The APUD Cell Series

The Scientific Basis of Medicine

Presented by Professor AG Everson Pearse.

University of London Audio-Visual Centre, 1973.

Introduced by Dr Ian Gilliland.

Produced by Peter Bowen.

Made for British Postgraduate Medical Federation.

Black-and-white

Duration: 00:39:52:17

00:00:00:00

<**Opening titles**>

<**Dr Ian Gilliland to camera**>

Professor Pearse is Professor of Histochemistry at The Royal Postgraduate Medical School and Consultant Pathologist to Hammersmith Hospital. He is internationally known for his contributions on this subject. He is the author of one of the major standard textbooks on the theoretical and applied histochemistry. Many new and refreshingly original ideas have flowed from his pen, none more so than the subject of this discourse, the APUD cell concept. Professor Tony Pearse.

<**Professor AG Everson Pearse to camera**

The APUD cells are a series or, if you like, a collection of endocrine cells which are situated in either known endocrine glands all over the body, or else diffusely in

organs which are not necessarily endocrine or not regarded as endocrine. Most of you, I think, will not be familiar even with the word APUD and perhaps I ought to first of all define it. It is, in fact, an eponym of a sort based on the initial letters of the most important cytochemical characteristics which are shown by the cells of the series.

<**Pearse over table listing the cells of the apud series**>

And these are either a fluorogenic amine content (that means either a catecholamine or 5-hydroxytryptamine or some other amine) or, and/or, the fact that they will take up the precursor of such amines, and these two best known are either dopa or 5-hydroxytroptophan (they will take them up, that's the 'u' for uptake) and the third item, they will decarboxylate them to the amine. So that is where the APUD comes from despite what anybody may think.

<**Pearse to camera then walks towards slide projections showing illustration of birds drawn by Fuller Albright, then updated version of this illustration by himself; narrates over them using indication stick** >

Now they have a long history, the cells of this series, about five hundred million years. But the concept has a rather shorter history and I thought I would just like to put it into perspective by telling you something about that.

Now in 1948, I was working for my MD thesis on the pituitary gland and I read a paper by that very fine endocrinologist, Fuller Albright, in which he maintained, on the basis mainly of clinical studies but also on certain operative gambits, such as, shall we say, gonadectomy, hypophysectomy – not hypophysectomy, gonadectomy, adrenalectomy and visual observation of events taking place in the hypothesis, that the pituitary hormone producing cells all came from the acidophils, with the exception of FSH which came from the basophils.

Now this is a picture which Fuller Albright drew himself, and he said 'birds of a feather flock together' and that is why he drew the picture in this peculiar way. But it occurred to me that a little bit of elementary histochemistry, and histochemistry was

quite elementary in those days in 1948, would show something better and this was because it was already known that FSH, LH and TSH, among the protein hormones of the pituitary, were in fact glycoproteins, carbohydrate containing proteins, and growth hormone and lactogenic hormone (as it was known then) were not, and ACTH was not either but was regarded as a polypeptide. And so a very simple piece of staining for carbohydrate showed which cells must contain the carbohydrate containing proteins.

And I drew this picture myself which showed quite clearly, and it's true to this day, that FSH, LH and TSH come from the old basophil series or, as they're sometimes now called, mucoid cells on the mucoprotein which they contain, and that these two as is, of course, obvious, come from non-mucoid, non-carbohydrate containing cells. And the only mystery was where does ACTH come from? And that's why I drew ACTH with his head in the air to indicate that he didn't know where he came from. And I tried to spend the next 15 years, was it, something like that, I can't count, finding out where ACTH came from.

00:05:37:00

<**Pearse walks to different slide projection and narrates over series of slides showing images of enzymes within the pituitary gland**>

But in the meanwhile, I worked on a number of cytochemical tests, a lot of them being for enzymes which I was interested in very passionately at that time. And I showed, fairly soon, that the presumptive ACTH cell in the human pituitary gland, as you see here, contained a large amount of non-specific esterase and also, in the human but not in all other animals, of a choline esterase.

And the next picture should show, I think, that we found also, in certain cells in the pituitary gland, a very strong amount of the enzyme alpha-glycerophosphate dehydrogenase which is supposed to be concerned with lipid metabolism. What the esterase is doing nobody knows to this day.

And the next picture shows another finding. Very early on in the 1960s we found that in formaldehyde fixed material, which is of course most material for a pathologist, you could get a very fine yellow fluorescence in the pars intermedia, in such animals as have a pars intermedia – this is a dog, it was also so in the pig – but there are certain cells that I think you can't see probably here in the pars distalis which also showed up with this fluorescence and this was presumably due, or we thought it was due, to the presence of an amine 5-hydroxytriptamine.

And the next one will show what happened. In 1963, sorry in 1962, Eleanor McGarry and her team in Montreal succeeded in showing, by a process of immunofluorescence, that ACTH came from the mucoid cells, and in the next year, with Susan van Norden, I was able to show this myself. And here is the picture in the human pituitary gland showing the ACTH cells distributed widely in the pars distalis.

Now at this point there were several problems that arose, and the next one should show me what happened. It was in 1963 that the advent of the new hormone, calcitonin, which then was said to be a parathyroid hormone, made it necessary for me, and other people too for that matter, to try to find out which cell it came from. It was very soon found that it didn't come from the parathyroid but from the thyroid as a result of the work of Hirsch and Munson in the United States, who extracted thyroid calcitonin, as they called it, from the thyroid gland. When the thyroid gland was investigated, it was very soon found, at Hammersmith, that the cells responsible for calcitonin effect were the so-called parafollicular cells which you see here in a silver preparation, this is a Cajal stain preparation.

It was in 1931, in fact, that Nonidez whose picture, or half his picture at least, will show on the next thing, because he was […]

<**Pearse over slide showing portrait of Nonidez**>

[…] Professor of Anatomy at Cornell who was working on the nervous supply to the thyroid and he found that his silver stains, which were meant to stain the nerves, stained these cells. And he said these cells are secreting an endocrine product

directly into the bloodstream. That was perfectly correct; the name of it was calcitonin.

<**Pearse narrates over series of slides showing images of enzymes within the pituitary gland**>

And the next one on here shows what happened as a result of further studies. We were able to show certain features of the C cells, as they are now called, in the thyroid gland, the calcitonin secreting cells, here they are. In some animals they contain a fluorogenic amine which is usually 5-hydroxytryptamine and that's what you see here.

The next one shows the … if they do not contain a fluorogenic amine, and they do not in the human or in the mouse, which this is, they will nevertheless take up, either in vivo or in vitro, dopa or 5-hydroxytryptophan and convert these into the amine, dopamine, 5-hydroxytryptamine, and store it in these cells where it can be demonstrated by a simple technique which I will illustrate in a minute.

The next one? And we showed, as other people had showed, and showed at the same time, that the C cells contained granules of endocrine type as generally recognised by electron microscopies as endocrine cell granules.

The next one also we have to go on to which shows that the next stage, and the stage which we had to go to, was to show that these cells contained calcitonin which we did by immunofluorescence as you see here. And we see here, calcitonin; I think this is a hamster pituitary gland showing the C cells, immunofluorescence with an anti-porcine calcitonin.

00:10:37:14

<**Pearse to camera**>

Now, what the result of all that was that I realised, as I should have realised a very long time before, but one doesn't somehow, that the characteristics shown by the C cells were precisely those which were shown by all the other cells in the pituitary, in the pancreas and elsewhere in the gut that I had been examining for so many years, that all these characteristics that these cells had were those of a series of cells. And it was then that I realised that I must get them together and on joining them all together, the characteristics which we now see on the next slide, […]

<**Pearse over tables listing APUD characteristics**>

[…] the characteristics as you've seen before begin with the APUD characteristics, and they continue on the next slide with the other characteristics. The non-specific esterase-5, the α-glycerophosphate dehydrogenase 6, and 4, one which I didn't speak about – the fact that most of these cells have large numbers of side chain carboxyl groups which can be demonstrated by a variety of methods, masked metachromasia or lead haematoxylin staining. And the 7th characteristic is not a characteristic but in fact something that one is obliged to do to prove the respectability of any given cell in the APUD series.

Now, the methods which we use, mostly, for demonstrating these cells are […]

<**Pearse over diagrams showing the main method for demonstrating APUD cells**>

[…] firstly and most importantly, and I must get out of the way here I see, APUD-FIF. This is formaldehyde-induced fluorescence by which one demonstrates in a cell the presence of an amine – catecholamine or 5-hydroxytryptamine, whether it's the natural one or whether you have put it in there or made the cell take it up. And this shows the process of uptake, decarboxylation and storage, freeze-drying and treatment with formaldehyde vapour at a high temperature, 70 to 80˚, the so-called Falck-Hillarp technique, which demonstrates by converting the amine into either a beta-carboline, something that had been known since 1953, or to an isoquinoline, both of which fluoresce, though in different colours.

And the next one on here shows the second technique which we are obliged to use, that is immunofluorescence, the direct method or the indirect, and we normally use the indirect technique which I may remind you shows an antigen in a cell, shall we say the hormones, say gastrin, by using an anti-gastrin and by demonstrating the presence of that anti-gastrin with an anti-globulin serum labelled with a fluorescent dye, usually fluorescein, made against the serum of the animal to which this antibody was made. So this is a rabbit, this is goat anti-rabbit here, labelled. And that's the way we do that.

And the third characteristic which we use is once again the electron microscopic appearance because in the electron microscope the cells normally, if they've got anything stored in them, contain granules. And these granules vary from absolutely black ones, to grey ones, to ones with a halo, large halo, to ones with a small halo and so on. And it's perfectly easy, though I haven't time to show you, to recognise a normal endocrine cell of the APUD series by virtue of the characteristic type of granule it has. It's quite another matter, as I shall say probably, when we get to tumours of these cells.

Well now, the list of APUD cells is quite a long one; […]

<**Pearse over tables listing different types of APUD cells**>

[…] I think there are 20 or so cells in the list. And the first slide which you see now shows the respectable members of the series, those in which it has been proven that a polypeptide hormone exists. Although, as a matter of fact, one of the things here, E'glucagon, is enteroglucagon or gut glucagon, as it is vulgarly called, and that is perhaps not a hormone yet since it's not been shown to be active at physiological levels, but I think it will be a hormone. You see that the majority of these are, in fact, gut derivatives; only the pituitary and the thyroid and ultimobranchial are exceptional.

And the next slide shows the list of APUD cells which are not respectable yet because they have not yet been shown to produce a polypeptide though they

produce many other things, amines and so on. At least they are APUD cells by their cytochemical characteristics and my proposition is that they will ultimately be found to produce polypeptides which may or may not be active as hormones.

00:15:15:00

Now what you should ask, I think, perhaps some of you might be asking, is why do these cells share these characteristics? And one has to think of several possibilities. And the first you see here.

<**Pearse over series of tables listing ontogeny of APUD cells**>

The APUD cells may share these characteristics because, being of diverse origin, they have evolved similar biochemical mechanisms for the production of a similar type of product, polypeptide that is. Or alternatively, in the next slide, you see that they may have evolved this similar set of biochemical mechanisms in response to similar specific secretory stimuli which may be aminergic or cholinergic. You've already guessed that they have aminergic mechanisms, they handle amines, they also have cholinergic mechanisms since most of them have got a choline esterase in them. The third possibility is that they have a common embryological ancestor and that they have retained, usefully or otherwise, a distinct and common set of ancestral functions.

<**Pearse to camera, then over series of slides showing examples of the APUD-FIF technique for labelling the neural crest cells, talks briefly to camera in between slides**>

Now, I will not dissemble – this third possibility has always, to my mind, been the only possible explanation and the difficulty is, of course, to prove that it is so.

Now, when I was working in 1948 on my thesis on the pituitary gland, its cytochemistry and function, I obtained this slide which is that of a 5mm human embryo, and it is a horizontal section of Rathke's pouch, which, as you perhaps know

is supposedly an ectodermal derivative coming from the buccal cavity outside the stomadeum. It is a triradiate pouch at this stage and there enters into it a contribution of cells, which you see in these light staining areas, which carry in the main vessels and which carry in what embryologists call mesenchyme. And I supposed, at that stage, that they carried in also certain other cells from the neural crest which might give rise to some of the pituitary cell types and, in particular, this would be the ACTH producing cell.

And the next one shows, very briefly, the consensus of some of our studies. We have used the APUD-FIF technique for labelling the neural crest cells as far back as possible. In preliminary studies we have found that in the chicken embryo, at earlier than 65 hours, you could label the cells in this way, that is to say, they would perform as APUD cells and thus you could see them. And we found in the mouse that we could do the same though, of course, not at the same stage because the mouse doesn't implant until 4 days. We found at the 10-somite stage in the mouse we could see a stream of cells coming down from the neural crest. And a slightly later stage, this is an example, we could see them entering the gut and its derivatives. This is actually a primary bronchus and one can see here the fluorescent labelled APUD cell from the crest entering the primary bronchus there.

The next one. These derivatives we have observed also going into the pituitary, into the ultimobranchial, into the carotid body, into the gut, into the pancreas, into the lung, into the urogenital tract. Now, in association with a French embryologist Nicole LeDouarin, we've been doing studies to try to determine by alternate methods the origin of the APUD cells from the neural crest. The work which she did, and does independently, depends on a technique known as allografting. She takes, to do it quite quickly, from an early embryo (about 50 hours say in the chick), a slice of the neural tube. And the next picture shows what she gets out. As a matter of fact it's not quite that. This is what she gets out and throws away. She takes from a quail, the similar part or a different part of the neural tube and cleans it of all mesenchyme associated with it by trypsinisations, so she has a neural tube with a neural crest on it. And she found, and this is her own idea, that the quail cells were marked with a biological marker, as she calls it, because they have in their nuclei a large blob of

chromatin whereas in chicks there's no such blob. This is then put into the hole in the chick embryo and the whole creation is then incubated for a further period, up to 18 days and longer. And the result, the next one shows, or at least this is an example of what it shows, is here in the graft hybrid; here is part of the chick host with the chick-type cells, and here is the sympathetic ganglion, long known of course to be derived from the neural crest. And you see here, once again, here is the quail marker, the biological marker of the chromatin blob in the cells, proving that that comes from the neural crest.

00:21:10:18

Now, in association with Professor LeDouarin, we have been making a number of studies of which I'll only show you one which is on the derivation of the carotid body.

Here is the carotid body of a chick. It's, I think, about the 11-somite stage, I have that actually on one of these things, it's 11 days so that would be many more somites than that, an 11-day chick. And here, down here, is the ultimobranchial body which is closely associated with it. But it so happens, we found, in the chick, that the amine which is contained and this is an APUD-FIF, formaldehyde-induced fluorescence, we found that the amine which is produced in the carotid body is 5-hydroxytryptamine whereas in the ultimobranchial it's dopamine.

And the next one shows the condition in a quail embryo, 11 days again, here is the carotid body, it contains dopamine. And what we found was that, <*moves to show graphs on separate slide*> here you see the chick embryo, the emission spectrum with a peak at 520 is that of 5-hydroxytryptamine. Here is the quail embryo, we've got the excitation as well on it, but it doesn't matter, and here is the emission at 480, that is the peak of dopamine. When she did the grafting experiment and we handled the material we found that her graph hybrid had a carotid body with the dopamine label in it. So not only is her biological marker stable to this extent that she can see which cells came from the graft, but we also found that our dopamine phenotype is also a stable marker for this purpose. And we're extending these studies <*walks back to*

previous slide projections> to try to show absolutely that the cells from the APUD series come from the neural crest.

And recently, we have succeeded in showing, and this is an ultimobranchial body, derived from a quail graft into a chick. This, by Professor LeDouarin's technique shows the nuclei of a quail so that it is derived from the quail neural crest. And this is an immunofluorescent preparation showing the presence of calcitonin in this graft. That shows that calcitonin is a neural hormone coming from the cells of the neural crest, a neural endocrine product. We do this with anti-dogfish calcitonin because the mammalian calcitonins, the mammalian anti-calcitonins, will not cross-react and the only anti-serum we have that does cross-react with the bird is the anti-dogfish serum. I don't think I would want you to draw any conclusions from that fact, however. The conclusions I want you to draw is that here we have for the first time 100% proof that at least one of the APUD cells is totally derived, and its product, from the nervous system and not, as is so long thought, from the foregut, i.e. from the endoderm.

00:24:22:00

<**Pearse to camera, then over slide showing the face of Professor Feyrter**>

Now I want to change off that subject of the neural crest altogether now and describe something of what happened in one particular organ – the gut, well, that's a large organ of course. Now, the first person who described the gut as an endocrine organ, though not in those words, was Professor Feyrter, as you see here, this was taken on his 65th birthday. He's now 80 and he lives in very happy retirement in his native Austria. He was Professor of Pathology in Graz, the University of Graz and also later at the University of Gottingham in Germany. And in 1938 he first enunciated his notion of a diffuse series of endocrine cells which he called a diffuse endocrine organ, or clear cell organ, Helle Zellen was his word, which he said was diffusely distributed all over the body. And these cells, when they were not clear cells, which merely means that their content had fallen out in the preparation that he made, they

were, very often, argentaffin, that is to say they would reduce silver solutions to metallic silver, as you see here, and come out black.

Unfortunately, his work was largely neglected, and this, and also by me, because I'm sorry to say the German in which he wrote was so obscure it couldn't be understood even by his fellow Germans, or for that matter by his fellow Austrians. And so his work was greatly neglected and it is only now realised that he foresaw with immense prescience that this diffuse series of cells did exist and he got most of the places and positions right. Now, what is known now as it is seen on the next slide […]

<**Pearse over tables showing the Wiesbaden agreement for naming endocrine cells in the stomach and then in the intestine**>

[…] which shows you the situation according to the so-called Wiesbaden agreement. In 1968, the situation was in a complete shambles – if you see in the left-hand column, the four or five places in the world who were working on the endocrine cells of the gut and using their own terminology. Three of the four happened to attend a conference in Wiesbaden and were persuaded by me to agree to speak the same language. And the language now, under the column Wiesbaden you see, it is now the convention to describe a cell, an endocrine cell, if you can, by the letter of its hormone, but if you can't, by some other letter which is common to everybody else. And so you see here the G cell for gastrin. The A cell is described now usually as the A-like cell because it resembles the pancreatic A cell, and the D cell is the pancreatic D cell, looks like it. The enterochromaffin-like cell, the next one, is described like that because it looks like an enterochromaffin cell but isn't, and the enterochromaffin cell is the same cell that Feyrter was working on, or the argentaffin cell, these are equivalent names.

And the next slide shows you the situation in the intestine. Now, in the stomach there were 5 endocrine cell types and in the intestine there are 6, and the same nomenclature is used, the Wiesbaden agreement nomenclature. The S cell was the small granule cell, now it's still S for secretin. The L cell is this year to be called enteroglucagon or EG cell since it produces the enteroglucagon and has been shown

to do so by immunofluorescence. The D_1 cell has very recently been shown by my group at the Hammersmith to secrete gastric inhibitory peptide, GIP that is. And we are busy looking for some source for all the other hormones. So you see there are 6 cells in the intestine, 6 endocrine cells, 5 in the stomach, that's 11 in all. And what I want you to conclude from this is that […]

<**Pearse over illustration of gut endocrine cells**>

[…] the gut contains a spectrum of endocrine cells, from the oesophagus right down to the rectum (this only goes as far as the jejunum), which changes, of course, as you go down. Certain cells are restricted, for instance the pylorus, the G cell, the S cell, the secretin cell, almost to the first part of the duodenum and so on. Nevertheless, there is here a spectrum of endocrine cells and these cells almost certainly, in fact certainly, respond not only to nervous and mechanical stimuli but also to changes in the lumen because it has been shown, conclusively to my mind, (and this particularly by Japanese workers who do serial electron micrographs more often than the rest of us do) that each of these cells has a long apical progress, reaching the lumen, and when it does so it ends in little microvilli and these microvilli differ from one cell to another and indeed you can distinguish the cell type thereby; so that they are able to respond to intraluminal stimuli as well as to the other stimuli, nervous and mechanical, which they have been supposed to respond to for so long.

00:29:39:00

<**Pearse to camera and over slide showing a television analyser and then further slides showing the pictures it makes**>

Now we have tried to get some idea of the size of the endocrine gut and we have used an instrument, a television image analyser, made by the Cyclotron Unit at Hammersmith Hospital.

And the next one shows the kind of thing we do, we analyse a section, of which this is one, which has been stained actually by a silver method which shows up the

majority of endocrine cells and this is in the glands in the stomach. And on estimating with the image analyser we find that a total of that area, 5% of that area, is occupied by endocrine cells, making even a simple calculation from that, we arrive at the fact that the size, and this is a fundus, the size of the endocrine fundus is certainly larger than the pituitary gland. And it is almost certain that the gut itself is not only the largest endocrine organ in the body but the most important.

Well, now, I want to talk now, since I am a pathologist, a little bit about the pathology of these endocrine cells of the APUD series and of the tumours produced by them. These have been called, by, in the first instance, by a charming Czech pathologist called Ilona Szijj, apudomas. That is, of course, a most frightful hybrid and one wouldn't use it except that it may turn out to be useful. Now, here's a list of some, this is a partial list, now, […]

<**Pearse over tables listing some of the apudomas, then to camera**>

[…] of some of the apudomas and these are named, and can be named, by the polypeptide which they produce, if they do indeed produce a polypeptide, and these ones do. The corticotrophinoma, the insulinoma, the glucagonoma, gastrinoma, calcitoninoma (which is a fearful name, it is usually called a medullary carcinoma of the thyroid), the enteroglucagonoma, the GIPoma.

And the next one. The secretinoma (which has not been found yet), the VIPoma (which has), the motilinoma has not been found, nor the cholecystokininoma, but these are names made up, then, some of them, on the basis of the hormone which they might well produce.

And the next slide shows the other side of the table; non-productive, non-productive doesn't mean they don't do anything – they don't normally produce a polypeptide hormone. The melanoma, phaeochromocytoma, the chemodectoma and the carcinoid. And in brackets the oat cell tumour. At the time I made this table up, it perhaps wasn't 100% certain the oat cells derived, or is a member, of the APUD

series. But I think it is very nearly 100% certain that it is so. And of course it does very often produce a polypeptide product, normally ACTH.

Now it's fortunate, I think, that the apudomas can be diagnosed rather simply by the same characteristics that were in the APUD list which they show very much better than their forebears or progenitors or whatever you like to call them. And these techniques are either […]

<**Pearse over tables showing diagnostic techniques for apudomas**>

[…] as you see them in this slide: simple histological methods – lead haematoxylin, masked metachromasia, argyrophilia. Or the next one, they are the enzyme techniques which I spoke about and, in brackets, tryptophan because a high tryptophan level is characteristic of several of these tumours, particularly the islet cell tumours and carcinoids. And the next one shows you the specific cytochemical methods: the uptake and decarboxylation of amines which, of course, gives you the APUD-FIF characteristic which is the absolute characteristic of the series. And the next one shows you that you must, if you can, diagnose or demonstrate the hormone by immunofluorescence and you can get a great deal of assistance from the ultrastructure. Now, I'll just show you three examples, I think, of that, if I may. Oh, I'm sorry that I've forgotten about these slides, that's quite typical.

<**Pearse over series of slides showing differences in the levels of endocrine cells in the gut**>

These just show that there are immense differences in the levels of the endocrine cells in the gut. This is the normal level, shown on the TV monitor, of the fluorescent cells, gastrin cells by immunofluorescence in the normal pyloric glands. And the next one shows you a hyperplasia, and the degree estimated by the machine is 30 times, and these types of hyperplasia of that degree are found in many conditions. They are found in acromegaly, in primary parahyperthyroidism, in pernicious anaemia and in some types of Zollinger-Ellison syndrome. It is not known whether there is a trophic hormone to the gastrin cells or not, and this is a matter to be worked out.

<**Pearse over slides showing characteristics of apudoma**>

Now the next one on here, should, I hope, if I'm right, yes, show you the characteristics of the apudoma. This is actually an enteroglucagonoma, proven to be so by extraction and assay and it shows the lead haematoxylin staining of the granules in the basal part of the cell, a typical situation for them.

And the next one. This shows you by immunofluorescence a gastrinoma. Gastrinomas are quite common, they are not always functional, that is they do not always give Zollinger-Ellinson syndrome, silent gastrinomas are quite common. And this is a silent gastrinoma, which is a small tumour in the duodenum of an old man. That's anti-gastrin serum showing that up by immunofluorescence.

And the next one shows you the granules in a carcinoid tumour. And I only wanted to show it to show that looking at granules in a tumour is a sport; you cannot tell from the look of the granule what hormone, if any, is being secreted by that tumour.

00:35:24:00

Now there are certain interesting things that arise out of this consideration of apudomas. And if we look at the next slide […]

<**Pearse over tables listing different cell types primarily involved in apudoma**>

[…] we find, if you look at the right-hand column, you find that in multiple endocrine adenomatosis, that's MEA type II, described by Sipple in the United States, there are a number of cells which are concerned: the melanoblast is not described by him as concerned but falls into this category by my computation, the carotid body type I, the thyroid C cell, the ultimobranchial C cell. And in the next slide, I think, we see the adrenal adrenaline cell and the noradrenaline cell are all, absolutely certainly, derivatives of the neural crest and they give rise to this type of multiple endocrine adenomatosis. On the other hand, the type I adenomatosis, or the Wermer's syndrome, so-called – the cells concerned are, very often, the pituitary somatotroph

(acromegaly, that is), the pituitary ACTH cell which gives you Cushing syndrome, the cells of the stomach which may be G, A-like, ECL the enterochromaffin cell. And on the next slide we see the rest of them – the intestine, endocrine cells, the endocrine cells of the pancreas and the endocrine cells of the lung. And on the next slide we see the cells which are concerned in these syndromes – the parathyroid chief cell is involved in either MEA I or MEA II. This cell is certainly derived from endoderm; it is derived from the endoderm of the pharyngeal pouches and is not a nerve cell at all. The pituitary somatotroph may be derived from Rathke's pouch or it may possibly turn out to be a neural crest derivative, we don't know. And the next one shows you the correlations and the derivations of these cells from the neural crest. Almost, well, quite certainly, it is the late rhombencephalic crest which gives rise mostly to the cells from which MEA II arises, though the spinal neural crest contributes something to the adrenal.

<**Pearse to camera**>

And on the other side, it must necessarily be, I think, a different time or a different area of the neural crest which doesn't arise, of course, all at once but starts at the head and goes on progressively down to the tail. And probably the early mesencephalic crest and the late mesencephalic crest which give rise to this syndrome MEA I.

Well, I just want to recapitulate then, by saying that the endocrine cells of the APUD series form a group whose ancestry goes back five hundred million years. And these are basically nerve cells which must have learnt, at some point in their history, not to respond to other nerve cells by, through a long process, by means of a neurotransmitter, but directly by secretion of that product, the neural transmitter which may be the ancestral amine directly to the cell next door. And, at some point in evolution they have changed over from the production of an amine to the production of a polypeptide which was originally the storage granule on which, and without which the amine would not have been successfully stored.

And this group of cells, then, represents the largest and most important, in fact, 90% of the bulk of all the endocrine cells of the body.

<**End credits**>