which is inhibited by phlorrhizin. (2) A mechanism which is prevented by anaerobic conditions (Matthews & Smyth 1960). It seems possible that this second mechanism is the one responsible for movement against a concentration gradient. Hence it seems likely that, as in the case of amino acids, the transfer by the intestine is a complex process and involves more than one stage. A scheme showing the possible sites of action of different inhibiting conditions is given in Fig 6. In this it is suggested that the phlorrhizin sensitive entry mechanism may be a facilitated diffusion. This is an interesting speculation but has not yet been proved.

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Motility of the Intestine

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It is known that peristaltic activity is entirely under nervous control, but a few years ago we were able to throw some light on the mechanism of the reflex and on its intrinsic nervous pathway (Bülbring, Lin & Schofield 1958). We obtained evidence that the sensory receptors, which trigger the reflex when the intestine is extended and the filling pressure rises, are situated in the deepest layers or at the base of the mucosal epithelium. The sensory fibres arise mainly from cells in the submucous plexus of Meissner which contains a large number of unipolar or bipolar neurons. Their axons make connexions with multipolar ganglion cells chiefly situated in the myenteric plexus of Auerbach. The submucous plexus appears therefore to be mainly sensory, while the myenteric plexus contains mainly the motor neurons innervating the muscle.

The peristaltic reflex was found to depend on the integrity of the mucosa. If the mucosa was removed, or asphyxiated, or a local anæsthetic was applied to its surface the peristaltic reflex was abolished. More recent experiments by Ginzel (1959) suggest that some sensory receptors might be slightly further removed from the mucosal epithelium, possibly in the muscularis mucosæ. Whatever their exact site, they are situated in close proximity to the enterochromaffin cells which are also found in the deep layers of the mucosa. The release of 5-hydroxytryptamine (5-HT) from these cells exerts an important subsidiary action on peristalsis. 5-HT is a sensory stimulant and it is known to excite sensory endings in many parts of the body. In the intestine, where it is locally produced and released in proportion to the rise of intraluminal pressure, 5-HT lowers the threshold of excitation of the mucosal nerve endings and thereby has a modulating influence on peristalsis (Bülbring & Lin 1958, Bülbring & Crema 1958, 1959).

The peristaltic contractions are produced by the concerted activity of an immense number of very small muscle cells whose properties we are only just beginning to understand. They are very thin and not very long, measuring about 5 μ by 100 μ. It is fascinating to think that these cells are really like a large population of independent beings, like a crowd of unicellular organisms, rather primitive, not so highly specialized as for example skeletal muscle, and capable of several functions, all united in one and the same cell. This cell can be the focus of excitation or it can be excited by a stimulus from elsewhere. It can also behave like a sensory receptor and, in addition, it can contract. Moreover, the intestinal smooth muscle contracts not only in response to a nervous impulse, but it can contract spontaneously, and it does so, rhythmically, like the heart.

Like the heart, intestinal smooth muscle has an intrinsic rhythm, it generates action potentials and each action potential is followed by a small individual contraction. Unlike the heart, these contractions can summate and this is the basis of what is generally known as 'tone' (Bozler 1948, Bülbring 1957). Spontaneous changes in tone are commonly observed and they are entirely the consequence of spontaneous changes in the frequency at which action potentials are discharged. If the frequency is high the individual contractions may fuse, like a tetanus, to a high maintained tone. If the discharge rate is low there is time for relaxation before the next impulse arises and the muscle tone declines.

One peculiar property of intestinal smooth muscle is that the more it is stretched the higher its tone. It endeavours to contract against the extending force. The stimulus is stretch, and the response is the same as the response of a stretch receptor, i.e. a burst of impulses or, if rhythmic discharge was already present, an increased rate of firing. Stretch deformation of the cells leads to a depolarization of the membrane which in turn leads to the firing of impulses. The cell produces the typical response of a sensory organ to its specific stimulus. However, the intestinal smooth muscle cell is not a specific receptor. To every

kind of stimulus, be it mechanical, electrical or chemical (e.g. acetylcholine or histamine), it reacts with a change of spike frequency (Bülbring 1955). The stronger the stimulus, the higher the rate of rhythmic discharge and consequently the contraction. There is a perfect correlation between the rate of spike discharge and the development of tension. This is found regardless of whether the electrical activity is recorded from a large number of cells by surface electrodes or by an intracellular electrode from one single cell.

The mechanism for integrating individual activities to produce a synchronized contraction is very efficient and it is due to the fact that transmission of excitation takes place from cell to cell (Bülbring, Burnstock & Holman 1958). The pacemaker for spontaneous rhythmic activity is not located at a constant site as it is in the heart. On the contrary, every cell is a potential pacemaker and this function shifts from cell to cell, now here, now there, each cell being able to drive its neighbour or to be driven by an adjacent cell. Thus, though the rate of the spontaneous discharge is often very regular, the individual spikes may differ considerably in shape and frequently represent a mixture of locally initiated and propagated action potentials. Excitability fluctuates partly as a result of the tendency of every cell to fire its own spontaneous rhythm, partly as a result of slow overall fluctuations in the membrane potential the origin of which is as yet unknown.

Recent observations have thrown some light on the mechanisms which determine the membrane potential and influence excitability of the intestinal muscle. Firstly, Goodford & Hermansen (1960) observed that the muscle is extremely permeable to sodium. Using radioactive tracers, they found that sodium exchanges at a rate which is 50 – 100 times faster than that of potassium; 90% of the total sodium exchanges with the outside within a minute. With such an astonishing membrane permeability to sodium, active extrusion of sodium must be of the greatest importance in maintaining a concentration difference between the inside and outside of the cell. Active cation transport requires energy, and normally, in this constantly active tissue, the cell appears to be rarely in a condition in which it can reach its resting potential. If the rate of energy supply is increased, however, a stable membrane condition can be attained, as was shown in recent experiments in which we measured biochemical and biophysical phenomena simultaneously and studied in particular the action of adrenaline.

Adrenaline inhibits intestinal smooth muscle. It stops the spontaneous activity, the tissue becomes electrically inexcitable, and the membrane potential increases. The muscle relaxes because the action potentials stop. In one muscle strip we measured these phenomena. In parallel strips of muscle, taken from the same animal and exposed to identical conditions, we measured phosphorylase activity. And we found, in every experiment, that simultaneously with the inhibitory effect of adrenaline there was an increase in phosphorylase activity (Axelsson *et al.* 1959). This enzyme accelerates the breakdown of glycogen. Our experimental results suggest that the stimulation of one reaction in a chain of biochemical processes might make more metabolic energy available for active mechanisms concerned with the stabilization of the membrane. Therefore, in this very unstable tissue, adrenaline leads to relaxation.

It is known that adrenaline has this inhibitory effect only in some smooth muscles, and that it acts in the opposite way on others, causing a contraction. Presumably adrenaline has a dual action: one on the membrane directly, causing excitation; the other on carbohydrate metabolism, affecting metabolic rate and thereby in certain tissues causing inhibition. Which of the two actions predominates depends on the state of the cell (Bülbring 1960). Adrenaline causes a contraction generally in those smooth muscles which are normally activated by their nerves. In the absence of nervous stimulation, they are quiescent, and their membrane potential is presumably stable. An increased supply of metabolic energy cannot make it more stable than it already is and thus adrenaline only exerts its stimulating action. But in the intestine the metabolic action of adrenaline predominates and activity is stopped. The increased supply of metabolic energy accelerates the active cation transport. This can be shown with radioactive tracers. During the inhibition by adrenaline the rate of uptake of potassium into the cell and the rate at which sodium is extruded are both increased.

The hypothesis can be tested in various other ways. For example, we exposed the tissue to a glucose-free medium in an attempt to deplete it of glycogen in order to see whether the action of adrenaline would be modified if there was no substrate for phosphorylase available. The first effect which is observed when the external source of energy is removed, is that the tissue relaxes. It relaxes, however, not because the action potentials stop. On the contrary they are discharged at a faster rate, but they now fail to produce a contraction. The restoration of glucose to the medium has two effects. It restores the contraction and it stabilizes the membrane. Thus, while removal of glucose increases membrane activity, the restoration of glucose to the medium stops it (Axelsson & Bülbring 1960*a*).

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