Intestinal Absorption

The Scientific Basis of Medicine

Presented by Professor David Smyth.
Introduced by Dr Ian Gilliland.

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<Opening titles>

<Dr Gilliland to camera>

Professor David Smyth is Professor of Physiology in the University of Sheffield. His career began in the Department of Physiology in the University of Belfast, first under the late Professor Milroy and then with Professor Henry Barcroft. Then after a year in Göttingen, he came back to join the staff of University College London and thence to Sheffield. He has written numerous articles in biology, in physiology and in medicine, and he was made a Fellow of the Royal Society in 1967. He has had a special interest in physiology of the gut, which forms the subject of today's discourse, intestinal absorption. Professor David Smyth.

<Professor Smyth briefly to camera and then over slide displaying Smyth's Law>

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There is a basic law which governs the rate of progress in experimental sciences which states that if you think of something easy to do, which has not been done before, further investigation invariably shows that either it is not easy or that it has been done before.

<Smyth to camera>

Occasionally, this law is relaxed and this happens most often when a new technique is discovered and it then becomes easy to do things which have not been done before. This is usually followed by a great surge of work to exploit the new possibility. This law was well exemplified in the study of intestinal absorption. By the late 1940s, it had become difficult to make much progress in this field despite of the enthusiasms of a few workers like Verzar, Frazer and Vischer. In 1949, the breakthrough came when Fisher and Parsons in Oxford produced a preparation of intestine which could show absorbed functions outside the body.

It had, of course, been known for many years that pieces of the intestine would function outside the body.

<Smyth refers to a diagram showing apparatus set up for observing movements of intestinal muscle and narrates over it, interspersed with talk to camera>

We see here a preparation which the pharmacologists have used for about 50 years in which a piece of intestine is removed from the body, tied at one end here, the upper end to a lever and the movements of intestinal muscle can be recorded.
In this case, however, it was only the muscular layer of the intestine that was alive. People had, in fact, tried to use such a preparation to study absorption, but this was always a failure. Fisher and Parsons realised the important condition for demonstrating the absorptive capacity of the intestine was to supply oxygen to the mucous membrane as, of course, in this preparation, a low wave oxygen, it is only the muscular layer which is receiving this and not the intestinal mucosa.

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<Smyth to camera>

Fisher and Parsons achieved this condition by circulating an oxygenated solution through the lumen of the intestine before it was removed from the animal. If this circulation was continued after removal then the isolated intestine was capable of surviving for several hours and its absorptive functions could be demonstrated. This technique was improved by Dr Wiseman in the physiology department in Sheffield who produced a more compact form of preparation, and we see here a simplified form of this preparation.

<Smyth narrates over diagram showing apparatus for studying absorptive function of intestine, interspersed with talk to camera>

Here we have a small piece of intestine which has been removed from the animal, tied at both ends here and the arrangement is such that fluid from this reservoir can be circulated through the intestine. It is then lifted up by this oxygen lift, which has the double purpose of oxygenating the solution and also providing the lifting force. And a preparation of this kind can show absorptive functions.

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One of the first experiments which Fisher and Parsons did was to begin by having glucose present in the two solutions, that is, the fluid inside the intestine, which we call the mucosal fluid, and the fluid outside which we call the serosal fluid. If they started with equal concentrations of glucose in these two fluids, they found, at the end of the experiment, the concentration of glucose inside the intestine had fallen considerably, the concentration outside had increased. <*To camera*> Hence, demonstrating the capacity of the intestine to transfer glucose.

One of the early experiments, which Dr Wiseman did, illustrates another important property of the intestine.

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<Smyth narrates over graph interspersed with talk to camera>

Dr Wiseman started off with a solution of D- and L-alanine on both sides of the intestine, that is, in the mucosal and serosal fluids. He found that while the amount of D-alanine remained constant in both the mucosal and the serosal side during the course of 100 minutes, the concentration of L-alanine in the mucosal gradually fell while that in the serosal fluid gradually rose. <*To camera*> This demonstrated that not only could the intestine transfer substances, but it had a higher degree of selectivity, in this case a stereochemical selectivity.

When tissues are removed from the body and function in saline solution, it is convenient to call this an in vitro preparation as distinct from in vivo.

<Smyth narrates over slide showing definitions of in vivo and in vitro, then back to camera>

The fundamental difference you see is that in vivo the organ is inside the animal and supplied with oxygen and nutrients through its own blood supply; in vitro the organism is removed from the animal, is maintained in a saline solution and is dependent on added oxygen and other nutrients. So that we can say that Fisher and Parsons produced the first successful in vitro absorbing intestine.

In 1954, a new in vitro preparation was developed in Sheffield by Drs Wilson and Wiseman, which became known as the everted sac. The idea of this preparation was that if we turn the intestine inside out, there was a much better chance of oxygenating the mucosa. To make this preparation a small animal is used, rat or hamster.

<Smyth narrates over diagrams showing everted sac technique and equipment used, interspersed with talk to camera>

The intestine is removed from the animal under anaesthesia and then the small intestine is everted on this glass rod. Once it is everted, small sacs can be made of

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the intestine. These can be filled with a syringe and then the small sac is put into this flask and is incubated in a saline solution, suitably gassed with oxygen or in the case of bicarbonate saline with 5% carbon dioxide added.

<Next diagram> Here is the kind of flask which we actually use for the purpose and you see this makes it much easier to pass the gas mixture though the flask, and also the threads on the end of the intestine are looped over this little glass hook so that we can readily remove the intestine at the end of the experiment.

<Smyth to camera>

These everted sacs, as they're now always called, provide an extremely convenient and easy way of studying the absorptive functions. I would calculate that in Sheffield alone since 1954, at least 100 000 sacs have been shaken and probably in the world all together, especially in the North American continent, the number is several million.

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Before going on to look at the other possibilities of these techniques, let us first face a question which may already have occurred to you: how are these experiments related to physiological absorption? In physiological absorption, the substance being absorbed, glucose or amino acid, is present in the lumen of the intestine.

<Smyth narrates over further diagrams and graphs illustrating intestinal absorption processes, interspersed with talk to camera>

It is taken up by the cells and is ultimately carried away by the blood so that it emerges in the vein, draining the intestine. In the in vitro preparation, the situation is quite different. The glucose is present in the fluid and in contact with the mucosa of the intestine, but it passes right through the intestinal wall and appears in the serosal fluid, which is a rather different thing.

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How are these processes related? <*Next diagram*> Let us look at a simplified diagram of the intestinal wall. Here we have the serosal layer, the muscle layer, the submucosa and the mucous membrane. This, of course, is a simplified diagram in which the epithelial cells are shown only as the enterocytes, the cells which are responsible for absorption. Now, in absorption, these enterocytes take up substances which are in the lumen of the intestine; they transfer this into the subepithelial base. The fate of this then depends on the experimental conditions. In physiological conditions, it passes into the blood capillaries and is carried away, or in the cases of fats into the lymph capillaries.

Now, in the in vitro intestine, there is no bloodstream to carry it away and the substances appear ultimately in this fluid here bathing the serosal side of the intestine. But if we look carefully at the fluid coming into this serosal fluid, we find that the first fluid which comes in is bloodstained and this suggests that it actually came through these vessels so that it would appear that, at least, part of the route of absorption here is the physiological one and, probably, this preparation is not so unphysiological as might appear at first sight.

<*To camera*> However, it is important to be sure that the experiments we are doing are physiological. And therefore, we also have other preparations in which the intestine is in a more physiological condition. The first of these is meant to answer the question of what substances disappear from the lumen of the intestine. In this we use a small animal, like rat, guinea pig again. <*Next diagram*> We open the abdomen under anaesthesia and we cannulate the two ends of the intestine. These are then connected up with this apparatus. Now, this apparatus is basically a method of circulating fluid into this reservoir down again into the intestine. There is an outer jacket here which keeps it warm. You can see that by this means we can circulate a substance through the lumen of the intestine. During the course of the experiment, we can take samples from the fluid here and at the end of the experiment, we can find out the total amount of substance left in the circulating fluid. <*To camera*> By this means, we can, therefore, study what substances leave the intestinal lumen.

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The other technique we use answers quite a different problem, that is, what substances are absorbed into the bloodstream? Now, for this we require a larger animal; dog or cat is frequently used. We open the abdomen under anaesthesia and we select a loop of intestine, <*next diagram*> which is drained by one main vein. This vein is then cannulated. The loop is tied off so that all the blood from this loop can be collected, all the venous blood can be collected in this cannula. If we put substances into it, and in this experiment here we put D- and L-alanine, we can recover these from the blood and we can readily show that the L-alanine gets into the bloodstream much more quickly than the D-alanine. <*To camera*> So you see that these other techniques help to confirm the in vitro experiments.

Let us now look at some of the results which we have obtained with these different techniques. Now, in the first place, they are particularly suitable for studying what are called kinetic problems. And by kinetic problems, we mean the relation between the concentration of substances in the lumen of the intestine and the rate of absorption.

<Smyth narrates over graphs demonstrating various types of absorption kinetics, interspersed with talk to camera>

Two distinctive kinetic pictures are seen: diffusion kinetics and saturation kinetics. By diffusion kinetics, we mean that the rate of absorption is directly proportional to the concentration. But, in fact, with most nutrient substances we find that this does not happen, but we find that as we increase the concentration the rate gradually falls off and ultimately approaches a maximum. We call this saturation kinetics with the implication that some essential process is saturated and when saturation is complete no further increase in rate can be achieved.

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<*To camera*> The development of absorption kinetics has been much influenced by enzymology and it is now common to speak of Michaelis-Menten kinetics and to apply the ideas of a Vmax and a KM to the rate of intestinal absorption. It will be

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remembered that in Michaelis-Menten kinetics, the Km is the concentration which allows the rate to proceed at half the maximum rate <*next graph*>. And just as in enzyme kinetics, it is now customary to apply also the Lineweaver-Burk plot in which we plot the reciprocals of concentration and rate and, hence, it can be determined the Km and the Vmax graphically in this way.

<Smyth to camera, then narrates over slides showing rates of absorption in intestine with different substances>

Another close analogy with enzymes is competitive inhibition. If we have two amino acids or two sugars in the intestine, it is easy to shown that they cause mutual inhibition. For example, this slide shows that if we have galactose alone in the intestine, we get a certain rate of transfer, but if we put glucose in at the same time, the transfer is greatly reduced. The galactose and glucose are competing for some essential mechanism. <*Next slide*> The same thing applies to the amino acids; we see here that if we have glycine present alone, we get a certain rate of absorption. If we have glycine and L-methionine, or glycine and L-proline, the rate is considerably reduced, particularly with L-methionine. We assume again that these amino acids are competing for some common mechanism.

<Smyth to camera>

These analogies with enzymology have been developed further by postulating substances called carriers, which in some way resemble enzymes. The resemblance is that we postulate an active centre which has a particular chemical configuration to which certain substances can attach themselves. And by this concept, we can explain both competition and also saturation kinetics. There is, however, another important function of the carrier in addition to those mentioned. Many of the nutrient substances, particularly digestion products of proteins and carbohydrates, are hydrophilic, that is to say, they are soluble in water but not in lipids.

Now, it is well known that all cells are bounded by a lipid membrane, so we have a fundamental problem as to how these hydrophilic substances can penetrate the lipid

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membrane to enter the cell. The simplest way to approach this problem is to postulate pores which are filled with water and through which water-soluble substances can pass.

<Smyth narrates over further diagrams illustrating passage of hydrophilic substances through cell membranes, interspersed with talk to camera>

Here we have the idea of a glucose molecule which is hydrophilic; it is facing a lipid membrane through which it cannot pass. We then postulate a pore in the membrane and now the glucose is able to pass through the pore and enter the cell. Now, if this is the case, we have already seen that the intestine can exert a certain selectivity. If this is the case –selection by pores – then, of course, selection should depend on molecular size. The small molecule can pass through, but the larger molecule cannot. We can easily put this to the test and we do so by using two sugars, glucose and mannose. <*Next diagram*> Now, as we see, these are both hexoses of the same molecular weight and of very, very similar structure. The only difference, in fact, is a carbon-2 where the position of the H and OH are different. Now, in spite of this very small difference, we find that glucose enters the cell very easily, mannose only with great difficulty.

<*To camera*> It therefore seems very unlikely that the selectivity of the cell is exerted through the size of the pore. I've already pointed out to you that L-alanine is absorbed more easily than D-alanine and again this rules out the possibility of selection by pores.

<*Next diagram*> We therefore postulate that the carriers also provide a means by which hydrophilic substances can pass through a lipid membrane. We postulate that we have a carrier here, which is lipid soluble. This carrier has got an active centre to which glucose can attach itself. The carrier with the attached glucose remains lipid soluble, it transports the glucose across the membrane and releases it at the other side. The carrier then returns emptied to carry more glucose. You see I've shown, by this geometric shape, that mannose cannot attach to the carrier. This is called the

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ferryboat carrier for obvious reasons and has been much used in ideas about intestinal absorption.

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<Smyth to camera>

The techniques I've shown you were also responsible for demonstrating another important feature of absorption which is receiving much attention at the present moment, that is the location of the enzymes which are responsible for the terminal stages of digestion. The classical theory of digestion postulated that the breakdown of the complex food substances was completed in the lumen of the intestine so that in the case of proteins and carbohydrates, we had amino acids, and hexose is set free in the lumen of the intestine. There had long been some doubts about this, but Dr Newey and I showed very clearly in Sheffield in 1962 that the terminal stage of digestion might take place, in fact, not in the lumen of the intestine but inside the epithelial cells. We showed this for peptides, but Crane and others in the United States showed it also for carbohydrates.

<Smyth narrates over slide showing measurements following saline and peptide circulation in intestine of rat>

The following experiment demonstrates very clearly a simple way in which this can be done. We used a preparation I described to you in which fluid can be circulated through the intestine of a rat. We circulated 50 ml of saline with 250 mg of peptide for 60 minutes. At the end of this period, we examined the circulating fluid and recovered 30 mg of peptide and this means that 220 mg of peptide had disappeared. Now, this could have disappeared either because the peptide passed into the cells or because enzymes were secreted into the circulating fluid which hydrolysed the peptide. We therefore did the second experiment, shown on the right-hand side of the slide, in which we circulated the same volume of fluid but without any peptide. After 60 minutes we collected this which now should have any enzyme in it which had been

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secreted. We added to this the peptide and incubated it for a further 60 minutes. And as you see, only 23 mg of peptide had disappeared.

<Smyth to camera>

There is no doubt in this experiment that most of the peptide disappeared because it is in contact with the epithelial cells. It either passed into the cells and was hydrolysed intracellularly or, as the Russian physiologist Ugolev has stressed, it might have been because of contact digestion. In either case, it was not because of enzymes present in the fluid circulating through the intestine. We now know, in fact, there's good evidence, that the terminal stages in digestion of both proteins and carbohydrates take place intracellularly.

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Let us now look at an entirely different aspect of absorption, which was again first discovered in Sheffield with the in vitro preparation and indeed could hardly have been discovered in any other way. It's well known that many tissues exhibit electrical activity in relation to their function, for example, the beating heart, the secreting gland, the conducting nerve, the contracting muscle. In 1960, Dr Barry and I were interested in studying the transfer of sodium and fluid by the intestine. We first studied the effect of a number of different sugars and fluid transfer and we found the following result.

<Smyth narrates over slide showing results of mucosal fluid transfer>

You see here with the in vitro intestine, when we had no sugar present, we got a certain rate of transfer, 0.38. When we added glucose, we got a very rich stimulation. Galactose, 3-O-methylglucose, 2-deoxyglucose caused no stimulation, but again fructose caused stimulation.

<Smyth to camera>

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Now, it seemed to us likely that the fluid movement was associated with sodium movement, and if sodium was moving, it was likely we could record some electrical activity. We therefore decided to study this problem further by recording the electrical changes across the wall of the intestine.

<Smyth narrates over diagram showing experiment for recording electrical changes across intestinal wall, and then over graphs of results>

The technique for doing this was to take a sac of intestine, as we see here. To have inside this sac, one agar bridge, and outside another agar bridge. These two agar bridges were connected with calomel cells and from this we could measure the potential across the intestine. We added glucose because we knew that this stimulated sodium transfer and when we did so we got an immediate potential. <*Next graph*> The potential is about 10 mV. It is instantaneous and lasts so long as the glucose is there. <*Next graph*> When we remove the glucose – glucose-free saline – the potential immediately falls back to zero.

Now, it's well known that phlorizin[1] is a substance which will inhibit glucose transfer, so we tried the effect of phlorizin on this glucose potential.

<Smyth narrates over graphs showing effects of phlorizin on glucose potential>

You see 10^{-5} molar phlorizin reduces the potential; even 10^{-6}, a very small concentration, has an appreciable effect, and 10^{-3} not only abolishes but produces a potential in the other direction. I'll come back to this later because this reversal of potential has some interest from quite a different point of view.

<Smyth to camera, then over graph showing effects of various sugars on potential>

[1] Spelt 'phlorrhizin' on graph in film. For consistency in these transcriptions the spelling 'phlorizin' has been used.

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The question of immediate interest is the cause of the potential. And the first possibility, which occurred to us, was that it was sodium movement stimulated by glucose metabolism. But it soon appeared that this was not the explanation because when we used other sugars, we see that galactose caused at least as big a potential, possibly slightly bigger. 3-O-methylglucose caused a potential, although so much smaller. And these substances I've already shown you did not stimulate fluid transfer.

<Smyth narrates over table of properties of various sugars>

Now, if we examine the different sugars, we can study and record various properties of them. In the first place some are actively transferred; by this, I mean that if they start in equal concentration, then we finish up with a higher concentration in the serosal fluid than in the mucosal fluid. And of the ones actively transferred here, we have glucose, galactose, 3-methylglucose. Some of them show an electric potential, the kind I've been talking about. And the ones which show this are the same: glucose, galactose, 3-methylglucose. Some cause stimulation of sodium and fluid, and these are glucose, mannose and fructose. Some cause stimulation of metabolism and again these are glucose, mannose and fructose.

<Smyth to camera, then over slide showing pyranose ring>

Now, it seems therefore that the ones that are actively transferred are the ones which cause an electrical potential, so that the potential is more related to the process of transfer than to metabolism. This idea can also be expressed in chemical terms. Crane has studied a large number of different sugars and has shown that all those that are actively transferred by the intestine have got a structure of this kind, that is, a pyranose ring, and the essential part of it is that the position of the hydroxyl group at carbon-2 should be the same as in the glucose. And this is the requirement for active transfer by the intestine.

<Smyth to camera, then over slides showing chemical structures of various sugars>

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Now, on the other hand, there is another kind of specificity, chemical specificity, in the intestine and that is the hexokinase specificity. Hexokinase is the enzyme which initiates glucose metabolism and all sugars with this structure are able to be attacked by hexokinase. Now if we look at the slide with different sugars on it, we can see that the glucose and galactose have got the Crane specificity. Glucose, mannose and fructose have got the hexokinase specificity. So you see it's possible to predict from the structure of the sugar how it's going to behave in the intestine. The very important thing is that glucose has got both these specificities.

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<Smyth to camera, then refers to and narrates over diagram on display board next to him>

There are thus two important functions in the cell which we have so far demonstrated: one is transfer and one is metabolism. Now, transfer of a substance like galactose is an energy requiring process. Same thing applies to an amino acid. These are substances which are actively transferred and therefore require energy. On the other hand, if we take glucose, glucose is not only transferred but it is also metabolised, so substances which are metabolised can supply energy, substances which are transferred will only require energy. Other substances also metabolised are the same as glucose.

<Smyth narrates over slide listing energy users and energy donors>

And we can now show the energy users and the energy donors. The energy users are galactose, 3-methylglucose and the amino acids: glycine, proline, methionine and the others. The energy donors, the ones which are not transferred, are fructose and mannose; they can be metabolised. Again, glucose falls into both these groups. It is not only an energy user, it is also an energy donor.

<Smyth to camera and then over diagram illustrating passage through intestine of energy user and energy donor substances>

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What happens if we have got two substances present at the same time which are energy users? Now here we have the idea of an amino acid being transferred and also, let's say, galactose which is an energy user. These two substances <*indicates amino acid and galactose*> will both require energy and the possibility might arise that they might complete for the energy available for transfer. On the other hand, if instead of galactose we use glucose, this is not only transferred but it can also supply energy. So that we might expect that this <*indicates glucose*> would behave differently from galactose in presence of an amino acid.

<Smyth to camera, then over slide showing results of glycine transfer rates>

Let's look at the results of an experiment which meant to test this out. We see here that when we had glycine alone in the mucosal fluid, we had a transfer, a certain rate of transfer. When we put galactose present as well, the transfer was very greatly reduced, but when we put glucose there, the transfer was increased. And this is in agreement with our idea that glucose is a donor of energy whereas galactose is a user of energy.

<Smyth to camera, then over: diagram illustrating effects of different substances on galactose transfer in the mucosal fluid; table of results>

Let's look at the two substances, glucose and galactose, present together because these are very interesting. If these were present, if we had glucose and galactose present in the mucosal fluid, I've already shown you figures showing that glucose inhibits the transfer of galactose and, of course, the reason is that they are competing for this one mechanism. But supposing now we had no glucose here, supposing we only had galactose here, but we had glucose here <*indicates serosal fluid*>, glucose could supply energy without competing with galactose for entry into the cell. And when we do this experiment, we get the results as we see here. Galactose alone, transfer 117 micromoles; galactose and glucose together in the mucosal fluid, transfer of galactose is inhibited; but put the glucose now in the serosal fluid and we get an enormous stimulation of galactose transfer. So this is

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consistent entirely with what we have postulated about competition for carriers and competition for energy.

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<Smyth to camera, then over slide>

The electrical potential we have seen is associated with sugars which are transferred against a concentration gradient and the potential itself, of course, must be due to some ion movement. Crane has developed an ingenious theory of the ternary carrier to explain this. And according to this theory, sodium and glucose move on the same carrier, and the energy for glucose movement is actually provided by a sodium pump. Now this sodium pump is responsible for the potential and therefore we can speak of an electrogenic sodium pump as part of the mechanism for glucose transfer. But I've already shown you that some sugars which are not transferred also stimulate sodium in fluid, and we can therefore speak of two sodium pumps in the intestine: <*slide*> one, electrogenic sodium pump stimulated by galactose and, in fact, the amino acids too; another one stimulated by mannose, a non-electrogenic sodium pump. Glucose again stimulates both of these, so glucose has a very special role in relation to the intestine.

<Smyth to camera, then over diagram illustrating water being pushed through a glass capillary>

You'll remember when I talked about defective phlorizin, I showed you that a high concentration of phlorizin actually reverses the potential. We did not think much about this at the time, but later we looked at this more carefully and another very interesting aspect of it appeared. We know that if we have a glass capillary and if we force water through this, we know, in fact, that the glass capillary is electrically charged and takes up some of the ions, a very small amount of the ions in the water. Now as a result of this, we find we get a potential across the capillary, and this is called by the physicists a streaming potential.

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<Smyth to camera, then over graph illustrating results of placing mannitol in intestine, and back to camera>

Now, following the work of Diamond on the gall bladder, we set out to see whether, in fact, there might be such things as corresponding potentials in the intestine. We would expect to find these if we put some substance in the lumen of the intestine which was not absorbed because it would increase the osmotic pressure inside the intestine, draw fluid into the intestine, through pores if they existed and, hence, might show these streaming potentials. The substance we used was mannitol which does not easily enter cells and is not absorbed by the intestine. And we see here the results of these experiments with mannitol. <*Graph*> Firstly, in the presence of glucose, which you'll remember itself causes a potential, that the mannitol reduces the glucose potential in steps as we increase the concentration. If we have no glucose present, it does exactly the same thing, reducing the potential, putting it in the opposite direction. <*To camera*> And there's, therefore, reason to believe that this is some kind of streaming potential. Probably, the term streaming potential is not really accurate because the size of the pores are rather different from those that you get in the physical experiments and perhaps better to call these osmotically induced potentials.

Now these osmotically induced potentials have a great interest in themselves. We have seen they are only produced by substances which cannot be absorbed and we can therefore use these to measure the size of the pores in the intestine. If we use substances not actively transferred, then only those of a certain molecular size will pass into the cells. These will not cause osmotic potentials and therefore we can tell by the size of this osmotic potential where are the substances entering the cell. From the molecular weight of the substance and the molecular size, we thus get an idea of the size of the pores. In fact, the result of this is that a molecular weight of something of about 180 is too big to go through the pores. Molecules which are smaller can get through the pores, and small molecules quite easily. And form this we can conclude that the size of the pores is somewhere about 4 angstrom units.

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Now, in this brief talk, I've tried to cover a number of points to show you how the introduction of a new technique can open up new possibilities for an old problem. Have all the easy things now been done with the new technique? Well, a good many of them have – they're bound to be in a few million experiments, but for those who ask the right questions there is still information to be obtained. In my opinion, the technique will, in the phrase of the Inland Revenue, be gainfully employed for some time to come.

<End credits>

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