known is how the sensitivity of these patients to gluten is translated at the cellular level by labilization of the lysosomal membrane of the granules of the epithelial cell. Immunological reactions may be involved in this sensitization.<sup>11,12</sup>

An untreated intestine of patients with coeliac sprue is the site of moderate to severe malabsorption, as has been shown by perfusion studies *in vivo*<sup>13-15</sup> and by uptake of radioactive substrates by biopsy samples *in vitro*<sup>16,17</sup>. The reduced absorption is presumably due to a large extent to the reduction in intestinal surface area.

Increased proliferation of the absorptive cells occurs in many other human diseases,<sup>18,19</sup> though to a lesser extent, and is always accompanied by similar morphological and cell kinetic patterns;<sup>19</sup> only quantitative differences are observed. It may not be necessary for labilization of the lysosomal membrane to be the trigger responsible for provoking this response; any action that causes the destruction of surface cells and therefore an attempt by intact crypts to compensate for the attack should produce the same overall result.

This situation is clearly observed in three experimental models. The first involves the response of the intestine to the infusion of acid into the lumen, a condition where a preferential attack on the surface cells occurs, together with a resultant compensatory increase in cell turnover in the crypts.<sup>20-22</sup> Riecken *et al* employed high concentrations of lactic acid for their experiments and observed a typical hyperregenerative mucosal lesion in the rat intestine.<sup>22</sup> Unfortunately, extremely severe experimental conditions were required to elicit a typical response, a fact that reduces the usefulness of the experimental model. Nevertheless, these investigators<sup>22</sup> were able to distinguish two stages of the hyperregenerative response; first, accelerated epithelial desquamation led to increased mitosis, prolonged crypts, and lengthened villi; then if the lactic acid concentration was further increased, the corrosive action was greater, the crypts were further enlarged, but in this case shortened villi were revealed.

The second experimental condition concerns transmissible gastroenteritis of swine. This is a viral disease in which the organism specifically attacks the surface epithelial cells without affecting the crypts.<sup>23-25</sup> As a result, a typical sprue-like syndrome develops, with blunt villi,<sup>23,25-27</sup> increased mitosis,<sup>25-27</sup> reduced enzyme activities,<sup>25,26,28</sup> and malabsorption.<sup>23,28</sup>

Furthermore, coeliac sprue has been closely mimicked in the experimental animal following injection of triparanol.<sup>29,30</sup> This drug appears to provoke labilization of the lysosomal membrane within the epithelial cell, liberating acid hydrolases which destroy the surface cells; eventually, a syndrome is induced which is formally identical with human sprue. In addition rats poisoned with triparanol also respond to a gluten-free diet although the normal rat is insensitive to the peptide.<sup>31</sup> This extremely important discovery indicates that the response of the intestine to a gluten-free diet is somewhat non-specific in nature. But it may possibly be related to the initial reaction provoking the hyperregenerative response of the gut, namely, the labilization of the lysosomal membrane which occurs both in sprue and in triparanol intoxication, though presumably not in porcine transmissible gastroenteritis.

One of the clinical situations in which coeliac-like symptoms arise is kwashiorkor, or infantile protein malnutrition.<sup>18,32</sup> In this case, no response to a gluten-free diet is observed, and the cause of the morphological changes observed at the cellular level is unknown. The histological alterations are accompanied by malabsorption,<sup>33,34</sup> reduced enzyme levels,<sup>35</sup> and a slight decrease in mitotic index.<sup>32</sup> In a recent paper,<sup>36</sup> amino-acid uptake *in vitro* by biopsy samples was determined, and it was concluded that the tissues were normal since their transport capacity did not change on treatment. Since no real controls were performed on tissue from normal subjects, this conclusion may be unjustified. On the other hand, rats treated with low-protein diets have been shown to have normal amino-acid absorption,<sup>37</sup> despite other changes which indicate the induction of kwashiorkor in the animals.

Marasmus, or malnutrition resulting from caloric deprivation, is a clinical entity which differs considerably from kwashiorkor.<sup>38,39</sup> At the intestinal level, coeliac-like symptoms are not present, disaccharidase activities are normal,<sup>40</sup> but there is a thinning of the mucosa and a very strong inhibition of mitosis.<sup>32,38</sup> Similarities with infantile marasmus have been observed in an experimental model using toads which have been kept without food for several months.<sup>41</sup> The animals were of course emaciated, but the intestine was one of the organs that was preferentially subject to autophagy. There was a strong

reduction in mitotic activity, as indeed has been found in other studies on the effect of starvation in mammals,<sup>38,42-44</sup> and histological study revealed marked atrophy of the villous structure. Amino-acid transport *in vitro* was reduced, but this could be entirely attributed to the loss of mucosal surface tissue.<sup>41</sup> Similar, but less extreme, atrophy of the mucosa has been observed in blind loops of rat intestine, where mitotic inhibition and malabsorption also occurred.<sup>45</sup> It has been speculated that this type of villous atrophy is due to a diminution in luminal nutrition,<sup>46-48</sup> a factor that might also be responsible for hypertrophy of the intestine following resection or hyperphagia.<sup>47</sup> (For further discussion on intestinal compensation in response to starvation,<sup>48,49</sup> intermittent starvation with hyperphagia,<sup>50</sup> resection,<sup>47,51</sup> or segmental juxtaposition,<sup>51,52</sup> all of which may ultimately depend on luminal nutrition, the reader is referred to the reviews cited, particularly that of Dowling<sup>47</sup> where the relationship of cell turnover and functional maturity to intestinal function in cases of compensation is discussed in detail.) Incidentally, Altmann has recently questioned the importance of luminal nutrition in determining villous size, and has proposed, with the aid of elegant experimental data, that pancreatic and biliary secretions contain a factor responsible for enlargement of the villi.<sup>53</sup>

One further point concerning intestinal atrophy in undernutrition is of interest. Autophagy of the intestine for nutritional purposes must presumably be delicately controlled, though how this process proceeds is unknown. A hint has been afforded by the demonstration of an increase in lysosomal enzymes in various tissues,<sup>54,55</sup> including the intestine,<sup>56</sup> during starvation. It can thus be mooted that this increase can be utilized to break down the tissue for other uses.

The effect of mitotic inhibition *per se* has been the object of numerous studies both in the clinic and in the laboratory animal. The immediate response of the intestine is negligible since the surface cells are not attacked. When they are desquamated at the end of their life cycle, they are no longer replaced and a highly inflammatory bowel results. This situation occurs in the clinic as a result of excessive radiation or after treatment with antimetabolic drugs. Generally, structural changes are observed, but clinically, gastrointestinal symptoms are slight.<sup>57-59</sup> This finding has been confirmed in the experimental animal when low doses of radiation or antimetabolites, such as folic acid antagonists or colchicine, have been applied. After a relatively small dose of 5-fluoro-uracil, Roche *et al* have observed a good correlation between glucose transport and the villous cell population,<sup>60</sup> and Perris demonstrated that after a low dose of irradiation, some transport mechanisms were more sensitive to the intoxication than others,<sup>61</sup> indicating that perhaps the biochemical mechanisms *per se* were sensitive to the radiation.

Often, more vigorous conditions have been employed in the experimental animal, both in the case of irradiation<sup>62-68</sup> and in the case of administration of antimetabolic drugs,<sup>69-76</sup> and similar results have been obtained with both models, although the effects of ionizing radiation may be complicated by other cellular effects or by extraintestinal actions.<sup>1</sup> Thus transport of glucose *in vivo* is reduced six hours after irradiation,<sup>62-65,67,68</sup> probably due to an effect on the adrenals,<sup>65</sup> before any intestinal damage has been observed. The transport capacity is either normal or slightly above normal at 24 hours, both after irradiation<sup>63,64,66,67</sup> or administration of antimetabolites.<sup>74</sup> Then 48 hours after either treatment transport was found to fall off abruptly, according to

both determinations *in vivo*<sup>66,75</sup> and *in vitro*<sup>67,68,71,74</sup> and histochemically determined enzymes were concomitantly reduced;<sup>77,79</sup> this corresponds to the time at which all attacked cells have been desquamated. Certain investigators have noticed that the extremely distorted tissue at this stage is still able to concentrate nutrients to a surprisingly good extent;<sup>68,74,75</sup> others have noted that normal cells are often interspersed with pathological ones as a result of radiological damage<sup>78,79</sup> During the recovery stage from either irradiation<sup>80</sup> or administration of antimetabolic drugs,<sup>74</sup> there is often a delay in functional normalization despite apparent morphological recovery. This could be ascribed to a temporary increase in cell turnover with a resultant immature cell population during recovery.<sup>81</sup>

Particularly in the case of colchicine, histochemical studies have shown that administration of low doses of the drug influence specific enzyme systems of the intestinal mucosa.<sup>82-84</sup> Thus disaccharidases<sup>83,84</sup> and certain dehydrogenases<sup>82</sup> are particularly sensitive to colchicine. These findings led Herbst *et al* to propose that colchicine acts upon the mechanism responsible for cell differentiation which is concerned with disaccharidase synthesis, and therefore that the use of small doses of colchicine may provide a useful model for the study of clinical disaccharide intolerance.<sup>84</sup>

There is some evidence that radiation and antimetabolic therapy have different actions on the gut. Hampton has compared and contrasted the structural changes produced by colchicine and by irradiation.<sup>85</sup> It is possible that radiation not only inhibits mitosis, but also has another effect—one possibility that has been discussed elsewhere<sup>86</sup> is that it labilizes the lysosomal membrane.

If the labilization of the lysosomal membrane may have played a role in some of the other syndromes that have been discussed, it certainly has a primary role in the intestinal response to ischaemia and shock. Severe ischaemia of the small intestine is a rare but catastrophic occurrence in the clinic.<sup>86,87</sup> Only rapid surgical intervention is capable of preventing death,<sup>88,89</sup> and even if embolectomy and arterial anastomosis succeed in preventing a fatal outcome,<sup>88</sup> malabsorption often continues for some time after revascularization has been effected.<sup>90</sup> Reduced vascularization of intestinal loops due to stenosis of smaller vessels gives rise to a syndrome known as 'intestinal angina' which is less drastic, but which is also often accompanied by malabsorption and may require surgical intervention.<sup>86,87</sup>

Several experimental studies have been performed to gauge the sequence of events in intestinal ischaemia and to reproduce malabsorption during the recovery stage. Acute ischaemia of a loop of intestine is a dramatic process, damage of the surface cells being evident after only 10 minutes, and complete denudation of the villi being accomplished within half an hour in small rodents.<sup>91,92</sup> This is accompanied by loss of all absorptive functions.<sup>92,93</sup> Some authors have used subtotal conditions (such as leaving the collateral circulation intact) and considerably less damage has been observed.<sup>94,95</sup> Lysosomal enzymes are massively released into the blood stream and lumen on total ischaemia of the gut.<sup>96-98</sup> On the other hand, the crypt cells are much more resistant, and in the rat, only start to be destroyed after two hours' total ischaemia.<sup>97</sup> Just as acute total ischaemia provokes a dramatic destruction, the recovery from these lesions is equally spectacular; it has recently been shown in dogs that mucosae that have been completely destroyed by one hour's ischaemia regain normal structure, function, and microcirculation 24 hours later.<sup>98</sup> If the crypt cells have been destroyed, an abnormal recovery

pattern would have developed,<sup>99</sup> as has also been observed in some cases of partial ischaemia.<sup>92,100</sup> On the other hand, rats surviving one hour's clamping of the superior mesenteric artery appeared to have regained normal villous structure after 48 hours but showed signs of an important malabsorption syndrome.<sup>101</sup>

The response to shock, both in human subjects and in experimental animals, parallels these findings in intestinal ischaemia.<sup>102</sup> The sensitivity of the intestinal epithelium to hypoxia leads to lysosomal release as a result of the reduced blood flow occurring in shock, and hence ischaemic changes in the mucosa occur.<sup>103</sup> The primary involvement of the intestine in shock has been elegantly demonstrated in experiments in dogs by Bounous and his coworkers.<sup>103-105</sup>

To the clinician, acute ischaemia of the colon is of greater interest than ischaemia of the small intestine, since it is less rare and since it can also appear as a complication after vascular surgery.<sup>106,107</sup> As a disease, ischaemic colitis has received considerable attention in recent years,<sup>108,109</sup> but few attempts have been made at reproducing the syndrome in the experimental animal. Four groups<sup>109-114</sup> have induced acute colonic ischaemia in dogs, and have succeeded in reproducing the morphological changes that have been observed in the clinic: total ischaemia of several hours' duration leads eventually to gangrenous destruction of the bowel, whereas shorter periods of acute ischaemia may produce stenosis of the bowel, or the colon may recover its structure completely.<sup>112,114</sup> The colon is less sensitive to total acute ischaemia than the small intestine, little morphological damage being observed after one hour's total ischaemia.<sup>113,114</sup> Nevertheless, the discrete changes observed were sufficient to abolish all transport functions.<sup>113,114</sup> After three hours' ischaemia, the damage was so great that only a proportion of the animals were able to regain structure and function of the ischaemic loop.<sup>109,114</sup>

Some of the traumas to which the intestine has been subjected, which have been discussed in the foregoing paragraphs, have led to denudation of the intestinal wall and loss of mucosal covering. One problem that has seldom been studied is how the intestine recovers so rapidly from such a disastrous state. Only in the case of colonic ischaemia have cases been recorded where the mutilated area remains free of epithelial covering;<sup>109,114</sup> the small intestine apparently always recovers, even if the cells remain abnormal. Recently a model has been introduced specifically to study the mode of regeneration of the epithelial covering, namely, preferential destruction of the mucosa by injection of formol into the lumen *in vivo*.<sup>115</sup> This investigation, which reveals progression of healthy tissue over the underlying muscular layers until the cells meet in the middle of the damaged tissue, may provide a key for mucosal regeneration.

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