[MUSIC PLAYING]

STEPHEN J. O'KEEFE: There are a couple of take-home messages that I would like to focus on. First of all, does nutritional support improve outcome from critical illness? It's very easy to give, but don't give something unless it's effective. Otherwise, you just get complications. Questions about enteral access? We're all gastroenterologists, so we're very clever at putting tubes in various orifices and so on, and when the gut's not working, we can get it working again.

Then a few notes about advances, recent advances, in short bowel syndrome. And finally, a few comments on the research that I'm doing on the microbiome. So let's move on here. For those of you who can't figure out what I'm trying to say, there's a very nice little book here-- it doesn't cost very much-- which I push, and it basically gives you the whole story from the beginning to end about the principle behind feeding patients, the need for feeding patients, and how you can do it.

It's also available online. So to kick off with, first of all, it's well been well-recognized for years that in any kind of disease, the higher the incidence of malnutrition, the worse the prognosis. This is illustrated by one collection of ICU studies reported in 1997 from five centers, followed for six months. And they looked at a variety of different diseases and their survival rate, and they divided them up into tertiles.

And basically those-- in each category-- those with the lowest BMIs had the highest-- sorry, the worst survival rates. So it just is a common pattern that you see, wherever you are in the hospital. When it comes to nutritional support, it's important to know how soon should we start. If somebody's immediately admitted to hospital-- acutely ill, they can't eat-- should we start with intravenous feeding? Because we can feed anybody in any situation now.

But no, there are things called body stores that were designed to support our recovery in illness, so we've been around for millions of years. And we haven't had TPN, or nutrition support, for many millions of years, but we've had through evolution our ability to hold onto food stores in good times to use in bad. And it's been shown that in health, you need to lose over 40% of your body weight before you die, so there's a big sort of window of opportunity there.

In severe illness, however, you become catabolic, and so therefore your expenditure of stores, particularly protein and energy, is escalated. And so, therefore, stores don't last quite so long. And we've estimated that in patients with severe necrotizing pancreatitis, for instance, protein stores would be completely spent within 11 days if you didn't start any nutritional support.

And then we need to talk about the importance of maintaining gut function, because if you don't use the gut, it stagnates and it behaves a bit like an abscess, because it's full of bacteria. And you get overgrowth, and microbes don't do what they're normally supposed to do. They can translocate and produce further problems. The bottom line is that nutritional support is never an emergency, unless you're severely malnourished.

And it's quite difficult to actually decide on who's severely malnourished in hospital. Probably the best way to do is to look at them, to get a global view. But also if somebody is severely depletion with a BMI, for instance, under 15, than we've shown that BMIs less than 15 are associated with abnormalities of the mucous membrane and decreased absorption. So therefore, it would seem a reasonable sort of endpoint to look at.

Nutritional support literature is full of observational and controlled trials. People believe in the inherent powers of feeding, and you're often besieged by patients' family, who come along to you and say, like, my dearly beloved's been in hospital for two weeks now and haven't had any feeding, and they're going to die. And so you know, you've got to have good answers to those questions.

There are no robust, randomized controlled trials comparing interventional feeding to no feeding in the ICU. Everybody is still afraid of doing that, because again, if somebody has been sort of mowed over by a steamroller or something, and they come in, everybody is going to say, look, we must give the body every chance of healing as possible. It's pumping the nutrients in that will allow the tissue to heal, ignoring the fact that our in stores can do that initially, and we don't have to actually start.

Uncontrolled trials have suggested that the energy deficit in the first week led to worse survival, fueling the belief that early feeding improves survival. So again, be careful about uncontrolled studies. And only recently have there been large-scale controlled [INAUDIBLE] studies published on the use of nutritional support, or the method of using nutritional support in hospitalized patients.

This was probably one of the first from the Belgian group, which looked at a large number of patients. It was over 2,000, and they were basically randomized to early feeding versus late feeding. And early feeding consisted of 20% dextrose, and after three days TPN if enteral feeding wasn't sufficient. Alternatively, they were given only 5% dextrose for a week, and then the same routine thereafter. And then they looked at outcomes.

And this shows that, in fact, it's quite clear that, in fact, if you use this form of nutritional support, you can achieve full nutrition pretty quickly-- almost within the first few days. So this is the enteral side of this parenteral stuff added together, and you get up to this sort of level. So this is late feeding, early feeding, late feeding, early-- sorry, this is late feeding, early feeding. So early feeding with parenteral feeding, you can get up to goal very quickly.

So does that, in fact, make any difference? And basically, the result showed the reverse, that late feeders had less ICU infections, less cholestasis, less ventilation, and obviously it costs a lot less money as well. So, again, you know, this just smacks against what you sort of feel, and you've got to try and look at the scientific basis for therapy in any disease state.

This was an uncontrolled trial. Adequate enteral protein is inversely associated with 60-day mortality in critically ill children, a multi-center perspective controlled study. So sure was multi-center perspective that it was not-- actually, sorry, it wasn't controlled. It was basically a cohort study. And they seemed to show that early feeding actually improved outcome in children.

But then this excellent group came along and compared early versus late parenteral nutrition in critically ill children, and it was a good study. It was 1,400 children, multi-center, randomized, controlled trial, to investigate whether withholding parenteral nutrition for one week was as effective as starting it straight away. And basically, their results showed that in the late feeding group, it was rather similar to the last study in adults, that mortality was similar. But there were less bloodstream infections. We had less catheters, IV catheters.

There was a shorter ICU stay, a higher likelihood of an early discharge from the ICU, shorter duration of mechanical ventilation, less dialysis, shorter duration of hospital stay, and lower plasma [INAUDIBLE]. So you know, this is pretty clear that there's absolutely no indication that jumping in and force-feeding patients or children as soon as they hit the ICU.

This is another interesting study, put together by intensivists, and they looked at septic-- the patient with septic shock who went into acute lung injury. And the [INAUDIBLE] studies, so it was a conglomerate from various different parts of the country. And they basically looked at trickle feeding versus full feeding.

And so basically, here they are. This is the early feeding group, where they gave TPN to top up patients, just like before. So it was enteral, parenteral. And this is the other group, where you put down an NG feeding tube, and you gave about 20 cc's per hour for a week, and only if they weren't weaned on that, that you'd consider full feeding.

And basically, it showed the same thing. It's actually at the bottom here. I'll have to try and take my specs off and have a look at-- it's not very clear. I don't know if you can read it. But with full feeding, there was no differences in infectious complications between the two groups. Despite receiving more prokinetic drugs, the full feeding group experienced more vomiting, elevated gastric residuals, constipation, and had more problems with glycemic control.

So again, showing that you need to watch out what you're doing. In all of these studies, what was interesting was that they found that if they looked at the subgroup that was severely malnourished, they actually did benefit from early feeding, which makes sense. So another thing my friend, Darren Halen, who has done all the feeding studies in Canada over the years, did a randomized, controlled trial of glutamine and antioxidants in critically ill patients.

So there was a lot of hype about glutamine, because they said it's a special amino acid that is the required fuel for the enterocyte. And so if you want to maintain enterocytic or intestinal function, you need to give extra glutamine. It really didn't ever make sense, because glutamine is the most common amino acid in the body, and you've got to be at death's door before you become deficient in glutamine. But it was one of those hip things to do, and Everybody jumped on the bandwagon, started giving glutamine-- especially our transplant surgeons here.

And antioxidants-- everybody thinks, well, these must be good. It's Vitamin C and things like that, selenium. You know, it's a lot of stress, operative stress, and so on. Give them a dose of that, and they'll probably do a lot better. And unfortunately, the trial was completely negative. It was multi-center. Large numbers again-- over 1,000 critically ill patients, ventilated with multiple organ failure.

But what was of real concern was those given the glutamine supplements actually had a higher mortality rate. So here you are not only just not producing any benefit, but you're actually killing patients off. So we come full circle around to what the metabolic requirements of the cell are, and if you look at a cell in section there, you can see that it has an organized structure, which is put together by lipids and proteins to form membranes and organelles within the cell itself.

Each has its own metabolic requirements, fluid and electronic requirements, and it's not by chance that that cell has evolved to eat a balanced diet. It doesn't just need water and electrolytes. It doesn't just need vitamins, but it needs everything together. It's what is in a normal balanced diet. And so it doesn't make sense to simply give something such as glutamine or antioxidants.

And so it boils down to this situation here, that we eat a normal diet, which replenishes our stores, which allows us to survive when we can't eat. They maintain cell function, and they maintain life. So what do we know about body stores? For water and electrolytes, it lasts days. And so therefore, if we starve somebody, the first thing that they die of is dehydration, or electrolyte imbalance. So that is critical, and that is an emergency, and that's part of resuscitation.

Water-soluble vitamins only last about a week. And in critical illness, you lose them even faster, because a lot are stored within the liver, and they disappear rather rapidly. And so therefore, it makes sense to start some sort of vitamin supplementation after the first week. Carbohydrates-- significant stores only last a few days in the form of glycogen, but thereafter you become ketogenic, and you mainly live on energy provided by fat.

Fat-soluble vitamins last longer, even months, and fat, that's where all the energy stores are. And there's approximately 75,000 kilocalories stored as fat, a quantity that would provide energy needs for approximately six weeks. So we're coming around to that four to six critical week level. Protein requirements are rather difficult to judge, because there's no particular, specific protein store.

They have said that muscle stores a lot of protein, but it is actually functional at the same time, so it depends. It's a matter of semantics, of whether you consider it a store or not. But with my mentor, when I was training in England, was a guy called John Waterloo, who was one of the protein gurus. And he helped me put this together and made it a sort of a calculation of how long protein stores would be, from knowing what the amount of protein in the body is, the rate of catabolism is, and extending that over a period of time.

And basically, if you're a normal, healthy individual with about 70 kilograms, with a BMI of 24, they would last about 37 days. But if you look at necrotizing pancreatitis, then the loss of protein is accelerated, and the whole thing is spent within 11 days. So that's the nearest we can get to basically assessing things. But as I said before, we should look at the patient.

And if you look at a patient like this-- this is a patient from when I was working in Africa-- it's quite evident that this guy, unless you feed him soon, he's going to die, whether he's got tuberculosis, HIV, or anything else. He'll die of malnutrition. This was not the bad study published by *The New England Journal of Medicine,* and they only accepted it because it was randomized and controlled.

And they looked at-- it's from Europe, predominately England-- over 2,000 patients, with unplanned admission to the ICU, randomized to enteral or parenteral nutrition. So you know, this is absolutely wrong. You don't randomize somebody with a functional gut to parenteral nutrition. It's actually bad practice and should never have done this study. Anyway, they did.

And they started within 36 hours, and they continued for up to five days. So again, full intensive nutritional support for five days is meaningless, as you're just going to get complications rather than any improvement in outcome. So note that there's no control group where they don't give anything at all. And 92% had no malnutrition, so what the hell were they doing?

The primary outcome is mortality at 30 days, which is again pie in the sky. And so-- surprise, surprise-- when they actually examined the results, there was no difference in all of the parameters measured, outcome parameters, so it was a total waste of time. So what I am trying to put across to you is that TPN and enteral feeding both have their own specific indications and should not be used interchangeably. One's not better than the other. If you've got somebody with a short bowel and they didn't have any gut, then enteral feeding's not an option. You give them TPN.

If they are acutely ill, but they got a functional gut, don't give them TPN, because you get complications rather than benefits. And if the patient, in fact, is marasmic, then obviously their stores are deficit, and you can only improve outcome by providing nutritional support in place of your stores. So now we go on to a few little studies that we did here. This was when I used to do a lot of nutritional support. We used to feed a lot of patients who were referred to us for TPN entry.

And a lot of them had upper GI obstructions. And I developed a technique of placing a feeding tube beyond the obstruction into the mid jejunum, and so we basically studied the outcome in a group of these patients. This is the sort of situation that if you do an endoscope, you go into the stomach, and you see this big mass. And anybody know what that mass is?

[INAUDIBLE]

Sorry?

Pseudocyst?

Pseudocyst, yeah. So it's a massive pseudocyst that's basically filling up the whole of the stomach. And along the side here, this is where what's left of the stomach that's basically squashed there. And so what we did is that we developed a tube within the tube system. You've probably seen them place now. I think [INAUDIBLE] do it. And so it is a two-tube system, so it's got an inner jejunal feeding tube, which goes through the outer [INAUDIBLE] tube and goes a considerable way down the small bowel, beyond the obstruction.

Then it's got the [INAUDIBLE] gastric tube, which has got a lot of perforations here, so it decompresses the stomach here. So say for instance you were blocked here, and you fed down here, it actually would not help, because all the gastric secretions would build up proximally. And so you'd get nausea and vomiting, so you'd vomit the whole thing out. So you must decompress the stomach at the same time. It's a basic principle.

And this shows that same patient in sagittal view, with a massive cystic pancreas falling on acute to chronic pancreatitis. And this is what's left of the stomach here, and you can't see very much at all. And there's a trail of the duodenum, which is also squashed all the way around here. And we put one of these feeding tubes in, so you can see it going through, just little spots of it there. It goes past the obstruction, and then into open bowel down below, where you can feed perfectly well without the need for TPN.

And basically, we found that in this group of patients that the duration of jejunum feeding was 25 days, as much as 145. If it was longer than 145, then they would have been discharged home and home enteral feeding. The individual feeding tube lifespan is important, because in the old days, we just put tubes in and we'd be told in the morning, oh, it's fallen that, or something like that. And you put all this effort into [INAUDIBLE] tube.

And then we developed this nasal bridle, which keeps things in quite well. So our tube life is actually quite good now. 60% were weaned back on to normal food, without the need of surgery. Only a small number were converted to percutaneous endoscopic pegs. Home parenteral nutrition, a couple of patients went home.

Surgery number, only 16% needed a surgical decompression. And of course, there was quite a high mortality rate, because these are very sick patients. So you can do actually remarkably well. This is not going to work here, because I don't have the chip with it, but if you look up YouTube, you can actually see it on here. This is the reference here. And this shows our technique of placing these tubes endoscopically, and it works incredibly well.

And it's actually remarkably easy to do with a little bit of practice, and it's quite fun. We've used this predominantly for acute pancreatitis. I've always had an interest in acute pancreatitis. And it's a devastating disease. It's the biggest nutritional problem in the hospital, because basically it is a catabolic disease with [INAUDIBLE] metabolic requirements. But also you've got this explosion in the middle of your gut, so it cuts off all function in the upper GI tract.

And so classically, they're all given TPN, but we've shown with this technique that when basically do it-- feed all of these patients enterally, if you actually place the feeding tube into the mid-jejunum, which you can do very easily with a transnasal endoscopy-- through the nose, all the way down. You can watch what you're doing. It's very safe. And there are three reasons why we do it-- because it relieves the obstruction, it produces pancreatic rest. So if you feed into the jejunum, it basically overcomes pancreatic stimulation, and so therefore you can provide enteral feeding without stimulation.

One of the GI fellows about 10 years ago helped me actually do those basic studies, which demonstrated quite well with regard to stimulation of gut, [INAUDIBLE] peptides. There's basically stimulation, which again suppress pancreatic secretion and improve outcome in acute pancreatitis. So this shows the disaster, because you're often presented with an x-ray, but you can't feed this patient.

Look at all the distension in the loops, the small bowel loops, and so on and so forth. But indeed, we've managed to get-- and this is the outer tube here going through the stomach, around the duodenum. This is almost at the ligament of Treitz. And then the feeding tube goes on all the way through here, then goes way down. And it's actually quite easy to get it far down, because the gut tends to be [INAUDIBLE]. So it's dilated, and you can just feed a guide wire down very easily and get into a feeding position.

So this is the bridle that I've talked about before, and it really is a godsend, because this is quite a fancy system that we've got here. It's the caricature of the feeding tube that I showed you before, the jejunal feeding tube. This is the gastric decompression tube, which is critically important. And this is the bridle, so you can see the string here going round. It goes around the septum and comes out the other nostril there. It's then tied to go over and clipped onto the feeding tube itself. And that's really improved our outcome dramatically.

So in summary, we have the tools to feed any patient in hospital. It doesn't matter how sick they are. When we're doing an acute pancreatitis, we're feeding patients even with compartmental syndrome, which is probably wrong, because I'm sure it didn't improve outcome. But it was a proof of principle. Enteral feeding is safer and more effective than parenteral nutrition, because it avoids all the complications of parenteral feeding.

Remember with parenteral feeding, you lose all the protective effects of the gut on cutting normal food down to a sterile food, which is then absorbed. It's sensed by the pancreas and the liver and distributed around the body. If you give parenteral feeding, you put it straight through a catheter into the right side of the heart. So it produces [INAUDIBLE] for thrombosis. Also you're connecting IV fluids and TPN frequently to the [INAUDIBLE] external ports, and so therefore the introduction of bacteria is almost commonplace.

And you lose the metabolic control of the liver and the pancreas, so you get high swings of glucose and [INAUDIBLE] and fat. And that accounts for every study that's been performed today has shown that enteral feeding is always preferable and less complicated than parenteral feeding. And we've talked about body stores and the maintenance of gut function.

So another research story at the moment is severe short bowel. So short bowel syndrome is a collection of different diseases of various severity. So theoretically, even somebody who's had a term [INAUDIBLE] has short bowel, because they lose the ability to reabsorb bile acids and B12. But you can usually overcome that by dietary modification. At the other end of the extreme, you've got somebody who's lost about 90% of their small intestine. And if they're maintained on a normal diet-- what's considered a normal diet-- they would die.

So it's that group at the end that we're talking about, who are totally dependent on home TPN to survive. So they continue to eat, because you've still got a small, small amount of bowel there. And that's important, because the majority of your absorption occurs in the duodenum. And the rest of the intestine is really there just for reabsorption of secretions, because in order for digestion to occur properly, you need to pour out large quantities of fluid and electrolytes, which allow the enzymes' ability to break down food into an absorbable form.

And so what's interesting is that those patients-- it's been basically shown that if you lose your colon, you need at least 100 centimeters of small bowel remaining to have any chance of getting off IV fluids. If it's less than that, you're going to be on TPN for the rest of your days. If you've got the colon remaining in contact, you can get away with only 50 centimeters of small intestine, because basically the colon adapts and takes over a lot of the digestive functions of the small intestine.

So there's been intent interest to try, in some patients-- I mean, the problem is that the more severe your [INAUDIBLE] failure, the worse your quality of life, because you go home and sure, you get back into society. But you're dependent on IV fluids all the time, so every night you have to hang up this thing. You've got a machine that's grinding away. It's not good for social life. It limits you. You have a lot of complications and effective complications [INAUDIBLE] re-hospitalizations and so on and so forth.

And so there's been intense research for something that will medically adapt or superadapt the remaining bowel, so they're gut peptides, which are basically GLP, or the glucagon-like peptides 1 and 2, PYY, all secreted by the distal small bowel and probably small colon. And GLP 2 through endocrine L cells. And they have remarkable properties-- slows gastric emptying, reduces gastric secretion, increases mucosal blood flow, stimulates the growth of small and large intestine, increases epithelial proliferation, and inhibits apoptosis-- a lot of the things that occur naturally without [INAUDIBLE].

So the thought was that since the term line has been lost, a lot of the L cells have been lost, so maybe there's actually a deficiency state. So let's try giving them products of these peptides. The problem if give the natural peptide, it lasts just a few minutes, because it's basically broken down by proteases. But if you switch a couple of the amino acids around, as they've done into nucleotide, you can actually increase the survival of that peptide within the circulation for a matter of hours, which then makes it possible to use it as a daily injection.

And initial studies, phase I and II, showed that in fact it did increase [INAUDIBLE] height and depth. It also increased plasma citrulline. So why do you think increasing citrulline might be important? Anybody know anything about the synthesis of citrulline? Keisha, you should know that. So citrulline is unique because it is only synthesized by the small intestine, by enterocytes.

And so you can see that if you actually fast somebody, and you measure their fasting citrulline, it gives you a read-off of enterocyte function. And interesting after this drug, the fasting citrullines are actually increased. It also increased fluid electrolyte absorption in short bowel patients. But you know, [INAUDIBLE] it had to be large-scale or controlled trials performed to actually prove its efficacy, because clearly it would be an expensive drug.

And it's basically an orphan drug, because there are not that number of short bowel patients with intestinal failure in the USA. And in order to recruit sufficient subjects-- was about 80-- we had to go overseas, so it was not only multi-center, but also multinational-- about 30 different countries, I think it was 27. So it was 27 sites and 10 countries across Europe and America to actually accrue that number. And what was important was that they had to go through a screening, an optimization, and a stabilization routine, because we're quite often referred patients from outside, who were on TPN and don't need it.

And so what happens is that a surgeon [INAUDIBLE] does a massive resection and says, I'm sorry, you've lost your intestine. But you can be kept alive on TPN. So they get trained, they get sent to a home care company, and they manage it at home. And then complications occur, and they get sent back to us. And they haven't realized that since the time of surgery, there's been an adaptation, and so you can actually wean them off TPN.

So it was essential for us to actually optimize patients. So what we did is that we looked at urine output, and we said that urine output of 1.5 was ideal. And it's a very clever measure of short bowel syndrome, so if you want to know somebody-- if they've got intestinal failure, put them on a normal diet and measure urine output. And if they pass less than one liter of urine a day, then they've got intestinal failure.

So the same thing that-- if you are using IVs or TPN, then you modulate the TPN to maintain urine outputs of between 1 and 1/2 and 2 liters a day. So if you're using a drug, then it basically increases absorption. And so therefore you need less IV fluids to maintain urine output of one to two liters a day. So it was based upon that premise. And if in fact the drug increased absorption by 1%, it would really be clinically meaningless, and so we chose 20% reduction in IV fluid requirements as something that was clinically significant.

And let's summarize the endpoint here, which shows that 63% of patients given [INAUDIBLE] nucleotide were able to reduce their IV fluid requirements by greater than 20% a day-- in comparison to only 30% of those given a placebo. And we talked about citrulline before, and citrulline of fasting citrulline was increased, suggesting it was increased enterocyte function. And although this was a blinded trial, we all knew which patient was on what, because we looked at the stoma.

And these sort of trophic effects were dramatic, because even here-- this is the stoma beforehand. This is after three months, after six months, and then after the drug was withdrawn. So you can imagine what's going on inside the patient as well, and it really is a very potent drug. And we did endoscopies, and as you can see, the villi is really dramatic. They're massive. And the only time that I've seen villi that size-- this is a normal endoscope. It's not a magnifying endoscope.

The only time I've ever seen that before is with short bowel patients who had acute rejection, and you get this amazing, proliferative response on recovery. So that is the cause for its improvement. And the overall conclusion was that [INAUDIBLE] two analogs were unlike growth hormone, because you can also improve absorption with growth hormone. But it's got all the other side effects. It gives you big lips and large jaw and acromegaly and things like that, which is not so good, whereas this actually is specific to the bowel and has fairly dramatic effects.

There is, however, some concern about the risk of malignancy, because it is a proliferative agent. And so therefore, it's mandatory that in those who've got colon remaining, they need to have annual colonoscopies to start with, and then spread it out to the usual three to five years if no polyps are found. So you know, there are a whole spew of new peptides being formed now in Europe and over here as well. Derivatives of GLP 1 have also been shown to be effective, so watch the space.

I should actually emphasize that the only way to predictively get somebody off TPN is small bowel transport, but not many people want to go through small bowel transplant. So OK. So I just mentioned patients with diarrhea, because often you're confronted with somebody who's got tube feeding going and diarrhea. And the common thing is oh, the diarrhea is because of the tube feed. Stop it, start IVs, and you shouldn't do that.

Basically what happens is the most common cause of diarrhea in hospitalized patients is disturbance of the microbiota because of all the antibiotics that we use. And we did a little study where we looked at this, and we thought, well, let's try and maintain the microbiota We know that the microbiota being hit bowel sorts of antibiotics and things, but those that are surviving, if we want them to regenerate, they need food.

And the food for microbiota is fiber, and most of these patients are given semi-elemental diets, which contain virtually no fiber. And so we looked at the possibility of providing supplementation. And this was, again, an uncontrolled study, looking at patients predominantly who survived from severe acute pancreatitis. And we progressively increased their fiber intake in the enteral foods over a period of time. And if you look at this column here, we got up to really quite reasonable levels-- 15, even as high as 30, almost at normal requirement levels.

But if you look at the mesh of different drugs and so on, nearly all of them were on H2 antagonists, which disturb your microbiota and, of course, antibiotics as well. And we then looked at the number of microbes contained within fecal samples, and you can see the black bar is the number that you see in normal, healthy subjects. And there's virtually no bacteria in those who have been critically ill for a period of time.

And when we look at the short-chain fatty acid production-- as you know, when fiber goes through the colon, it's metabolized to short-chain fatty acids, which are the predominant fuel for the colonoctye. So if you don't feed the colonoctyte, it doesn't work, and you get diarrhea. So that's why short-chain fatty acid production is very important. And we showed that levels were much lower than healthy subjects. But most importantly, we were able to show that with fiber supplementation, we got significant increases in all of the short-chain fatty acids.

A very interesting study was published by Al Verdi's group in M Bio from 2014, where they looked at really, really sick patients in the ICU, most of whom didn't survive. And they sequentially looked at the antibiotic use and changes in the microbiota And you know, you really should read it, because it is very interesting and informative. But basically, this is the course of the hospitalization until death. And these are the doses of different antibiotics that they were given all the way through, as they get progressively stronger and stronger.

And if you look at the cultured species from stool, basically it changed dramatically, with a large appearance of Canada. So Canada tended to replace normal bacteria. Canada can't produce short-chain fatty acids. It didn't do any good, and you get a lot of potential pathogenic organisms coming through, and most of them are drug resistant.

If you look at the [INAUDIBLE] around similar RNA content, what's remarkable is that you've only got one or two different type of genera, enterococci, and enterobacteriacae. To So all of the normal diversity is disappeared.

So in this situation, you're a sitting target for overgrowth of things like c. difficile. And if you get c. difficile on top of this, you're dead. So what can we do about it? It's very difficult to know.

Fecal transplants, we can't avoid using antibiotics. But I think it's important to understand that if there is something going on with the bowel, you're confronted with a patient with a lot of diarrhea, see if you can ease off on the antibiotics, and see if you can increase the fiber content of their diet.

So finally, I'll just mention a few words and some interesting studies that we're doing on the microbiology with regard to cancer risk. And I would suggest to you that if you change your diet, you can change your cancer risk. And this is very important. Because if you look at colon cancer-- and that's what we're studying predominantly-- colon cancer is a Westernized disease. It's mainly in Westernized societies.

And its variation around the world varies about 50-fold. So dramatic changes. It's very rare in Africa, rural Africa, but has an extreme instance in Alaska, the native people who are Eskimos. And it's basically associated-- a lot of studies have looked at epidemiology, and they've measured dietary intake at the same time, and they have correlated the two. And they found that population with increased risk had higher intakes of red meat and more fat and processed meats, whereas those with lower risk, such as Africans, have higher intakes of fiber, fruit and vegetables.

And putting all this stuff together, Doyle and Peter, in their classic study in 1981 suggest that over 90% of all GI cancers are due to differences in the diet. That really is dramatic. And the great thing about that is it means that about 90% of GI cancers are preventable.

Just to show you that this is an environmental disease, it's not genetic, about 5% of colon cancers do have a genetic element or a hereditary element, I should say. This is a classic study of Japanese immigrants to Hawaii at the turn of the last century. And at that stage, the instance of colon cancer was very low in Japan. But within one generation of change to an American diet, it actually increased to the level of native Hawaiians. In fact, it was even slightly higher. And obviously, this can't be explained by genetic changes. It's explained by the environment.

So I had the pleasure of living in Africa for a while and practicing as a gastroenterologist, and what was interesting is that if we did colonoscopies, it was usually for an acute colitis or something like that. And we never saw polyps or colon cancer, which is extremely rare. In some of the more Westernized populations, it was beginning to appear. But overall, it's a prevalence of only 500,000 of the population.

In stark contrast, coming back to the USA here, nearly every African-American that I did colonoscopies, found a small polyp of one sort or another. And they've got the highest rate in the lower 48, greater than the 65 per 100,000. So you can see, that is a dramatic difference between the two, and kind of similar genetic background.

So we think that it probably is due to the diet, from the reasons that I said before. And what is specific about the African diet? It was first recognized by Dennis Burkett to be associated with a low instance of infective disease, particularly colon cancer. Traditional diet was rich in complex carbohydrates from grains, beans, wild vegetables, fruits, and low in meat and fat, and its fiber content was over 50 grams a day.

Now, this is important because the recommended dietary intakes for fiber in the USA by the USDA is 22 grams a day for women and 38 grams for men. You know, these we're, at the moment, pushing to get them to change them. To double them basically, to 50 grams a day. Because they were actually based on the amount of fiber that's necessary in the diet to prevent cardiovascular disease. Nothing to do with the colon. They didn't understand what the colon needs fiber for in those days. So we're making a little bit of progress.

And say to me, well, you can't eat 50 grams of fiber. Well, you can. And even some groups today in the Congo area that has to, for instance, eats up to and even in excess of 100 grams of fiber a day. Mainly, again, because they are predominantly vegetarian. And if you look at the African diet, it has a lot of fresh produce; yams, which are good carbohydrate source. And they grind up corn, so it's full, unrefined corn.

And if we look at the American diet, it's basically got screwed up through the years. So it tends to be grilled and fried. It has a lot of fat. The carbohydrate that is present is in highly refined form, with virtually no fiber. We wash it down with a few beers. Preservatives, we're in Pittsburgh, so we cover everything in ketchup.

So where are the fruit and veggies, and where's the fiber? So you can see that we've erred a long way from where we actually came from. And it's important. Because we evolved over millions of years, and the diet that we had then was nothing like this.

So what we've hypothesized, that it's not actually the diet itself, but it's the way that the diet affects the microbiota to produce metabolites, which maintain the health of the colon, such as short chain fatty acids, as I've said already. And the time is getting late. I've got a few minutes, have I? OK.

For those of you who have an interest, if you look at this *Nature* review that we wrote just recently, it lines up the number of benefits of nutrigenesis. So butyrate is one of the short chain fatty acids, and it has a remarkable effect on cell metabolism, epigenetic regulation. It's anti-proliferative, immunomonitory, anti-inflammatory. It maintains mucosal health, because butyrate, and not glucose, is the main energy source for the colonocytes. So it maintains resistance.

And it also stabilizes the microbiology as well, so it has an enormous number of regulatory effects. And what was interesting is that we said, well then, OK. How do we know it's the diet that actually accounts for these differences in colon cancer rates between Africans and African-Americans. So we did a unique study where we actually switched their diets.

So we went out to Africa, and we took over a lodge in a rural area. We housed 20 Africans for two weeks, and we gave them terrible Westernized food. Lots of burgers and fries and all those delicious things. And we measured the microbiota and the mucosa before and afterwards.

And we looked in the mucosa at biomarkers of cancer risk. You obviously can't wait for cancer to develop. But there are biomarkers, such as peripheration, measured by Ki-67 and inflammation as well. And for African-Americans, we did the same. We put them into the CTRC here, and we gave them African food, which is high carbohydrate, high fiber, for two weeks, and compared the differences.

And what was just published recently in *Nature Communications,* we produced reciprocal changes, not only in the key biomarkers of cancer risk-- so cancer risk increased in Africans given a Westernized diet and decreased in African-Americans given the African diet. Just two weeks. OK?

And inflammatory markers switched reciprocally as well, looking at specific biomarkers. And when we looked at the occurrence networks of the microbiota, there were dramatic changes. So this is African-Americans where there are a few interactions. And after a change to an African diet, you see a whole lot of other interactions open here. So the complexity and diversity of the microbiota changed dramatically.

And in Africans given the Westernized diet, you can see that they lost a lot of these metabolic pathways. So it's absolutely amazing. And this is MRI changes in metabolites. Again, showed a swing from one side to another. A lot more metabolism when people are given the African diet.

And I put this down just to give you some idea of where we are going. Because we always thought that the Krebs cycle was complex. This is the Krebs cycle, just in here. Metabolism, actually, is all of this here. So you have a lot of learning to do. It's color coded on whether it deals with amino acids, protein, fats, and so on and so forth.

But just suffice it to say that after the dietary change, the significant changes occurred to the left in Africans and to the right in African-Americans. So there's not just little changes. There are dramatic changes throughout. And you can imagine what's happening in the preneoplastic cells, the same sort of changes.

So we're going back to that original cell diet. Talked about you're changing the micro environment, and so you're changing your cancer risk. And so I can basically tell you that with dietary change, we can reduce the incidence of colon cancer in all Westernized countries up to 20 fold, which is really dramatic and far better than any drug can possibly do at the moment. And that's basically it.