Obviously, the available energy is distributed into two channels. It is utilized (1) for the contractile mechanism, and (2) for the stabilization of the membrane. Adrenaline, in the early stages of glucose depletion has the same effect as the restoration of the exogenous glucose. Only, adrenaline achieves its action by making energy available from endogenous sources (Axelsson & Bülbring 1960*b*).

After glucose depletion has proceeded to such an extent that the glycogen store is depleted, adrenaline has a stimulant action. It depolarizes and causes the discharge of spikes. The inhibitory effect is also converted into a stimulant effect in the presence of iodoacetate, a metabolic inhibitor.

Another simple way of increasing metabolic rate is to raise the temperature. We observed an effect analogous to that of adrenaline if the temperature was quickly raised, e.g. from 27° to 37°C. This produces in the intestinal muscle a transient cessation of spike activity, muscular relaxation and hyperpolarization of the membrane. Conversely, if the temperature is suddenly lowered over this range, activity is accelerated.

It is clear that in rhythmically active smooth muscle of the intestine the rate of metabolic energy supply is an important factor influencing membrane potential and excitability. The tissue which is continuously in a condition of excitation requires a very active mechanism for keeping up the differences in ionic concentration. The tendency to depolarize (due to the peculiar properties of the membrane, particularly its high sodium permeability) is constantly opposed by forces which try to stabilize the membrane. It may be that sodium occupies a key position, in that normally the changes of the intracellular sodium concentration which influence the rate of sodium extrusion are also coupled to the rate of metabolic energy supply.

It is too early to attempt an interpretation of clinical observations by results obtained on a cellular level. This connexion will have to be developed by future work.

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Clinical Implications of Recent Advances in the Physiology of Motility and Absorption

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Those engaged in clinical research in gastroenterology have long been acutely aware of the urgent need for experimental work at the cellular level, and the new techniques are in many ways more physiological than many of the bizarre surgical procedures which have dominated gastrointestinal physiology in the past. For example, the traditional methods of the experimental physiologist have continued to obscure rather than clarify the physiology of the intestinal movements since Bayliss & Starling remarked in 1899 that there were more 'discrepancies of fact and opinion' in this branch of physiology than in any other. The response of intestinal smooth muscle to stimulation was capricious and unpredictable. Sir Henry Dale (1957) stated that the fundamental problem was that 'different tracts of apparently similar involuntary muscle give opposite responses, not only to impulses in nerves with the same anatomical connexion, but also to the artificial application of one and the same chemical transmitter of the effects of such impulses'. Yet this problem has now been largely resolved by the development of *in vitro* techniques for recording simultaneously the functional, biophysical and biochemical changes in a single smooth muscle cell.

In this way, Dr Bülbring has shown that adrenaline, for example, has two actions which are often antagonistic, one on the cell membrane and the other on the metabolism of the cell; and it is now possible to understand how adrenaline may cause either contraction or relaxation of a muscle. From the clinical standpoint it is interesting to speculate whether smooth muscle cells may suffer from some biophysical or biochemical disorder which renders them resistant to a transmitter such as adrenaline. Such a disorder might explain the mysterious clinical problem of why the cardiac sphincter fails to relax in achalasia or cardiospasm. In this disease the body of the œsophagus is completely denervated and therefore incapable of conducting peristaltic waves. The cholinergic innervation of the cardiac sphincter on the other hand is intact (Ellis, Kauntze, Nightingale & Trounce 1960), but the sphincter is not in a state of spasm, and although it does not relax reflexly on swallowing it contracts in the normal manner at the end of the act of swallowing (Edwards & Rowlands 1959). The only drugs which will relax the sphincter are the nitrites which act directly on smooth muscle. Since the circular muscle of the cardiac

sphincter in normal persons appears to respond to nervous stimulation by relaxation (Ellis, Kauntze & Trounce 1960) it seems that either the muscle cells of the sphincter are refractory in achalasia or that insufficient transmitter substance is released. Presumably this difficult clinical problem could be resolved by applying Dr. Bülbring's techniques to strips of the cardiac sphincter removed at operation.

Although Dr Bülbring's work has clarified the behaviour of the individual smooth muscle cell, it is difficult for the clinician to visualize how the activity of the muscle cell links up with the intramural nerve plexuses, not to mention the extrinsic nerves. The fluctuations of intraluminal pressure in the human intestine, as measured with open tubes or radio pills, produce a spontaneous basic rhythm. The frequency of this rhythmic pattern varies at different levels in the intestine but is remarkably constant at any one level, falling from 11 per minute in the duodenum and jejunum, to about 8 per minute in the terminal ileum and about 2 per minute in the colon. The precise meaning of these intraluminal pressures is not at all clear and their relationship to the tone or tension of the intestinal wall is obscure (Edwards & Rowlands 1960). It is therefore tempting to equate these pressures with the spontaneous rhythmic activity of the individual smooth muscle cells in Dr Bülbring's preparations, each cell being its own pacemaker. However, it seems much more likely that the resting rhythmical pressures in the human intestine reflect the activity of the muscle wall as it is influenced by the intramural nerve plexuses, and I think it would be premature to discard the useful concept of a pacemaking area in the duodenum (Milton & Smith 1956). It is much easier to understand the peristaltic activity of the human intestine in terms of Dr Bülbring's work, because it involves an intrinsic nervous pathway which is triggered by a rise in intraluminal pressure. Hence, the sudden distension of the lumen by a bolus of food, for example in the œsophagus or duodenum, stimulates peristalsis and rapid transit through these areas, in contrast to other areas such as the colon.

Very little is known about the effect of motility on absorption and it is therefore difficult to link together the recent physiological advances in these separate fields of study. The biochemical activities of smooth muscle cells are adversely affected by loss of potassium and therefore this is an important factor in the pathogenesis of ileus. Again, malabsorption often occurs in patients with systemic sclerosis, presumably because of the gradual disappearance of the smooth muscle cells so that the intestinal loops become distended and immobile.

However, it is much more difficult to determine whether defective motility is an important factor in causing intestinal malabsorption in cœliac disease and other forms of steatorrhœa.

The techniques available for studying the problem are so inadequate that very little is known about the relation between motility and absorption even in normal subjects. Neither intestinal tone nor the rate of transit of food can be measured accurately in the human intestine. Nor is it always possible to distinguish between peristaltic activity, which tends to reduce the period of contact between the absorbable material and the mucosa, and segmental activity which favours absorption (for example of water from the colon). There is some experimental evidence that drug-induced hypermotility increases the absorption of glucose and methionine in normal subjects (Cummins & Almy 1953), and that hypomotility induced by propantheline reduces the rate of sodium absorption, but the correlation between the amount absorbed and the amount of motor activity was not impressive (Groisser & Farrar 1960). However, it seems likely that current studies using radio-pills and other modern techniques to record motility, will show that defective motility plays some part in reducing the absorption of a wide variety of substances in gluten-induced cœliac disease. An interesting and important link between motility and absorption in this disease is the recent observation by Schneider *et al.* (1960) that certain fractions of gluten will inhibit the peristaltic reflex when applied to the serosa of isolated loops of the jejunum of rats. This inhibitory effect does not occur if the gluten fraction is instilled into the lumen or if it is incubated with normal mucosa before being applied to the serosa. The gluten fractions probably act by decreasing the release of acetylcholine (Schneider & Bishop 1960).

The demonstration that gluten has this 'toxic' effect on peristalsis perhaps strengthens the view that in patients with cœliac disease it may also be 'toxic' to those enzymes in the mucous membrane which play an essential part in intestinal absorption. This has always seemed probable but there is no direct evidence for it. On the other hand, there are several cogent objections to the view that the malabsorption in this disease can be attributed entirely to atrophy of the villi and the consequent reduction in the total absorbing surface. Thus the delayed absorption of protein, which was recently demonstrated so elegantly by Crane & Neuberger (1960) using the stable isotope ^{15}N, may be partly a consequence of the toxic effect of gluten on peptidases in the mucous membrane. This would fit in with Professor Smyth's observation that protein passes into the luminal cells mainly in the form of peptides which

then undergo intracellular hydrolysis. Similarly the process of fat absorption involves re-esterification of long-chain fatty acids within the mucosal cells, and Dawson & Isselbacher (1960) have recently shown that homogenates of jejunal mucosa from patients with idiopathic steatorrhœa have a greatly diminished capacity to esterify these fatty acids. Although this may be partly explained by the reduction in the total number of mucosal cells in this disease, it is possible that gluten may be 'toxic' to some of the co-factors which are necessary for esterification. Moreover, Milne *et al.* (1960) have recently shown that in some rare metabolic disorders there is impaired transport by the jejunal cells of certain specific amino acids. Thus the absorption of l-tryptophan was delayed and incomplete in Hartnup disease, and the transport of lysine and ornithine by the jejunal cells was grossly impaired in homozygous cases of cystinuria (Milne *et al.* 1961). Milne and his colleagues also obtained suggestive evidence of delayed absorption of d-tryptophan in Hartnup disease, and this provides further evidence in favour of Professor Smyth's view that the absorption of d-amino acids also involves an active biological process.

Dr Bülbring, in her studies on the relation between 5-hydroxytryptamine and motility, observed that peristalsis was stimulated when 5-HT was introduced into the lumen of the isolated guinea-pig ileum because it lowered the threshold of excitation of the sensory receptors in the mucosa so that the peristaltic reflex was elicited at a lower intraluminal pressure. In man, however, the instillation of 5-HT into the jejunum had no effect on intestinal motility as recorded by a balloon (Hendrix *et al.* 1957). Nor did the ingestion of large amounts of 5-HT in the form of bananas cause diarrhœa or any other abdominal symptoms in a group of normal subjects, although their urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) was elevated into the range which is commonly regarded as diagnostic of carcinoid tumours (Connell *et al.* 1960). It may well be that species differences are important because Dr Bülbring found that the effect of 5-HT was much more obvious in the guinea-pig than in the rabbit, whereas the administration of 5-HT by mouth to mice is said to have the same effect as large doses of senna (Collier 1958). However, it seemed possible that overproduction of 5-HT might occur in some patients, for example those with chronic simple diarrhœa of unknown ætiology, but we found that the excretion of 5-HIAA was within normal limits in this disease and also in patients with steatorrhœa. Kowlessar *et al.* (1958), however, found that the urinary 5-HIAA was slightly elevated in patients with 'symptomatic non-tropical sprue' but it returned to normal levels when the symptoms had been controlled by a gluten-free diet. We cannot explain the discrepancy between their findings and ours but it is difficult to understand why there should be an overproduction of 5-HT if it is true that the motility of the intestine is depressed in this disease. Thus Dr Bülbring found that active peristalsis released 5-HT from the mucosal epithelium in proportion to the rise in intraluminal pressure, and it has also been reported that in man the 5-HT level in the blood rises when peristalsis is stimulated with mecholyl or magnesium sulphate (Adams 1960). Thus it appears that 5-HT is liberated in association with increased intestinal activity.

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Meeting May 9 1961

Professor A C Dornhorst delivered his Presidential Address on **Circulatory Dynamics**

Meeting July 21 1961

The meeting took the form of a Public Report Session following the Ciba Foundation Symposium on **Pulmonary Structure and Function.** Dr Dickinson W Richards (New York) was in the Chair, and the following papers were read:

Functional Anatomy
Professor A A Liebow (New Haven, Conn.)
Control of Breathing
Dr J H Comroe (San Francisco, Calif.)
Distribution of Ventilation and Blood Flow
Dr H Rahn (Buffalo, N.Y.)
Gas Uptake and Diffusing Capacity
Dr R E Forster (Philadelphia, Pa.)
Mechanics of Breathing
Dr J Mead (Boston, Mass.)