HSF Patients' Day

Wednesday 13th May 2015

S E S S I O N O N E

Baroness Estelle Morris

Ladies and Gentlemen, thank you, thank you for coming and I wonder if we can make a start; we've got such a packed afternoon that if we're late starting we'll be late finishing and that won't do any good to people who are travelling. My name is Estelle Morris and I have the honour of chairing the Hughes Syndrome Foundation so I just want to welcome you and give a little bit of a feedback really on the work that we've been doing in the charity over the last year.

It has been quite a big year for us in a way. You know, with all these organisations, they go for a while and then all of a sudden you feel as thought you've made some progress and you've made a bit of a jump. And even if it's not a huge jump or we are not exactly where we'd want to be, we do think we've made several jumps over the last year, so that is good and we very much look forward to building on that as we go into the next year.

I just wanted to feed back a few of the areas where we've been working and sort of acknowledge your contribution and ask for your support. Really I suppose we've got three main purposes and one of our objectives, our first objective, is to support patients who have already been diagnosed or people with the condition who are yet to get a diagnosis, which, as you know, is a great number of people. And this year we've, really building on the work that we did with re-launching the website, it has proved very successful and we monitor the use of the website quite carefully. Showing off a bit but we even get people from overseas now who are accessing the information on the website and saying how helpful it has been to them. And that took a long time getting together but in terms of offering support and high quality information to our patients and to others, we feel as though it's a real big jump from where we were. So we welcome that. We will keep our eye on it and with all these technical things it is keeping it up to date that is the challenge but we will endeavour to do that.

The second thing where I think we've made good progress this year, but we've always done a little bit of this, is in the paper information, the newsletters and the leaflets that we are able to send to patients. We had the regular newsletter but we are supplementing that with, I suppose they are fact sheets, for people to improve their awareness and their knowledge and try to answer their questions.

And the third thing, which you will find on our website, is that we realised that very many of our members phone us because they don't know where provision for treatment is within the area where they live. Not everybody can get to London or wants to have to travel to London. So what we did over a period of about twelve months, we drew up a list of all the consultants who specialise in Hughes syndrome APS and that is now on the website. That is an additional piece of information that will be useful to you.

Our second really objective in the charity is to raise awareness. We get this from all our patients that if only GPs knew what to look for all that pain of waiting for the diagnosis would be lifted, all that anxiety and, more important than that, treatment would be quicker and treatment would be more appropriate to the condition that people have. And you are the best at knowing that raising GP awareness is not the easiest thing to do but it has got to be high on our list of priorities and again I think we have made progress with that. Kate has produced a wonderful leaflet for GPs and we have some available, it's either at the back of the room or on the tables below. But if you could take that to your GPs or to the Health Centre or to anywhere where it is useful to leave lying around. I don't think there is a magic solution to raising GPs awareness; it is not something we can sit around doing nothing about and then just hope happens. We are working on a number of fronts but that leaflet that's got good quality information is something that you can help us with by making it available to your medical staff.

The next thing we try to do is media awareness. Those of you who trace these things or whatever, we get a lot of articles in the media about people with Hughes Syndrome and they only, this is a terrible thing to say, but we can only get into the media if we've got somebody who is willing to actually tell their story. The media aren't interested in reporting the science or supporting the facts but if we can attach that science and attach those facts to a person and how it's affected their life, well then that makes what the newspapers and the media would call 'a good news story' and we are very, very grateful to all those members who have been prepared – because it is not easy and I'm not sure, it's not something everyone would want to do, but for those people who are prepared to tell their story, that really helps us to get that coverage. And what is really interesting, out of every bit of media coverage we get, we get a general practitioner or another member of the public coming back to us to say, "I've learnt from that. I didn't know that and maybe I've got that or maybe some of my patients have got that." And so that 's another way of raising awareness.

Some of you may know that we were lucky enough to secure a debate in the House of Lords just before the General Election on Hughes Syndrome and we are now following that up. Just let me say perhaps two sentences about how we are doing that. It's all right having the debate but the debate doesn't change anything. The key thing is what you do having had the debate so just before the shop was shut over the other side of the river for the General Election we did meet with Earl Howe, who was the Junior Health Minister and replied to the debate. We found him very helpful and we've got a number of leads to follow up. Where we want to get to of all those issues that we raised, if we were to pick out one, which we think we can do, and that's the important thing; something that is doable, is actually to get some national guidelines so you put into the structure of the medical profession some guidelines making it easier for practitioners to identify symptoms, test for it and treat appropriately. And already in the last couple of weeks we've had some meetings with Clinical Tsars as they are now called and we hope to take that forward. I really hope that when we meet again next year that is something on which we will be able to report.

And the last thing we're here to do is to support our membership and that's you. Everybody in this room is a member. Thank you for that. Without you there would be no reason to exist but without you we couldn't exist. We're hugely dependent upon the money that you raise for us. And some of you do some remarkable things in terms of raising money; anything from little children making cakes because they've got Mum or Dad, Aunt, Uncle, Brother, Sister with Hughes Syndrome, or people who run marathons and cycle miles and are able to get us money in that way. But however much it is, it is very gratefully received and is the core of our funding. We do apply for grants and like all charities some we are successful with and some we are not as successful with. But we will keep on going and we know that is something we have to turn our mind to.

So I don't know how many this applies to but you are all members, that is why you are here. What would make it easier for us is to manage the membership and to make sure it is up to date and, to be really honest, we don't lose any of our members, is if you do it by direct debit. We never require

anybody to do that because we're not here to make life difficult but it really helps the charity if you were able to renew your membership by direct debit and how to do that is really easy and you can find it on the website.

So in terms of thanking you for your support and the fund raising, in return I've asked you would you possibly get rid of the leaflets at appropriate places wherever you can? If you can move your membership to direct debit that would be helpful. If any of you feel that you've a story that you'd like to share with the rest of the world that would be really helpful too. I know that Kate would be willing to hear from you on that. And just to thank you for the partnership; we've all got different roles in our Foundation but every one of us plays a role and every one of us is either a patient or a practitioner so we are all in the same business if you like. We've all got a vested interest in the Foundation getting stronger so that we can deliver what we want to deliver.

And now I just want to thank those people who've organised today. I can't tell you how, you know, it all runs, touch wood, it all runs really smoothly but without Kate and Yvonne and Lynne and our team of volunteers who you can see downstairs it wouldn't run at all. So on our behalf can I thank Kate, Yvonne and Lynne and all the volunteers for everything they've done, it's wonderful? Can I thank our sponsors without whose general financial assistance this would be so much more difficult to get together? And can I thank all our medical staff who willingly give up their time to spend the afternoon with us. We all know that every one of their clinics is bursting to capacity with people who can't even get on the clinic waiting list and every single year these people say, without persuasion, with me really having to ask them more than once, that they want to come here and share their knowledge with us. We are eternally grateful and it makes a real difference.

And that leaves me just to introduce Professor Graham Hughes, who is our patron, inspiration and our founder and no Patients' Day would be the same Graham unless you started it off. So we are delighted that you've agreed to do that today and we look forward as ever to hearing what you have to say. Graham, I wonder if you could come up.

Professor Graham Hughes

Hughes syndrome: 30 years old. What have we learnt?

Thank you very much, Estelle, for those kind words and thank you all for coming. The most important session in many ways is the question and answer session at the end so I thought in my short talk I'd use it around questions. So ten quick questions, some of which we can answer, some of which we can't.

First of all, what is Hughes Syndrome? And there are I know quite a number of new people here so I apologise to those who know all these things. So this comes from a little booklet, "Do you have any patients, doctor, with migraine and headache, with a DVT or a clot of any sort, with a current miscarriage, with a memory loss and with a tendency to young strokes even, TIA or Transient Ischemic Attacks?" And these are the features of Hughes syndrome. Thirty years ago we gave it the name Anticardiolipin syndrome and then we changed it to Antiphospholipid syndrome and the boffins and you will hear today even that is the wrong name strictly speaking. So Sticky Blood is what the media call it and it's kind of what's stuck.

The main pointers, teenage migraine; "Did you have migraine as a teenager?" "Yes, doctor, all my teenage years, it went away but it came back later and now it's a major problem." A tendency to clots? You don't have to have that tendency; we think that it's more sludging of the blood than clotting but I'll come back to that because there are some doctors who say, "This patient can't have Hughes syndrome because she

hasn't had a clot or a miscarriage." Recurrent miscarriage you will be hearing about it in the next talk. And cold circulation; one of my patients calls it corned beef skin, is quite classical.

How was it discovered? Well in 32 years ago we reported it, first of all at a thing called the ((Hebadon?)) Society, which was in 1982 and we'd been working in the world of Lupus, which is a cousin of this syndrome and particularly interested in the brain in Lupus and things called antibodies, which react with brain phospholipids. And bit-by-bit we set up assays and very clear, very quickly, and Estelle has told you about the large clinics. One of the virtues of large clinics is you see patterns of disease and we saw these groups of patients with what is now called Phospholipid syndrome.

So we described it in two British journals, the BMJ and, those of you who are in the know, know you can't get into American journals, but we published it in the British Journal of Medicine and this was the same year presentation both at the Hebadon Society in '82 and at the Skin Society, that other features are headaches, epilepsy, chorea – that's a St. Vitus Dance, multiple abortions, peripheral thrombosis, demyelination – that's a fancy word for MS, or Multiple Sclerosis like features in some patients, Budd-Chiari – that's a name given to a clotting in the liver, which is rare but we see it, and other clots.

So that's the syndrome many of you know only too well the features. Bringing us up to the present, we are now into the thirteen international conference and every two years or so there is a world conference on Hughes syndrome. And this was the meeting arranged a year and a half ago, which a number of the colleagues here spoke at, run by two colleagues here, ((Hugh de Schonfeld?)) on the right and Dr Levy on the left, an outstanding meeting. And I want to show just a couple of slides from that.

Here's one: in the Americans there is a group led by a group in New York who are trying to do what has been done here by your charity and that is try and get some figures because MPs, the media, all want the figures. And although these are very crude they are sort of a nice piece of work. For instance, of all patients with current pregnancy loss, maybe 12%, we think more, are antiphospholipid positive. Strokes and with dementia; some it's a cause of heart disease and something that I'm going to mention, DVT.

What are the main symptoms? Well this is a picture of a vein, which looks lumpy and narrow in places, and this is a clot in the vein. And funnily enough it presents with a swollen arm and in my textbook of medicine, which goes back a few years, it was ascribed to a tight pyjama sleeve, which I think is rather interesting.

The big story of course has been pregnancy and you will be hearing about that from Hannah Cohen next. And it really has been a wonderful thing. Many of you know we have an annual meeting at St. Thomas's of mothers and babies and they all come and have jelly and ice cream and vomiting and things like that.

Pregnancy outcome has been dramatically increased and I just want to show this to introduce the next talk. The brain seems to be particularly vulnerable to lack of oxygen or impaired oxygen supply and the brain is stupid, you know, if it gets not enough oxygen then you get either headaches, memory loss, balance and what we try and do is scan the brain. This is an MRI scan showing little white dots for those people who have had many clots and for those people who have severe cerebral features, severe headaches or balance, this should be done at some stage in the investigation.

I mentioned migraine, common; memory loss, common, very common and a lot of our people don't come out with this until the doctor asks, "Any problems in memory?" "Yes, I am the joke of the family, I can't remember which exit at the roundabout or I can't remember words."

What are the tests? Very simple, let's not make it complicated. There are two simple boxes that the GP must tick, and unfortunately you need two; and they are Anticardiolipin, which is the main test. Some

patients are negative on that test and therefore you need another one with this terrible name Lupus Anticoagulant. It's a historic name. And in the last decade a new test for those other people who are negative, called Beta Two, but that's small print for this meeting I think.

What is the treatment? Treatment simply at the moment is either some way of keeping the blood flow better and the choice is, of course, aspirin, Heparin and Warfarin and again you will be hearing about treatment later on this morning.

But I'd like to show one remarkable slide and this is really extremely interesting. For about a year we had at St. Thomas's a young registrar in Psychiatry working in the unit, and David will remember that, and he was doing fancy memory tests. You know, one of these one-hour jobs where you remembered words and all the rest of it. And on the left is a young woman of about 40 with memory problems and Hughes syndrome and she was down at the thirteenth percentile on his memory scale. She couldn't remember words. She had four weeks of Heparin, which is a trial that we do in many patients to see whether we are on the right track, and there she is, 82% word finding. And our Professor of Psychiatry, who is very good, said, "There is no psychiatry drug that does anything near that."

Are there any new drugs? Yes there are and I'm going to pass on that one because you will be hearing all about that this morning.

A common question of course for us as doctors, what if the treatment doesn't seem to be working? "I am on Warfarin, doctor, but I'm still getting headaches, balance is a problem and I'm not right." By far the commonest reason is very straightforward; if you look at that little yellow book of anticoagulant results, the thing called the INR, the thickness or thinness of the blood; our patients often need a higher INR and again you will hear about that in -. And this cartoon really shows that if the blood thickening process drops then you get the syndromes. And I think of it as Tesco's milk; normal milk, INR 1, half-cream milk, INR 2 and you really need it to be in the 3 range.

Does lifestyle, diet, going out in the sun, does that affect Hughes syndrome? It almost certainly does and I just want to show one very interesting study, carried out by a colleague of mine from India, New Delhi; he was the rheumatologist running the Lupus Clinic in New Delhi and he went and worked for a year in Kuwait. And what he found was exactly the same frequency of antibodies, anticardiolipin in Kuwait and in New Delhi but the Arabic population in Kuwait had twice the number of clots, suggesting maybe that lifestyle, diet, the more healthy diet I guess in New Delhi, contributed.

Last but one, will my family get it? Now many of you were here last year and you kindly answered an anonymous questionnaire. And the question was, do you have a family history of autoimmune disease; and by that we mean thyroid, MS, rheumatoid lupus or those. And patients in the audience, 60% had a mother, aunt, sister with autoimmune syndrome, whereas their husbands or accompanying persons have a lower incidence. So the answer is yes, there is a genetic component if the doctor goes into it in detail. It may not be Hughes syndrome but it could be, for instance, thyroid.

Last question, very commonly asked because of the confusion of the terminology, will I develop Lupus? The answer is pretty well a resounding, no. And this shows in again primitive form. It is very common for the arrow to go one way. In other words, if you have a lupus clinic, one in five patients has got Sticky Blood. So it is definitely a small percentage of you in the audience who may have lupus will have this. But if you are primarily antiphospholupid and no evidence of lupus, the chances of developing lupus actually are very small and this is now 32 years, more than 32 years on.

But I'd like to end with this slide really. This is what I call the big three; and doctors in the audience should know this. There are three things that go together like terrible triplets; Hughes syndrome patients often get a lazy thyroid and then often have accompanying Sjogren's. What is Sjogren's? Fibromyalgia

- aches and pains, fatigue, dry mouth, dry eyes. So that is not often asked about but it's treatable with quinine. It is a very treatable thing and I am sure there will be questions about this.

So I want to end by showing, you know we all write books and we are given books by patients and one of my patients gave me this, Mills & Boone, you know, love stories. And this one is called, 'Specialist in Love', cheap books with lots of mistakes in them and this bit on the next page was 'Fergus shook his head, "No thanks, Jeff," he began to write in the patient's notes, systemic ((longferstemotheratosis?)). In his untidy hand he scrawled the inevitable symptoms, the ((outaneous?)) signs, which included the well-know butterfly ((erythema?)) on the face, frontal alopecia ((?)). He refrained from writing two words, which this disorder signified, potentially fatal.' That's the sort of stuff people are reading.

My last patient is this young girl. I like to show her because she tells us such a story. She came over from Romania by train, it must have taken days, and she had a diagnosis of lupus and her symptoms were of seizures, epilepsy and memory problems and they thought she had cerebral lupus, which is inflammation. And there you can see on grossly large steroid doses. She came over to us and what she had was mini lupus, not much at all, but Hughes syndrome, Sticky Blood. And she is actually now perfectly well, on Warfarin, on life-long Warfarin, this is about 25 years ago and it shows the great importance to those of us dealing with connective tissue diseases to get the diagnosis right.

Thank you very much indeed and thank you Estelle for all your work and to Kate. It is a great pleasure to welcome Hannah Cohen. We've worked together over the years and she is going to tell us about the management of pregnancy.

Dr Hannah Cohen

How to manage APS in pregnancy

Thank you Graham. Good afternoon ladies and gentlemen. So, for those who don't know me, which I think are many in this audience, I am a jobbing haematologist, that's a blood doctor, and I have a great interest in Antiphospholipid syndrome, including in pregnancy, patients who have pregnancy problems.

So we all want pregnancy to end like this in every woman but unfortunately in patients with Antiphospholipid syndrome this isn't the case. Now it isn't always so because yesterday in my antenatal clinic, where we see patients after they've had their babies, they come back. And I saw three patients actually who had Antiphospholipid syndrome with a history of many miscarriages between them and they all had successful pregnancies. So we can do it. But what do we see?

So pregnancy in Antiphospholipid syndrome looks a bit like this. We see early miscarriages, i.e. in the first twelve weeks and that occurs most commonly so 15% of women who have recurrent miscarriages, which is three or more consecutive miscarriages, have Antiphospholipid syndrome. And if we are thinking about sort of total numbers that equates to about 6,000 new couples each year come with recurrent miscarriage. So that's a huge problem and what happens here is that time and time again they just do not get beyond twelve weeks.

We may also see late miscarriages, we may also see patients who have got Aluguel, which means intrauterine growth restriction, which means that the baby simply isn't growing properly and that is because the baby is not getting sufficient nutrients from the placenta. And we also see preeclampsia, where women have high blood pressure, swollen hands and feet and can get very ill indeed and can even have fits and it can even be fatal.

And we quite often see premature babies in women with Antiphospholipid syndrome and last and so distressing, we also see stillbirths. So it is really a very bleak picture.

And what is really important is if we are treating women with these conditions that we treat them early and this is because what sets the scene for all these complications is what is happening very early on at what we call the implantation stage when the fertilised egg attaches itself to the lining of the womb and then goes in and it's here that we have to focus if we are going to treat. There is no point treating way up here. And that is such an important principle we all need to be aware of.

So many years ago, when I was a child, we did this study, in 1997. I went as a new consultant to St. Mary's and I said, "I'm really interested in this subject." And Lesley Regan still has a very large clinic there where she saw lots and lots of miscarriage patients. And I said, "Let's get together." And we did and we did a trial and what we did is we gave women either aspirin, which a lot of women were taking at any stage, because what we also showed there was that if you give no treatment and you follow up pregnancies, only 10% of women had a take home baby.

And so we knew aspirin did some good and women were taking it, but we added Heparin injections and what we found, and we did this in 90 patients, is that with aspirin alone about 40% of women had a live birth but when you added the Heparin it was about 70% and so that was a definite improvement.

So there was one group in which we wouldn't do this, and that is women who have already had thrombosis because in such women you've got to give them a big dose of Heparin because here we were using quite a small dose. So what happened subsequently is that there were obviously various trials and then I think what I call the wilderness years because for many years it was said that Heparin, you don't need it, aspirin is good enough and there were trials saying that. But the time has come because now what's happened is that analysis of several studies, five studies, has shown that Heparin plus aspirin is what you need. And one of the major proponents that was contesting our findings has actually recently published a study where they were using Heparin as well. And the current guidelines say you need to use Heparin so that is absolutely the case.

However, it doesn't always work because after all it is only about 70%, what about the other women? And so we need to think of what other things we can use as well as aspirin and Heparin and I think here we are coming into a very interesting phase. But before say anything about that I want to bring this to your attention – what we call non-criteria Antiphospholipid syndrome and I think this is very important for all women who have antiphospholipid antibodies, which may come and go for example; or they have the very low levels, which are said in the international classification not to be important. We have suspected for many, many years that yes, they are important. And these women, it has been found, also seem to respond to the same treatment that the classic Antiphospholipid patients do. So we have been battling away with this for many, many years and recently a review got accepted on this subject, which really I think means that we have moved forward with this and now it is being generally accepted. And what we have here is the women that don't fit into that classical category; so women who have two miscarriages.

I say, unexplained, because technically you are supposed to show that the woman hasn't had a chromosome abnormality in the foetus, which has caused the loss. And we know that can happen; that can happen quite a lot, and that is in fact the commonest cause of a pregnancy being lost. But that doesn't mean that antiphospholipid antibodies wasn't contributory – anyway that's how I think about it. And so three non-consecutive miscarriages, late preeclampsia, because when we talk about preeclampsia the current criteria, which I have to tell you are going to be updated at the Turkey meeting, the international APS meeting, which is next May and I've been invited to be on that panel.

And then also things like other pregnancy complications and then also things to do with IVF because IVF now is increasing and we know that if patients lose their pregnancy, so either they have a miscarriage after IVF or even they don't get that far, that antiphospholipid antibodies may be implicated and the same goes for the laboratory criteria. We believe that less strict criteria are relevant for patients with Antiphospholipid syndrome problems in pregnancy.

And now what next? Well there are treatments other than Heparin and aspirin. So this is one and Beverley Hunt published a study where they showed the patients where aspirin and Heparin doesn't work, they gave them low doses of steroid and what they found is that whereas these patients had a 4% take on baby rate, that went up to over 60%, so that is one thing. Another thing that is being thought about is hydroxychloroquine, which is pretty standard treatment for patients with lupus but not so with patients who have got Antiphospholipid syndrome on its own and there is evidence that this may be useful. And Beverley Hunt is leading a study, and I am very pleased to be asked to be involved in that, called Hypatia, which basically is hydroxychloroquine against a dummy in patients, adding that to their standard treatment. And I looked up Hypatia, because I have to confess my ignorance, and she, it is a she, was a philosopher and mathematician in the fifth century.

And the other thing is complement; well complement is there to protect us from invading infections but we know that antiphospholipid antibodies can actually trigger off a complement response and that can actually lead to problems like miscarriage. And there is a lot of work suggesting this in experimental studies, in animals for example, and there is some work suggesting it even in people. And so complement is something that is really of great interest and I am participating in an international study, where we are looking at the effects of a complement inhibitor but not in patients who are pregnant at this stage. But nevertheless we are very pleased that the company has chosen Antiphospholipid syndrome to test their drug out on because we never know, we may be able to get to pregnancy in the future.

So I simply wanted to end up with mentioning to you what Graham alluded to, the APS Action, which is an international group, which has now over 25 centres internationally, where what we are trying to do is network. And so we know that it is hard to do the antiphospholipid studies but if you collaborate you can and so we are all trying to work together to do this. And this was our last meeting in Boston last December, or November and, whilst not all the important people in Antiphospholipid syndrome are there we are very pleased that quite a number of people have got involve with this group. So I think I'll end there. So thank you very much.

Chairperson

Thank you very much Hannah. As I said at the beginning, we're keeping the questions to the end and I forgot to say, but if any of you have questions you would like to ask and don't want to ask them personally, put them on a piece of paper and give them to Kate and her team, maybe in the tea break and we will try and answer them.

Well it is now a great pleasure to welcome Beverley Hunt. Beverley are you here, who is a consultant here in haematology and a guru as far as I am concerned on all the new drugs.

Professor Beverley Hunt

Anticoagulation Q&A session

So I've got no slides at all, how about that? Good afternoon everybody and I want you to ask me the questions you want to ask about anticoagulation because I am always aware that I give a short talk and then there are thousands of questions. So the floor is yours. Who has got a question? Okay, there's a lady at the back. Is someone going to be a roving mike or shall I do it myself, I need the exercise!

Q1. Okay, hello, well I had a stroke; a massive heart attack and now I've developed lupus. My heart attack was because I was under-coagulated based on my INR with coagucheck. So after my heart attack I was nearly dead but the doctor gave me, put me alive, I don't know how and the doctors in Bristol, I live in Somerset, near to Bath, the doctors in Bristol told me, you have to have your blood tested in robobrain tuboplasty not coagucheck, the poison that you, that you react, that your – give you, I don't know, gives you the wrong readings. So I was under-coagulated and that is why a blood clot, this is in my -?

So we have, I know a lot of people who have got Antiphospholupid syndrome, Hughes syndrome, have got their own home monitoring and here we have a case where somebody has got a home coagucheck and it sounds like their INR was lower than the real INR and it's quite a common problem and I think not everybody with Hughes syndrome can do home monitoring. If you want to think about it you should get a machine and you need to run that machine in parallel with the laboratory tests when they take blood from your hand, from your arm and check that the machine is good enough for you.

And actually I was in the Lupus Antiphospholupid clinic this morning and someone was doing home checking and their INR at home is always 0.6 less than the true INR. And she could cope with that because she was saying, "Okay, so if the machine says 2.4 that means actually my real INR is 3." So she was running herself in that way but not, you can't do that all the time. Some people have an antiphosphorate antibody that would interfere with the testing in the coagucheck and they won't get reliable results.

So the answer is when you first get it, check against the laboratory and every time you get a new back of the little packs that you can check your blood with, it is worth checking it against the laboratory.

Anyone else got any questions in that area? Here we go.

Q2. Thank you. I wonder how work is progressing on antidotes for some of the newer treatments like Vibrox and Apixaban?

So I have to ask you, why do we need an antidote?

Q2. Something can go wrong, catastrophically wrong and one needs to come off the anticoagulation very quickly.

Okay, and how often does that happen?

Q2. I hope rarely, but in a car crash for instance?

Okay, so if you are on Warfarin, you're Warfarin tablet you take today is really working in two or three days' time. And what it is doing, if this is your normal clotting, my clotting is down here; a lot of you are up here. And when you are on Warfarin it keeps you at the same level all the time, 24 x 7. The new drug thinners such as Riveroxaban and Apixaban, you take a tablet, maybe in the morning, and it takes your blood up very quickly up to that level and then down again and then up and down. So every time you take one it lasts for about 24 hours.

And you could think about the new blood thinners in a lay way as if they are just like taking a tablet of low molecular weight Heparin because actually Riveroxaban and Apixaban have exactly the same effect. So they don't thin the blood in the same way. They don't have that long-term effect of Warfarin and when we look at the trials we find they have a much lower risk of bleeding. The number one nightmare of bleeding is that you bleed into your head and you have a much lower rate with the new blood thinners and the trials are starting to suggest that if you do bleed, which isn't very often on Riveroxaban and Apixaban, you bleed less so there is less catastrophic.

So I am saying to you, I'm not sure you need an antidote because it wears off very quickly but we do have an antidote so if someone did have a catastrophic bleed on one of the new ones, we would give exactly the same agent that we give when people are on Warfarin. We use PCC, so we give them an injection and it doesn't quite reverse the effect but it gives them a boost to cope with the bleeding.

So the new antidotes, the direct antidotes are already in clinical trials. Clinical trials are going on worldwide; they probably will be licensed at the beginning of 2016. But do we really, really need them? So we've got probably five or six hundred people on new oral anticoagulants. They are doing very nicely thank you very much. They hardly ever bleed, whereas compared with those on Warfarin we've had an enormous number of problems. And they have only had to reverse somebody once and that was when they came off their bike, one of my cycling friends, fractured their ankle and they reversed very well.

So there's an awful lot of worry that there's no direct antidote but do we really need it? We don't have a direct antidote if you are on fragmin or clexane, there isn't one because we don't need it because it wears off very quickly.

Q3. Hello Professor, just a quick question about INR, having taken it being done for the last six years and weekly, very rarely beyond two weeks and it's up and down like a whore's drawers, what is the trigger for that please? Do we know a trigger?

So are you going to tell us about what you eat?

Q3. I have a very good diet.

What does that mean?

Q3. What do – I don't know.

How does Warfarin work? How does it thin the blood?

Q3. I've no idea.

So now where are some of my pupils? Here we go, would you like to tell everyone?

Male: Okay, Warfarin works by removing the vitamin K from your system, which is required for clotting. vitamin K is in all green vegetables, particularly like broccoli or runner beans or cabbage, going down to the lesser, which are eggs. So you need to know what you eat. If you eat a varied diet then you will have a varied level of vitamin K unless you monitor it.

So Chris gets full marks; he gets a gold star and a pat on the back next time he comes to clinic. So how Warfarin works is that it antagonises vitamin K. So if you have a day where you have a lot of vitamin K the Warfarin can't fight it very well and the following day the blood is a little bit sticky, well the next few days. If you don't have any vitamin K, say you are ill and you don't eat properly, the following day the Warfarin can really get a grip.

So it's all about consistency in your diet and regulating your vitamin K. British diet, vitamin K is mainly in green vegetables. If you were Japanese it would be a nightmare but we are not Japanese and we don't eat fermented fruit, so green food = vitamin K, the only food that isn't green that has got vitamin K in is cauliflower. So you need, most people, and I've taken dietary histories from an awful lot of people, they have cereal or toast for breakfast or they have nothing. They have a sandwich for lunchtime and then somebody cooks in the evening. Cooking in the evening you need about the same sizes pile of greenery on your plate every day and the day that you have flu and you don't want to eat anything, somebody boils up some peas for you and you shovel them down because then that makes sure you get some vitamin K, okay?

Now I know that a lot of people here also have lupus and they take painkillers and some of the painkillers to interfere. You do need to try and get consistent with having roughly the same amounts of the painkillers every day. So it's consistency and then what about alcohol? Darling you don't drink! Well that's really sad. Would you like a drink? You can have a drink but you have to have the same amount every day. So that's all right, yes, I am not expecting a bottle of red wine every day; I'm suggesting a glass, okay.

Q4. Hi, I concur with everything you said about vegetables because I, my husband thinks I am going to reincarnate as a rabbit but as long as you eat a lot it's fine, as long as you eat it regularly. I find exercise actually has a more dramatic effect on my INR than the vegetables that I eat. I've been self-testing for about, I don't know, it seems about nearly ten years and if I do a lot of running, which I am trying to do, and do a lot in the gym, I find I have to increase and I can increase my Warfarin up to about 12 mg a day for a normal of between 8 and 9, the more exercise I do, presumably because my body is metabolising the drug more? Is that just -?

It's a new one on me. Does anyone else have this same effect? I think we have to say to her that you have to run the same distance every day don't we? But it's quite – ((speaker at a distance)) okay, that's very interesting and I'm going to log it for future studies. Any other questions, there's one down the end.

Q5. Hi, thank you, I wondered if there's any information about stress and the INR because I find if I am particularly stressed or fatigued and/or both, it really does have an effect?

Well when I get stressed I go for the biscuit tin, so what do you do when you get stressed?

((speakers at a distance))

Q5. Sorry, I don't think I know what I do, do I? ((response from someone)) I shout!

She shouts at her husband. I don't think shouting at your husband will alter your INR, so it's not meant to be affected by stress so I don't quite know what's going on there. Maybe you are not so well when it makes you stressed? I don't know, I'll think about that one.

Q6. Hello, I was on Warfarin for quite a long time and self-testing. I am now on fragmin because of various things that Graham investigated and a colleague of his ((PV Savondra ?)) with clotting in the ears. But my question relates to self-testing when I was on Warfarin and an interesting thing that happened to me after I had cardiac bypass surgery and for three months after I'd, post operative, the self-testing was way out. I was – my coagucheck machine was telling me that I was twice the INR level that actually I was in the lab, have you any ideas why that is? Certainly ((Roach ?)) didn't have any ideas.

Did it go back to normal?

Q6. ((inaudible response))

And what tablets were you taking that were different?

Q6. What tablets was I taking? At the time when it, when I had the TIA, which was a couple of days after coming home from the heart surgery, well I was on most of the tablets so the only odd one was probably amioderone.

I'll have to go and read up about amioderone. But you shouldn't be affected in that way by the surgery. It will be something either in your diet or your drugs. I can't think what else it could be, sorry. Can't answer everything you see!

Q7. I am just a little bit confused; I have had two thrombosis, both in the eyes, so I've had two retinal vein occlusions. Even though my INR is between 3 and 4 I've had the second thrombosis so as I have to keep such a high INR should I really be better, I still have all the problems in my brain, headaches, memory loss, balance, even with that high INR. Would it be safer for me if I was on Riveroxaban?

So I can't talk about you personally because we are not in a doctor situation so it is difficult to answer that one. I can talk to you about Riveroxaban and Riveroxaban has only been tried in patients who normally run an INR of 2 to 3. So if we look at the tens of thousands of patients that have gone into trials for the prevention of stroke in AF and the treatment of venous thromboembolism, we are comparing with an INR of 2 to 3. We wouldn't know what dose to use in patients who are running an INR of 3 to 4. We are talking, looking at Dr Cohen over there, about perhaps doing such a study but it's going to take quite a long time to set it up because we don't know where we are starting from. So Riveroxaban absolutely isn't the answer for you, sorry about that.

Q8. Thank you, hi, I am on Riveroxaban myself and I suppose if I have a concern mine is less to do with a bleeding incident but more to do with the fact that the Riveroxaban wears off quite quickly, so therefore, you know, sort of 12, 15, 20 hours after taking my Riveroxaban am I still as covered as I was 12 hours previously?

So if we put you on the low molecular weight Heparin you'd get the peak and then you'd get the trough and the Riveroxaban curve is very similar and it covers you for 24 hours and we know that these low molecular weight Heparins such as fragmin and everything are very good in the prevention of venous clots and Riveroxaban is very good in the prevention of venous clots and there's a message here. It is that you probably don't need to have high anticoagulation with Warfarin 24 x 7 if you are running an INR of 2 to 3 and you are okay on Riveroxaban. Yes?

Q9. I am just wondering if there are any alternatives to Warfarin if you can't tolerate Warfarin?

So – Dr Cohen and our team have been running a trial of Riveroxaban in Antiphospholupid syndrome. We've finished but we are not allowed to talk about the results are we Dr Cohen? And it was in people who've had previous deep vein thrombosis or pulmonary embolism and who are running an INR of 2 to 3. So I'm afraid you are going to have to wait. Mum's the word! Sorry but I'm not frowning am I?

Q10. Hi, yeah, I was just wondering whether or not infections affect your INR because I certainly, if I've been in contact with people with infections or I am getting an infection my INR will drop because presumably my antibody levels are increased because of my immunology?

So when you get an infection your blood gets more sticky. When you go into hospital or are unwell or you have surgery your blood is sticky for six weeks afterwards. When you get pregnant and after pregnancy your blood gets more sticky and if you've got very brittle, for want of a better word, Antiphospholipid syndrome I think a lot of people notice when they are unwell that they might have a few more episodes. Your INR shouldn't really drop that much if you have that and it may be because you are not eating so much because you don't feel so well that you have just cut back on your food and you are maybe not eating as much greenery.

Q10. I have had a drug reaction on another drug, which was causing pancreatitis and other, it was a lipid-lowering drug, fenovibrate, I'd been on for a very long time and it was that reaction I think that has thrown it all out. But I'm taking 10mg of Warfarin at the moment, which is pretty heavy.

Let's stop you there. The clinics drive me nuts because they say to some of the patients, "Oh, you are on 22 mg of Warfarin, that's an awful lot!" It doesn't matter. If you are on 22 mg of Warfarin it takes 22 mg to thin your blood, that's fine. That just means you've got a really, really healthy liver and enzyme system and you need that amount to overcome it. So don't worry about the dose. I know a lot of the clinics say, "Oh, you can't go above this dose," that's not true. Whatever dose you need you should take and not worry about it.

Q11. Could I ask what is the right level of INR? Does it vary from individual to individual? And I've also read that there are some people who have a higher INR level or at least they notice when it drops that their symptoms of APS can increase, so is there a sort of optimal level you should reach?

So I wish we all agreed on this. So the guidelines say that if you have got Antiphospholipid syndrome you should run your INR between 2 to 3 starting out and if you obviously have clots on that then you have to run at 3 to 4. We disagree here at St. Thomas's. Dr Cohen disagrees. We think if you've had what we call a clot in an artery you need to run an INR between 3 to 4 and there are many, many people who have had brain problems who seem to notice that when the INR is less than 3 they have a foggy head or they get symptoms. And for me it's almost like saying, when someone comes to see me and I've met them for the first time and we don't have a diagnosis and they say something like that I think, oh they've got Antiphospholipid syndrome and actually we have to public this, don't we? We have to prove, because all the other doctors snigger at us and say, "Oh, you can't be right!" But I really do believe that patients can tell their INR. Is that enough? Good.

Chairperson

Thank you very much Beverley and I am sure there will be more questions along this line. Just in, I've got a lady, and she may be in the audience, who does the Daily Mail crossword every day and the time it takes for that she compares with her INR and it's a beautiful graph, it really is linear. Anyway it is a great pleasure to welcome Anisur Rahman who is going to talk about what is new in the Antiphospholipid syndrome. Welcome back!

Professor Anisur Rahman

Some thoughts on the future of APS

So thanks very much Graham and thank you for the invitation to speak again at the Hughes Syndrome Foundation. So I'm going to talk about the future and the reason I'm talking about the future is because the thought of how things change in medicine over the years has been on my mind recently and I will tell you why?

My father qualified in medicine in 1959 and then he practiced for almost 50 years before he retired and the state of medicine when he started compared to when he finished was completely different. The treatment of almost all diseases was almost completely different during that period. I now, I don't go quite as far back as Graham, but I've been a doctor more than half my life now, qualified in the late '80s and again many things have changed completely. Some things haven't changed very much. So as an example, I'm a rheumatologist; the treatment of rheumatoid arthritis has changed out of all recognition during the time that I've been a doctor. The treatment of back pain has hardly changed at all during the time that I've been a doctor. Some things change some things don't.

So last September my daughter started medical school for the first time, so I started thinking well, look that's what it was like for my Dad, that's what it was like for me, what's it going to be like for my daughter when she practices as a doctor hopefully? In fact to celebrate the fact that she'd gone to medical school I gave her my Dad's old medical dictionary, which he'd bought in the 1960s and he'd passed it on to me, I passed it on to her. Ironically she doesn't actually read it because she's 19 and she looks everything up online. It's completely useless to her but it gave me a good feeling to give it to her.

So I gave it to her and in giving it to her I kind of looked through it and some of the words are just unrecognisable; you just don't even use those words any more. That's how medicine moves on.

So that is why I started thinking about what will things be like for the Antiphospholipid syndrome as we move on in time. Okay, so these are the things that I would like to cover. In the next sort of ten to twenty years from now what will change? So if you think about a patient with Antiphospholipid syndrome, who may be treated by my daughter twenty years from now, who will be tested? Not people with the syndrome but who will we check, who will we screen to see whether they've got the syndrome or not? How will those tests be done? And when people have the syndrome what treatment will they have and how will we know whether treatment has worked? Those are the things that I want to cover.

So let's look at the issue of testing first and really what you have to do is think about what do we test people for? Why do we test people? So I am talking about people who don't have a disease. It is quite obvious why we test people who do have a disease. If you've got a person with diabetes then you are going to have to test their blood sugar every so often because you need to know what it is. But if you've got a person who is not known to have a disease, when would you want to screen that person?

So it all depends on what tests you have available. So if your test is very reliable so that the meaning of the test is clear. If it's positive it's definitely positive and if it's negative it is definitely negative that's a good test, which you might be quite keen to use. And example of that test for example is the HIV test. So the HIV test now is really very accurate. You might have to repeat it once or twice but if it's positive that person has been exposed to HIV. It is almost never wrong that test. And equally if it's negative they probably haven't been exposed. So it's a good test in that way. It's a very reliable test.

So you want the test to be reliable but you also want the test to be beneficial to the patient. You want to know that knowing the result of that test will be helpful. Now that's true of the HIV tests now because nowadays in Britain if you are diagnosed with an HIV positive test there's lots and lots and lots of treatments you can have and generally those patients tend to do well on treatment. But it wasn't always the case. So when I first qualified in the 1980s there was essentially no treatment and if you were diagnosed with that you were probably going to die very soon. It was a horrible thing to have and furthermore, and some of the people in the audience may remember this, there was a time when even having the test would make them put your insurance premium up, even if it was negative, because the insurance company would assume that you were the kind of person who lived a lifestyle that was risky. It was completely wrong of course but it was a reason why people didn't want to have the test. The test wouldn't do them any good and it might do them some harm. So that's not the case now with that test.

But as a sort of philosophy is that it's not always right to do the test, sometimes it's not the right thing to do the test for a person. So where are we with APS tests then? How does that fit into this paradigm? So are the APS tests reliable enough? And the truth is they are not perfectly reliable. None of the tests that we have is perfectly reliable in that you can say, "Okay if you've got that test, you are going to have APS. If you haven't got that test you are not going to have APS." There is no test available for APS like that.

And what we talk about in medicine is false positives. A false positive test is where a person tests positive but they don't really have the disease at all. So they are worried but they shouldn't be worried. They don't need to be worried. Now Graham produced a very good example of this when he talked about people who are told they have the lupus anticoagulant and think they've got lupus when they haven't. In fact Graham illustrated it very well with that excerpt from Mills & Boone romance, drawn I believe from his extensive collection of Mills & Boone romances. It is not well known actually that Graham is one of the world's foremost collectors of Mills & Boone romances and really I want to say to you Graham, don't be ashamed. It is nothing to be sorry about. I know you travel a lot and, you know, you've got to read something!

So in his quote from the Mills & Boone romance he said that people were very frightened of having lupus because, mistakenly by the way, they think that there is a very high chance of dying. Now that's not actually true but I'm not going to talk about lupus but it tells you about how if the person has a test and it's not done for the right reasons and it's not explained properly it can make that person very worried and afraid.

Now with the APS test the figure is about 5%. If you took a thousand people who were completely well and tested them, about 50, about 5% would be positive. So that they would be wrongly positive and you would not have done them a favour by doing that test. So that's a problem. The test isn't completely reliable.

And secondly, what does a positive test mean? So if you are positive what is the treatment? What are you signing up to for the treatment? And as others have alluded to, currently the main treatment is something like life-long Warfarin and life-long Warfarin is no joke. It's a big deal to be on life-long Warfarin. I am sure many people in the audience know about that. It could have side effects and of course if you know that without it you are going to have a stroke, you are definitely going to take that on but if you've just got a positive test and you don't really know whether you are going to have any problems or not, well that's then a big deal.

So the fact that we don't have a perfectly reliable test and equally we don't have a treatment, which doesn't have in itself lots of side effects, both of those make people quite cautious about using the APS test as screening tests; by which I mean tests on people who are not currently known to have the disease.

So let's talk a little bit more about screening tests that exist and who gets them? So I've colour coded this slide. There are some screening tests, which everybody gets, they are applied to the whole population and one of those is with new-born babies. So those of you who have had new-born babies in hospital you know that somebody comes in and wiggles their hips around and they prick their heel to get a blood test. Why do they do that? Because those tests are very, very helpful; if you wiggle the baby's hips around and find that they've got a hip problem from birth you can do something about that and your baby will be able to walk just fine. If you didn't do that test at birth you would miss something very important and that would be bad for the baby. So this is a test that everybody should have. We are happy with that, everybody should have that test.

So in the red are tests in people who have had something bad happen to them. So they've already had a clinical event. So my example here is having your cholesterol taken after you've had a heart attack. If you go into hospital with a heart attack now you are a patient, now you are a person with a heart problem, so of course everybody wants to make your chances of being well in the future good. So they are going to do all sorts of tests. They are going to do cholesterol, they are going to do glucose, they are going to do blood pressure and it's quite right that they should do them.

The week before or when you hadn't had a heart attack, maybe nobody was interested in what your cholesterol was. But now something has happened to you it becomes important. So that is the second type of test. A test you do when something has happened to a person.

And then the third type of test is a test, which you don't give to everybody, but you also don't wait until something has happened. You do it on the law of probabilities. You say that this particular person or group of people has a high risk of this happening to them so we'd like to find out whether they have the test before that thing happens to them. So an example of that is blood pressure in people who are above a certain age.

So I think in many parts of the country when you are over 50 you get a letter from your doctor inviting you for a check up where they will do your blood pressure and cholesterol. Why didn't they do it when you were 49? Why did they wait till you were 50? Because the risks that they've worked out become higher above a certain age so above that age it's worth doing the test because it will make a difference. So those are the three sorts of tests.

And the same is true of some cancer screening in people who have a very, very strong family history. You wouldn't do that for everybody but if they are at very high risk because of their family then you would do it. So those are the three types of test. So now let's use that colour code for the Antiphospholipid tests. So we don't want to do those on everybody and I hope I have made that, I have explained that sufficiently when I talked about the false positives. If you did them on everybody you would probably harm more people than you would help because many, many people would be worried unnecessarily because we just don't know what is going to happen to people who are positive at the test. Some of them will get APS but many of them won't.

So here's the red areas, now you would think the red would be quite clear. The people who have had something bad happen to them. Well why wouldn't you want to test those people? So let's look at this. There are people who have thrombosis like deep vein thrombosis or pulmonary embolisms; so you might say, yes, we should test those people. But it depends what sort of thrombosis it was. Was it a very tiny thrombosis just affecting a small area of somebody's calve that went away over a couple of days? Is it worth testing that person? Well I don't know. If it's a very big thrombosis or it's multiple thromboses then it's worth testing. But you can see it's a grey area, it is not as clear as you think.

What about stroke? So if it's an 85-year-old person with a stroke, well lots of 85 year old people have strokes. Maybe if you tested you won't be doing them a favour. Maybe that is not the right thing to do. But if it's a 30-year-old with a stroke or a child with a stroke, which sometimes happens, then clearly something is seriously wrong and you should do the test.

And what about miscarriages? So Hannah talked about miscarriage and she talked about numbers. So just to pick one thing from her slides, she talked about three consecutive miscarriages. So the actual criteria for this syndrome say you should have three consecutive early miscarriages in order to be considered for this syndrome. Well that's a pretty mean thing isn't it? If you are somebody who has had two, do you have to earn your way to the test by having a third? Does that make any sense? Not really but it's a grey area again. So there are all these grey areas.

So that's the red. You'd think it was easy but it's not always as easy as you think to decide who should get tested. And lastly the blue, the people who haven't had any clots, who haven't had any miscarriages but you think they might be at risk. For example people with lupus, Graham's slide showed that a proportion of people with lupus go on to have APS and certainly in our lupus clinic it is standard practice that everybody gets tested.

Migraine, well that's another grey area; some people with migraine get APS, many people don't. Should we test all people with migraine? Would we make people worried unnecessarily? It's a tricky one. So to put all this in a sort of pictorial way, this diagram, the big circle around the outside represents everybody. We are all in the big circle. The white area of the big circle represents people who we are absolutely sure we shouldn't do the test. There is no need to do it. It's not good to do it. So I put myself in the white area. I am not going to have an Antiphospholipid test. I don't need one, I don't want one, it's no good to me. Neither am I going to ask any of my family to have it because none of us have any reason, any clinical reasons to have the test.

But to give you a contrast, I've never had the Antiphospholipid test but I did once have a Lupus test. I had a test which is called antinuclear antibody and that is a test, which is done in people with, who might

have a reason to suspect lupus. So why did I have it? Because I had a skin rash, which turned out to be nothing very exciting, just an allergy, and I went to see a skin doctor and he sent me for the test. Maybe he sent me for the test because he knew who I was and said, "Oh, I'd better test him because otherwise he'll be cross." But anyway he did.

So I went for the test; I thought, I haven't – I'm not going to have this. Lupus is really uncommon in men, I don't have any symptoms of lupus, I don't know why I'm having this? But the doctor told me to have it, so I had it, I had the test but I remember at the moment when I was opening the document with the results of the test, in the full expectation that it would be all fine, I thought, well what if it's positive? What am I going to think about that? I know I haven't got lupus, I know, I've got specialist knowledge. And yet still in my mind I was thinking, well how will this change my life if it's positive? Will I be worried every day if I get a bit of aching or joint pain? Will I avoid the sun? You know it can do things to your mind this idea that you have a test and the test is positive. So you really have to be careful.

So the white area is people who definitely don't need the test. The red circle, the small dark red circle in the middle is the people who definitely do need to have the test. You are absolutely clear. So these are the people for example who have had several thromboses one after the other, this is the child with a stroke. This is the person who has had five miscarriages one after the other, those people, there is no doubt about it, they need the test. So what about the pink area in between? The pink area in between is the people in whom we are just not sure. We are not sure whether it is worth testing those people or not? We don't know whether it will be good for them?

And where we want to go is to here, sorry, there. We want it to look like that. We want the big red area in the middle, the one where we know the test is useful, to be much bigger and the pink area to be much smaller. We want there to be less uncertainty.

So how are we going to get from here to there? And the main way is probably going to be developing new tests. So what tests do we have at the moment? So the current tests that we have are the anticardiolipin test, the anti beta two glycoprotein 1 test and the lupus anti glycolyn test, which Graham told you about. What is wrong with them? Nothing up to an extent but they are not perfect as I told you. If you have them all done and if more than one is positive, particularly if all three are positive then that increases your risk. It tells you something a bit more, okay, but it's not perfect. So how can we change the balance? How can we make that red circle bigger by doing better tests?

So remember the ideal is a test I can do and I can say, "Right, this is 100% this test. If you are positive in this test you are going to have APS, if you are negative in this test you are never going to have APS." That is my dream. That's the test I want. It doesn't exist, not now. However the good news is there are lots of people all over the world trying out new tests. I've listed some on this slide: anti domain 1, which I am going to talk about in a minute. Anti PSPT, this is a bit like cardiolipin; anti annexin, which is something which sits on the walls of cells; IGA, which if you look at the left side of my slide it says IGG and IGM, those are two sorts of antibodies. IGA is a different sort of antibody and there are even others.

So what's this? Where am I going with this? Where I am going is that in ten or twenty years time when my daughter is practicing I don't think there will just be these three tests; I think there will be a basket of tests that people can do and the combination of all those tests will then enable us to be much more clear about a person's risk. That is what I think is going to happen.

So now let's move on to – oh, summary of tests, yes. Combinations of new tests could help have greater certainty but how are we going to know? How are we going to know that combination is good? There is only one way to know and the way to know is to do the combination in really, really large populations of patients, thousands of patients, so you can really be sure what the test means. Okay and an example of that is the use of cholesterol to predict heart attacks and the use of bone density scans to see if people

have osteoporosis. The reasons we are sure those are good tests is because they have been tested in thousands and thousands of people and that is what we as a community of APS doctors need to achieve. And it can only be done internationally; no one country can do it by itself.

So now turning to treatment; so this is a bit like Graham's slide – Warfarin, aspirin, Heparin and I've added hydroxychloroquine, which Hannah mentioned with the Hypatia studies. So these are things that can be used at the moment. So what do we need, how do we want things to improve, what treatments do we want? We want things that are at least as effective as Warfarin and Heparin. We want the things that can be used long-term in asymptomatic patients. And this is something I want to stress. Most patients with APS feel well quite a lot of the time so what we are treating them for is to prevent them from having something. We are giving them drugs every day to stop them having a thrombosis or a stroke or a miscarriage; so most of the days of their life that they are taking their drug it is making no difference to them except that it is preventing something; it is not making them feel better. And that means if I design a drug that has terrible side effects, makes you have diarrhoea every day and I say, "Do take this. It doesn't matter if you are going to the toilet twenty times a day because it is stopping you having a stroke." Well you are not going to take it are you because the price is too high? It's got to be something that has few side effects.

So that's the next bit, side effects. So you have to have some targeted treatment and the thing about Warfarin and Heparin, good as they are, is that they are not targeted. All they are doing is that they are repressing clotting altogether. So similarly is if you've got a society where you've got a very small proportion of people running around causing mayhem, damaging stuff and you want to stop them. One way is to put police and tanks on every corner so you repress everything; so you'll definitely stop that, but you will make life difficult for everybody else as well.

That's what Warfarin is like. Warfarin supresses all the clotting in your body and what you really want to do is just target those miscreants, those bad individuals, just take them out of the picture and then everybody else would be happy. So what I want is a drug, which will target just the problem in the Antiphospholipid syndrome. So this is a picture of the problem in the Antiphospholipid syndrome. This is a molecule called Beta Two Glycoprotein 1; we all have it all the time in our blood. Everybody has it; it's a normal thing to have and it doesn't do harm to most people. Now the Antiphospholipid antibody, which I've shown in the blue at the top, attaches itself to one end of Beta Two Glycoprotein 1. This is how it causes problems. The end that it attaches to is called domain 1 and the other end, the end at the bottom, the hook, is called domain 5.

So what happens next is that the antibody attaches to the domain 1 and because the antibody has two arms it can link two of these Beta Two GP1 molecules forming a sort of tripod arrangement and that tripod arrangement is the thing that causes the problems in the Antiphospholipid syndrome because it attaches itself to the surface of cells and those cells then react; receptors on the surface of the cells are stimulated and that causes the production of signalling inside the cell a change in the behaviour of the cell. That is what happens. That is how Antiphospholipid syndrome is caused.

So you can see from this diagram that there are lots of ways in which you could potentially block this. You could, for example, you could stop the antibodies binding here; you could stop the domain 5 binding here, you could stop the receptors from reacting and you could stop the signalling monitors. You could do all of those things. Is that pie in the sky? No, it's not pie in the sky because people have already tried it in mice. There is a mouse model of APS. Mice, which get something like APS and drugs, which block all those things have already been tried in mice and several drugs are being developed along these lines. We are developing one in my research group and at least one drug, which targets Antiphospholipid antibodies, called ((retoxilab ?)) is already being used in a trial, not with tremendous success I have to say, but it shows you what can be done.

So there's every chance actually that in the next twenty years new drugs will be available. I would put my, I was going to say my hat, but I watched Paddy Ashdown the other day, so I would put David's hat on the fact that there will be new treatments for the Antiphospholipid syndrome.

Okay, so we've got these new treatments, but how can we really be sure that these treatments work? And this is a tricky one. So the standard at the moment is Warfarin or Heparin; so if I want to invent a new drug and I want it to be used, I am going to have to persuade doctors at large and patients at large that my drug is better than Warfarin or Heparin. How am I going to persuade them? Currently I'm going to have to do a trial saying my drug stops clots even better than Warfarin. So if I have 1,000 people on my drug, fewer of those people are going to get clots than the people on Warfarin. Or if I have 1,000 pregnant women, more women on my drug will have a successful pregnancy than the women on Heparin and aspirin. That's what I have got to do. That is the standard

And the problem is the current treatments are pretty good. If I have 1,000 on Warfarin not many of them will actually get clots hopefully, so my drug has to be unbelievably good to prove that it's better. It might be better but how am I actually going to prove that it's better? And here's an example of how this works. You've heard about Riveroxaban from Beverley; this is trial that was done in Riveroxaban. This is nothing to do with the Antiphospholipid syndrome. This is another group of people who are prone to having clots, people who have had total hip replacements. So in this study they have said, "We want to prove that Riveroxaban is better than Warfarin for people who have had hip replacements."

And this is how they did it; they had a huge number of patients, more than 3,000 patients, and they divided them into two. Half of them the night before they had the hip replacements started the Riveroxaban, half of them started Warfarin, and it was continued for 36 days, okay? Now it was blinded and that means that neither the doctors nor the patients knew who was getting which drug. That is important to make sure it's fair. And at the end of it 1.1% of the Riveroxaban group had a clot or a pea or something like that and 3.6% of the other group, So look at the numbers, there was only 3.6% of the Warfarin group of those 1,500 patients had a problem. If they'd only tested a hundred patients, they would have had no way of being sure because you would have had four people in one group and one person in the other group and that could have just been a chance finding.

That's the difficulty with doing trials like this. So it's really hard to prove that new treatments are better. So how are we going to get out of this bind? Well there are several ways. You could do enormous trials with huge numbers of patients. The problem with that is there aren't huge numbers of patients; Antiphospholipid syndrome is not that common within our country. So to do it you would have to have a really big international study and not only would it be difficult, it would be enormously expensive to do it. It could be done but it would be difficult.

And also you have to think about the patients. Patients are signing up to something, if you are a patient and you've been absolutely fine for ten years on Warfarin and I come to you and say, "Well there's this new drug, why don't you try that?" You might say, "Okay, and if it goes wrong doctor what is going to happen?" "Well you might get a stroke then." And you'd say, "Well, you know, actually Warfarin is good. I don't think I want to go into the trial." So patients take more of a risk than doctors going into trials, especially if they are doing all right as well. And the corollary of that is often trials can only recruit the most difficult patients, the patients who can't be managed on the ordinary drugs, because those patients have an incentive to try something new.

So if you've got a patient who is having clot after clot after clot on Warfarin they might say, "Yes, I'll take your new drug." But that's the hardest patient to make better. So your new drug might fail because all the patients who signed up for it were the hardest patients to treat.

So what do I think could be done? Well I think there's a really big thing here and it's in red, all the things I've said to you completely ignore that APS causes other symptoms. APS is not just about thrombosis and miscarriage. Although some patients with APS feel well most of the time, many other patients with APS have symptoms like migraines and fatigue and joint pain and rash; so how do we know that our new treatment won't make those things better? Wouldn't it be sensible for us to measure whether there is an effect on those things as well, not just concentrate on the thrombosis?

And you can see that might be cleverer because somebody might not be – you might have two patients, one is on the new drug, one is on Warfarin, neither of them has a thrombosis but the person on the new drug says, but I feel great. I feel so much better. Neither of them have got a thrombosis. They won't show up in the sort of trials that I am talking about but they might show up if we looked at it in a different way and the thing at the moment is there isn't a way to measure that. We don't have a method to measure that in APS and I think it would be good if we could invent a way like that. And I think that is something that doctors and patients can do together because it can be a question of asking patients, "What is it that you would really like the new drug to do? What things would you like to feel better about? Of course you don't want to have a stroke or a clot, we understand that, that is taken as read, but what else?"

So, in summary, can we find a better way? Well clearly prevention of thrombosis will always be important and pregnancy loss as well; but can we improve other things like migraine, rash and joint pain? There is also a thing called health-related quality of life. So health-related quality of life means questionnaires where they ask you about your life and they talk about things, which have changed because of your health. Interestingly in the Riveroxaban study, which both I think Beverley and Hannah have talked about, this is quite a small study. As you heard nobody is allowed to tell you the results but actually I don't know the results so it doesn't really matter but the study was not designed in the first place to find the difference between the numbers of clots, it's too small, it hasn't got thousands of patients. But what is could find though is whether the quality of life is different? That's right, isn't it, Hannah? Because one of the things they are measuring is the quality of life; so it might be, I don't know, I don't know the results, but it might be that the people on Riveroxaban say, "Not only have I not had a clot but my quality of life is so much better. I don't have to keep turning up for these blood tests all the time." So it could be and I think we should try and measure quality of life.

And to finish I think perhaps doctors and patients together can find a better way to do APS trials so that in twenty years' time when hopefully my daughter is practising, she had more options. Thank you.

Chairperson

Thank you very much Anisur for your very clear talk. Your mention of having a rash reminds me of when I was young, I did for nearly twenty years general practice for three weeks every year and I remember a lady coming in with a rash and this lovely old GP that I worked with and I said to him, "What do you think of this rash?" And he said, "Oh it's either NM or SDSD." So I said, "Well what's that?" And he said, "Well NM is nothing much and SDSD is some dreadful skin disease!"

Anyway the last speaker before the break is my colleague David D'Cruz; I should tell you that David was Honoured at the British Society of Rheumatology last week giving the important Hebadon Round, which is a great honour and I gather was a huge success, congratulations.

Professor David D'Cruz

APS and the kidneys

Thank you very much indeed Graham, it is indeed a great honour to follow your footsteps; 32 years ago you have the Hebadon Round then and I followed in your footsteps because Graham, in that Hebadon lecture, was when he first presented patients with Lupus Antiphospholupid syndrome and so I did the same thing a couple of weeks ago. I presented three patients with Lupus Antiphospholupid syndrome.

Speaking of Anisur and rashes, I don't know if people know the story, we had a cat and the cat started limping. It didn't look too well so my wife took the cat to the vet and the vet looked at the cat and the vet said, "Mrs D'Cruz, your cat has got lupus." And so Yvette came home and said, "God he's got lupus!" I said, "What do you mean he's got lupus? What were the blood tests?" And she said, "No, no, he just looked at the paw and went, the cat's got lupus." And it was true the cat did have lupus, it had discoid lupus of the paw and I did a bit of research and it's true, cats, dogs and horses all get lupus but it was supremely ironic.

So my task is to talk about Antiphospholupid syndrome and the kidney; it is a subject that is not talked about too much in these sorts of meetings but as I think I will persuade you, it is highly relevant. So what do the kidneys do? Where are they? So the kidneys are in the abdomen, we've got two kidneys, and essentially what they do is that they get rid of your waste products in the urine. They tightly regulate your fluid balance, how much water you take in and get rid of. It controls blood pressure and the kidneys regulate the production of blood cells using the hormone called erythropoietin and it regulates acid base balance.

What happens when the kidneys fail? It is fairly disastrous, you have high blood pressure, you start leaking protein in the urine and because of the leakage of the protein you start retaining fluid and then you start to accumulate the waste products of the body, which we can measure in the blood and that tells us a lot about kidney function.

So we recognise that kidneys can be affected in lupus and they can certainly be affected in Hughes syndrome and in Antiphospholupid syndrome. Distinguishing between the two can be really, really difficult but it's really important because the treatment is completely different. So we know that in patients with lupus, this is an inflammatory condition, you have what are called immune complexes that settle in the filtering mechanism; these little round things are the filtering mechanisms that actually filter the blood and get rid of the waste products and keep the important aspects. But these become inflamed. These are very inflamed meralai and the treatment for this inflammation is immune suppression; corticosteroids, ((britansilone ?)) mycophenolate.

The kidney can also be affected in Hughes syndrome and Antiphospholupid syndrome but the mechanism is completely different. The mechanism in the kidney is blood clotting thrombosis or ischemia and the treatment is not steroids or immune suppression, exactly as Graham showed in the patient who was wrongly treated with steroids, the treatment is blood thinning and anticoagulation.

So I talked about blood pressure and we know that blood pressure can be a problem, indeed it was Graham in fact who first alluded to this in his Prosser White oration in 1983 when he, very sharply, observed that patients with this broken pattern of this corned beef appearance on the arms and the legs, called livedo reticularis. Graham noted in 1983 that patients who have this livedo reticularis often have blood pressure that is very difficult to control; it goes all over the place and that is one of the drivers for strokes, very high blood pressure.

He drew attention to this correlation and he said at that time, "This is something to do with the kidney." He didn't know then exactly what but there was clearly a correlation between the kidneys, livedo reticularis and high blood pressure. And it is now clear that one of the causes at least of high blood pressure is narrowed arteries to the kidney. We showed this in a study some years ago. We did this imaging study called MR Angiography and it is a magnetic study of the kidneys and we showed very clearly that this is the aorta, this is the main blood vessel, which is completely normal. This is the right kidney, this is the left kidney, and if you look carefully here you can see that artery is very tightly narrowed and when you have a narrowed artery to the kidney that reduces the blood flow to the kidney and the kidney then reacts when it sees reduced blood flow in the kidney it reacts by pushing the blood pressure up to try and get more blood into the kidney.

And that was just an artefact, you can see here, this is a proper arteriogram that confirmed that renal artery stenosis, in other words narrowed arteries to the kidney was a real phenomenon. And our guru, John Scoble, who is a nephrologist here is a national guru on this particular problem, the narrowed arteries to the kidney. We showed these pictures to John and he said this is unique, he's never seen this before. The usual cause of narrowed arteries in the kidney is atherosclerosis, hardening of the arteries and you see a very ragged appearance and then you see narrowed arteries there because of the blockage. The other one is called fibro muscular dysplasia, which is a sort of muscular problem. This is neither of those.

This is an almost unique picture that we see in Hughes syndrome and it is worth investigating I think in patients with Antiphospholupid syndrome who have got very difficult to control blood pressure. We have a level threshold for investigating these patients with this particular test.

Now how common is kidney involvement in Hughes syndrome? This is a very large study, it is a European-wide study organised by Richard Severa, the Euro-Antiphospholupid cohort, he's got a thousand patients across Europe. This is what he calls a registry study, so colleagues around Europe collect information on their patients and anonymously upload all this information to this registry so we can draw conclusions. And of these one thousand patients he found about 3% of patients had kidney involvement. Essentially the kidney involvement was due to blood clotting; clotting in the kidney, clotting in the arteries, clotting in the veins.

Now this is almost certainly an under-estimate because the way to make this diagnosis is to do a kidney biopsy and I'll come back to that. So Maria ((Tactinidu ?)) in Greece has drawn up some diagnostic classifications for us as doctors and kidney doctors and histopathologists and she said that if you do a biopsy you need to have some of these appearances and it's not important really but it's a way of characterising exactly how to differentiate blood clotting in the kidney from inflammation in the kidney from lupus.

So here was a patient, the usual story on a Friday afternoon I get a telephone call, "David, you've got to take this patient! She's got lupus, we've done a biopsy, she's really sick, she's coming in an ambulance." "Fine, send her over." She arrives in the ambulance and she is really very unwell; she is only 25, she's had lupus, she's had a kidney biopsy. Here's the left kidney and you can see the needle track of the kidney biopsy and what these big lumps are is a blood clot. So this patient has bled after having a kidney biopsy. They have not bled once, they have actually bled twice, you can see two areas where this patient has bled. So this was very serious and it's a recognised complication of kidney biopsies.

Well what does a kidney biopsy do? The reason you do a kidney biopsy is to get tissue to look down the microscope and differentiate lupus from clotting and that is why this young woman had a biopsy but she bled.

Now over the next few years I noticed that these patients were different. They had a very serious risk of complications after bleeding. So sadly we had one patient who died after a biopsy; we had two patients who lost their kidneys because the bleeding couldn't be stopped. They ended up having an operation to remove the kidney to stop the bleeding and save the patient's life and numerous other patients had bleeding that was very difficult to treat. They had to have what are called embolization procedures to stop the bleeding and they had blood transfusions.

So we looked at this. Natasha Jordan, who was my PhD student, she is now a consultant in Addenbrooke's, we just looked at this in all the patients we've had with renal biopsies. We looked at all 215 biopsies that we've had over the last ten years or so at this hospital and Natasha just simply divided this group of patients into three; those who had straightforward lupus and wanted to do a biopsy to find out how involved the kidneys were from the lupus? The other group of patients were lupus with antiphospholupid syndrome; so in other words these were lupus patients who had had a blood clot or that had had miscarriages or indeed both miscarriages and blood clots. And there was a third group of patients who had lupus and as Anisur and Graham have pointed out, these were patients who didn't have blood clots or thrombosis but they had the antibodies. They had persistently positive antibodies.

But they all underwent a renal biopsy because all these patients had abnormal kidney function; they had protein leaking or they had blood pressure, so there were very good reasons to do a kidney biopsy. So our simple question was, in these three groups of patients, was there a difference in the risk of bleeding after a biopsy. So here we are – I'll take you slowly through them. Green is no bleeding, blue is minor bleeding and red is major bleeding. Along the bottom here are the lupus patients; these are the lupus patients with antiphospholupid syndrome, clotting or miscarriages and these were the patients with the antibody alone but no clotting or miscarriages.

And you can see that very clearly there was an increased prevalence or risk of bleeding in these patients with lupus and antiphospholupid syndrome, much more than the straightforward lupus patients alone. So it confirmed our impressions that there was something different about these patients. Now it could be argued that this was a technical problem, you know, many of these patients were on Warfarin. Maybe we didn't stop the Warfarin in time, maybe we didn't follow the protocols and so we wanted to address this question and the biopsies at this hospital are done by the radiologists. So you take them down to the X-ray department, the skilled radiologist will do an ultrasound scan, find the kidney, put some anaesthetic in and then do the biopsy. But they will not do the biopsy until they've seen the clotting screen on the day of the biopsy. So in other words it is a very simple blood test, it tells you whether your blood is too thin. If the blood is too thin they will not do the biopsy.

And indeed we had all that information and you can see that at the time of the biopsy the clotting screens were all completely normal right across the board even though they had major bleeds or no bleeding there was no difference in the clotting screens. It was safe to do the biopsies from a technical point of view. So there was something different going on here.

So we then looked at the question, was there a difference in what we found on the biopsy? In other words was there something in the biopsy that was associated with the risk of bleeding? So the question was, and we had all this information, we had all the biopsy reports and for Natasha it was a very tedious project but Natasha read all 250 biopsy reports and then asked the question, was there a correlation between clotting in the kidney and bleeding? Now that sounds a bit counterintuitive but that is exactly what we found. So along the bottom here are patients who have had a major bleed, patients who have had a bit of bleeding and patients who have had no bleeding. And TMA essentially is clotting; so in other words the more clotting you had the more risk of bleeding you had.

Okay, it seems a bit counterintuitive but that is exactly what we found. So why was this? So here was a patient who, in fact I presented him at the Hebadon Round, he had a lot of biopsies and the last biopsy he was really very ill. He ended up having his kidney removed to stop the kidney bleeding and to save his life. So we had the whole kidney to analyse rather sadly but here's the tissue and here's the blood vessel from that kidney. What is different about this? The difference is that the vessel was very, very, very thick. Okay, what this technical terms means inter((mormedian ?)) fibrosis is that the vessel was very thick.

So my simple mind, I questioned this, so if I stick a needle in my kidney, in my blood vessel, it should vasoconstrict, it should clamp down and stop the bleeding. But if the vessel wall is very thick, you can imagine sticking a needle in here, the vessel is going to stay open. It is not going to clamp down and vasoconstrict and I thought that was possibly the reason why these patients were bleeding.

So we then asked that question. What was the prevalence of this thickening of the blood vessels in the kidney and was there a correlation with bleeding risk? So again, major bleeds, minor bleeds and no bleeding. The black is severe vessel thickening and once again you can see that those patients who had the severe vessel thickening were the ones most at risk of bleeding. So in other words, my thoughts were probably correct. We were sticking needles into blood vessels that were very stiff and weren't clamping down in the normal way and that was increasing the risk of bleeding.

So in fact this is supremely ironic, the very lesion you want to diagnose with a kidney biopsy is the one that gives you the greatest risk of bleeding. So we're in a big dilemma here because we are trying to diagnose clotting in the kidney but we are giving them the risk of bleeding and we need to know because the treatment is very different. It is not steroids, it is not immune suppressants, it is anticoagulation. So this is a really difficult problem.

Now this is an important paper from a French transplantation group published in a very important journal, The New England Journal of Medicine, last year and this was a group of kidney transplant specialists who had quite a good experience of transplanting patients with antiphospholupid syndrome. So these were patients who had essentially lost kidney function, they were on dialysis, they had a transplant and it was a big transplant unit. They had a whole bunch of normal transplants if you like, so these were patients who had lost kidney function through the usual causes, diabetes, high blood pressure and other causes of kidney failure who had undergone a transplant and then they had patients in the green and the orange, these were the antiphospholupid syndrome patients who had had kidney failure and then had a transplant.

By chance some of these patients received a drug called Sirolimus to protect them from rejecting the kidney and others didn't. And what was very striking here was that those patients who did not receive this particular drug, Sirolimus, lost their kidneys. So this was a great tragedy, you know, it took all the expense and the trouble of transplanting a patient with a new kidney and they've lost the kidney. So there is something again very different about these patients.

What was different about them? One of the things about kidney transplants is that the transplant doctors really want to know what is happening in the kidney after a transplant. So they do regular kidney biopsies on these patients just to make sure there is no rejection or ischemia or other medical problems and so here is a representative sample from an ordinary patient who had a transplant, for example for diabetes or high blood pressure, and it looks pretty normal. And here is a patient with antiphospholupid syndrome with a new kidney, who had this drug, Sirolimus and here is an antiphospholupid syndrome kidney who did not. And again you can see here that the vessels are really, really thick. This phenomenon of interval hypoplasia was seen and it was very striking.

And so again this is the same problem, stiff or thick vessels cause a risk of bleeding and it also increases the risk of losing your kidney transplant. So what they then went on to show, and the details aren't important, but what they did show was that this drug protects you from developing stiff blood vessels in a very elegant series of laboratory investigations. So we learnt quite a lot about this. We know quite a lot about the mechanisms and Anisur is one of the leaders of the field here in understanding the mechanisms of thrombosis. So we know a lot about how clotting occurs with the lining cells of the blood vessels becoming activated, these monocytes starting to produce stickiness, platelets being more activates and complement activates as Hannah mentioned.

But this opens up a whole new pathway here, this particular pathway here is the pathway that is blocked by those drugs. So one day, as Anisur pointed out, maybe one day one option might be to consider this drug or something like it to prevent the stiffening that we see in the blood vessels.

So what are the messages that we learnt because this was a long and hard and quite a difficult learning experience but what are the messages that we learnt. We learnt that if you've got a patient with lupus and you want to do a biopsy, if the patient has not had their antiphospholupid antibodies tested they should be tested. If they are positive and certainly if they are on Warfarin, then you need to be careful but we are now thinking very, very carefully before doing a biopsy in these patients because the risk of bleeding is so very high we're sometimes not doing the biopsy at all. We're just going to say, "We are going to treat you for both. We are going to treat you with steroids and immunosuppressants for lupus. There is pretty good evidence that there is clotting in the kidney so we are just going to anticoagulate you because the risks of anticoagulating somebody are less than the risks of bleeding after a biopsy." But this is a really, really difficult area and it requires consultation with our kidney specialists and ourselves on a weekly basis.

So thank you very much for your attention and thank you for inviting me.

Chairperson

Thank you very much David and congratulations, very much leading this field. Well it's time for a break, I've enjoyed this morning and thank you to the speakers and we go out for a cup of tea I think for fifteen minutes is it? Thanks a lot.

S E S S I O N T W O

Professor Graham Hughes

I'm delighted to welcome Diane Eaton from Anticoagulation Europe, important for all, well almost all of you, in the audience and we're going to talk about INR and self-testing. I'm sure there'll be questions about this. Can I just remind you of two things, Kate's asked me to say if you could fill in the form, I think there's an assessment form, and I think it's like British Airways, I think you have to say 'do you think this meeting is either wonderful or superb'. Anyway, Diane, welcome.

Diane Eaton – Anticoagulation Europe

INR and self-testing

Good afternoon everybody. I'd just like to start by saying that, well thank you very much to the Hughes Society for inviting us to speak today as representing Anticoagulation Europe, but also as a patient on anticoagulation. So I'm going to take you through a very swift journey about my personal experiences of warfarin. I will say at this stage I do have a clotting disorder but it is not APS, it's called antithrombin deficiency, but it's quite unusual and you'll hear a little bit more about that as we go along.

So, a little bit about ACE first. We're a charity like the Hughes Syndrome and we're dedicated to supporting patients who are on any form of anticoagulation or antiplatelet therapy. We also provide information, education support to patients, and we have a dedicated helpline as well.

Very much like other charities we aim to heighten awareness of VTE and for those already on medication to help support them and we are striving to create a first class service for anticoagulation.

We do a lot of collaborative work with other medical professionals, with charity, with industry and with government. We're members of the ASMA which is the Anticoagulation Self-Monitoring Alliance and this organisation was set up in 2012 to promote and stimulate awareness of self-monitoring for warfarinised patients and we're campaigning continuously to ensure that we can try and get the monitors on prescription for patients and to raise awareness of the opportunities of self-testing.

We provide patient expert opinion, or perspective, to NICE and were involved in the recent guidelines for the coagulometers for testing INR. And I'm very pleased to say that we were very, very active and successful in campaigning to get the strips for the machines, the devices, onto prescription a few years back. So that's a little bit of an overview about ACE.

So this is me, obviously not yesterday or today, but back in, well, when I was 15 years old and this is actually one of my school photos as I was just about to go into the sixth form. And my story starts with the day that I came off a hockey field with a big lumpy leg and I wondered what had happened, and that situation landed me in hospital, I was in hospital for just under three weeks with people scratching their heads wondering why a young girl, healthy and fit, had developed a clot in the leg.

So from there, it was a really profound moment for me because I was young, I was healthy, I was enjoying life, I was just about to come up to do my O-levels, and many of you may not know what O-levels are but if you do it was a really difficult time for me in terms of my education. And the outcome of that was that I'd been diagnosed with having a clotting disorder called antithrombin deficiency, it was formerly known as antithrombin deficiency III.

So I was told that I would be on lifelong warfarin, that it was a condition whereby I was going to be at a much higher risk of having blood clots and if I didn't take my anticoagulation treatment then I was going to be putting myself at risk. So a pretty scary time.

So the consequences of having this was first of all those words, you have a chronic disease or disorder, not something you want to hear when you're, well at any time in your life. I was told there was only warfarin available and so that was it, I just had to get into regular monitoring etc. I was told there was risk of further VTE and that it was a genetic disorder, and that there was a 50/50 chance of if I ever had children in the future that the child may be affected.

I was also advised by my consultant at the time not to have children, and I think this was because they didn't have enough research or perhaps some guidelines all those years ago, back in the early '80s, on how to manage someone with this condition.

So along with sort of being very anxious about what was going to happen to my education, my future career, my life, what was going to happen, was I going to have to change plans, and my general health and wellbeing and whether or not someone was going to want to be with me if I had a sort of a bit of a problem. So this really at that time, and I'm condensing very much here, I felt I didn't want to be perceived as being an ill person.

So what happened from thereon? Well, I spent 25 years in anticoagulation clinics for monitoring and dosing, and some of these clinic settings were at the hospital or at the community setting, either a GP surgery or another clinic. And I did a little quick sum a few years ago, just to say that I'd actually spent around six months of my life sitting in these clinics. However, I do add the caveat that I'm glad those clinics were there because they were looking after me.

The impact on the work setting. I didn't actually go to university, I did all my professional training when I got into the workplace, and I didn't go to university, simply because I was frightened of leaving the clinic that I was attached to at that time, and I think that's really important, because for some people they may be making decisions, younger people making decisions, and I'm really glad now that there is so much support out there to help people actually just have this sort of seamless approach into furthering their education.

I was very lucky, I had very sympathetic employers who understood that I had to go for these tests and they gave me time off to do that, but I worked in central London and I was travelling to Harrow to have my blood tests, so usually the clinics were at two o'clock in the afternoon and I was going after lunch and not being able to go back to work and I dreaded if I got a recall the week after because obviously that meant I was going to have to take some more time off.

So, white coat syndrome, I describe as most of us know, is when you walk into a clinical setting you might be absolutely fine, you might be feeling great but something there just gives you that gentle probe, oops, you've got a little bit of a problem here that you're managing.

I talk about the yellow book syndrome because I used to be quite fearful of that dropping on the doormat and have I got a passport for a couple of weeks where I don't have to go back to clinic. So two syndromes there.

And with warfarin when I certainly was diagnosed with my condition and told to go on warfarin I wasn't given any positive information at all, it was all a list of nos: don't drink, don't change your diet, don't eat too many vegetables. And as time grew it became that I seemed to be challenging all the time - well hold on a minute, I've got to really make sure that I can adjust my life or certainly adjust my warfarin to suit my lifestyle as well.

It all changed, a very nice sunny holiday picture here, in 1998, having been on warfarin for all those years, I went on holiday with my family, we went abroad, and I wasn't very well, I was quite poorly, and I started to feel quite ill, and I started to for the first time ever in my life notice that there was blood in my urine.

As soon as I got back home I went to my GP and explained what had happened and the GP said, well you need another INR test very, very quickly.

Within several hours I had the phone call to tell me to go to the hospital immediately because I needed to have a reversal. I normally average about 2.5 or certainly between two and three, and I'd gone up to ten, so I was experiencing some real problems there. And that's when I felt very, very concerned and worried about, well is this the start now of the sort of decline in my health.

I'm naturally quite an assertive person so when I'd taken my deep breath I decided to have a chat with my anticoagulation nurse at the hospital and she actually introduced me, surreptitiously pulled out a leaflet and said, "you might want to read this", and it was about one of the devices for self-testing which I had no knowledge of at all, it wasn't advertised anywhere, and this was sort of on the borders of the time when the internet was just starting to launch.

So I looked at it and said this is fantastic, I want to get one, and I literally phoned up the manufacturer, and I know this is very sort of unorthodox, but this is what it was like all those years ago, I phoned the manufacturer up and said, "please, please, I want one of these machines, and I want it now". And they said, "well hold on a minute, we need to have a chat with you about what it does etc", and we did the deal in the hospital over a cup of coffee and I went away with my machine, my device.

At that time the strips weren't on prescription so I had to buy the strips but I was so determined to have something that would give me the reassurance that I could look after my own INR without the implications of not being able to go on holiday or travel or do anything again. And what was fantastic, and I always call this particular nurse my guardian angel because she saw that fear in my face when I had that reading of ten, she chose to give me that piece of paper to tell me about the device, knowing that I would act responsibly and I would liaise with them and that's what I did. And for about three or four months I was having venous sampling and also having the self-testing, the results, and away I went. So for several years I was just literally phoning in my results and I was being dosed over the phone which worked absolutely brilliantly for me.

This slide's got a lot of information on so I'm going to just go through it very quickly, but I'm assuming there's lots of people in this room that actually know what the device looks like and have some knowledge about self-testing. What I would say is that after I've spoken and if anyone wants to see or ask me any questions please do at the end of the sessions today. The results come up on a screen, it's very easy to operate, I've also got another member of my family, my son who's got the same condition, he's been self-testing since he had a DVT and a PE when he was 19 years old.

So we get the result, we enter it in our record book and I'm very privileged along with my son to now be able to self-manage our dosing, so we're entrusted to actually be able to adjust our dosing slightly if we need to and we have parameters to do that so it's not just like well, finger in the air, I think I'll do this, there are parameters and we have to obviously make sure our healthcare professionals know what we're doing there.

So we're updating our own personal records, I'm actually using an app as well now which is great and I'll explain that a bit later to you. I appreciate that some people like me are very lucky that I'm pretty stable, my son's pretty stable, but obviously people with APS may not be as stable as someone like myself so that can be a problem. And also I know from reading from your website, from Hughes Syndrome website, that, and what's been spoken earlier today, is that there are some people that might need to have a different test, the LA test, and will have to, as Beverley was explaining, run in conjunction if they're deciding to self-test with having venous samples to see how the readings will correlate together.

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So just coming to what I currently do at the moment in terms of updating, I'm managed by my GP, I moved to an area whereby I had to introduce my own GP into self-management or self-monitoring at the time because they didn't have anybody in the practice that was doing it and they run their own anticoagulation clinic as well.

What we do is we arrange for me to attend twice-yearly and I have my device and the practice device and we do the test at the same time and that's the QA there that's covered, they're happy and I'm happy obviously because I want to make sure that I'm keeping in range.

My repeat prescriptions, we've got a sort of little system going whereby I don't want to keep phoning in with my results to the specialist nurse, what I do is every time I put a prescription request in I write my latest INR result and the date on the prescription so it can be uploaded then into the practice system. And of course I've got my yellow book and I have an app which my family and most of my friends know to look for if they need to.

What's really, really helpful and we have lots of people at ACE that find this invaluable in terms of self-testing is that when I go to my dentist which I attend very regularly I can do my INR test the day before or even on that morning and I've got a result there. And also when I've ever been to have chiropody treatment or I'm currently having a little bit of physio, my physio can then be updated as well, so they've got a real clear picture of where I am at that particular moment.

And I also remind locum doctors if I ever see a locum doctor at my GP that I'm on warfarin and that I'm self-testing and self-managing, simply because some of the newer GPs coming through may not be familiar or may not have encountered someone who's actually able to do that, so I'm spreading the word as such.

So very briefly, the value added here, you can see I'm a real advocate, it works for me, it works for a member of my family and I've actually got other members of the family that are going down this route, including a young child who's being self-tested by his mother, gives me personal control, that's really important, I like to just get on with my life, do what I can do, and that certainly does do that.

I have learnt so much about my condition and how to manage it because I have awareness of my body, of my diet, when I feel unwell, and so this is really, really helpful to me. It's given me peace of mind for myself and my family, including my husband and my kids as well and again, flexibility's really key here. There's no restrictions, I'm very fortunate that my GP is happy to prescribe my strips, I never have a problem with that and I hope that continues for the future because we are hearing that some people are being denied now or certainly restricted as to the strips.

I love the clinics, they're wonderful, you meet lovely people in there, but I don't want to spend time in the clinics if I can avoid, I've got other things to do in that time. And it makes me feel as if I'm normal, I am normal, but I've got this sort of underlying little problem and I want to be normal in my own mind.

We mentioned about the family there, so just bringing this up to what you should do, if you're thinking about self-testing as well, I might have inspired you, some people may already be doing it, some people will say I never want to do this, I'm quite happy to go to the clinic setting, but if there's any of you that's had a bit of a eureka moment here please speak to your healthcare professional before you do anything, it is absolutely important or vital that you get their buy-in and you also have an understanding with them, or they do, of why you want to do it and what you're going to achieve from that, because it's not just well I'm going to go off and do it and give them my results, it's far more complex than that in terms of process.

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The machines at the moment are not on prescription, we've been fortunate enough to get them through NICE guidelines, diagnostic guidelines, back in September. The indications are for atrial fibrillation and heart valve disease. Now the challenges there are that they did not extend to every person who takes warfarin for any other disorder or disease which we did protest loudly about. So the machines have been proven to do the job as such, the challenges can also be that at local levels your clinical commissioning groups, the CCGs, may not embrace self-testing or self-monitoring for patients, they may only have one particular protocol or process for actually getting people's INRs tested. And so if you're really interested and if you want to pursue this then do come and speak to me or get in contact with the Hughes Syndrome, the simple reason is because you've got so much information on the actual website there which will help you gain a great understanding about the condition.

So I hope I haven't gone over time but thank you very much for listening and it's been a pleasure to be invited to speak here today. Thank you.

Professor Graham Hughes

Thank you very much indeed. It's a great pleasure to welcome our next speaker, Sofia Georgopoulou, who's going to tell us about exercise in this scenario. Welcome.

Sofia Georgopoulou

Exercise participation in people with APS

Thank you, Professor Hughes, and thank you everybody for attending the national patient day.

For those of you who know me I'm not Karen Hambly and for those of you who don't know me you can suspect I'm not Karen Hambly, but Karen sends her sincere apologies, she couldn't be here today to present her research. I would like to ask you to bear with me if I can't answer many questions if there are questions in the end, because I'm not very familiar with the studies, Karen's study, and I've contributed very little towards the end of it. But I'll try to do my best.

So, Karen's study is about exercise participation in people who have antiphospholipid or Hughes Syndrome. Now, the aim was to look at patterns, how much exercise or physical activity people with APS do undertake, and in order to do that an online study was carried out to see how frequently people with APS engaged in physical activity and then look at something called self-efficacy and all those perceptions and how those things relate to people who take regular versus irregular exercise.

So as you probably all know, exercise, or physical activity, is a good thing and the more exercise you do the greater the health benefit you get out of it; there is a dose response curve as it is called. And people who have chronic illnesses and also in autoimmune conditions physical activity levels tend to be lower compared to the population that doesn't have APS or any other chronic illnesses.

Now, a little bit about people who responded to the study, as I said before it was an online study and there were different sections to the questionnaires. There was a link forwarded by Kate, the Hughes Syndrome Foundation manager to all the people who are members of the Hughes Syndrome Foundation and have been diagnosed with APS. It was self-reports, 268 of you responded to the questionnaires, the average age was 47 years and people were on average nine years post diagnosis. However, 60% of people had symptoms for more than ten years, 85% were female and 59% had primary APS. So it's more or less typical of what you would find if you did a study like that.

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A little breakdown of the frequency of physical activity in patients with APS in the people who responded. So as you can see, three times a week or more we've got a black column which signifies all participants, the one in the stripes is primary APS and the ones in the dotted column are secondary APS patients, and as you can see about 31% to 32% engage in physical activity three times a week or more.

So no significant difference there between the groups, but when it comes to once or twice weekly we can see that primary APS patients tend to get more exercise once to twice weekly compared to secondary APS patients. So it seems to drop. Once, twice monthly, the same, there doesn't seem to be a great difference, people tend to be inactive with no regular exercise, that's about 5% and as you can see there is no significant difference between the groups there either, however when it comes to being inactive due to limitations posed by APS and other conditions you can see secondary APS patients tend to be quite inactive and that difference is quite significant compared to primary APS patients, probably because they have comorbidities of the conditions that impose an extra burden on them.

And there's always a group who didn't know or didn't want to answer the question, importantly gender and age was checked and there was no significant difference between as to those two variables, although people who were engaged in a regular activity tended to be a bit younger than the others, but not significantly.

Now, because I'm a health psychologist I work at the academic Department of Rheumatology here at Kings I can tell you a little bit more about self-efficacy and illness perceptions because that's sort of my field. So self-efficacy is the degree of confidence people have in their ability to achieve certain goals or aims they've set in their lives, and that can be general so it could be anything relating to your work or to your personal life, or it could be more specific such as chronic disease, self-efficacy, so the degree you feel confident you can self-manage your condition effectively. And one of the sub groups in that domain is exercise self-efficacy. So how confident people believe they are in their ability to engage in physical activity once they have a physical activity regimen drawn up for themselves.

So questions asked in the study were how confident are you that you can do gentle exercises for muscle strength and flexibility three to four times per week and do aerobic exercise such as walking, swimming or bicycling three to four times a week, and exercise without making symptoms worse. And people had to respond on a scale from one to ten, one being not confident at all to ten being very confident to those questions. So the higher the score the more confident people tend to be that they can actually engage in physical activity without making symptoms worse.

So some analysis on that issue. You can see people are split, there is a total sample of people and regular exercisers and irregular or non exercisers, and you see that chronic disease, self-efficacy, is much stronger in people who take regular exercise, 7.10, compared to irregular and non exercisers which is 4.42. So that means people who tend to take more regular exercise have stronger confidence in their belief in their ability to do so. And when they looked at whether exercise self-efficacy was different in people with primary versus secondary APS there didn't seem to be any statistically significant difference, which means APS, whether you had primary or secondary wasn't really a factor in engaging in physical activity.

Now, illness perceptions, that's a concept ((?)) from health psychology again, so when you get diagnosed with a condition you tend to develop certain beliefs about your condition, based on which you try to manage that condition and develop certain behaviours. Now, these perceptions are formed from information you get from any source, from your healthcare professional, from the internet, from people who have the same problem or from previous experience of this condition, and then all of this information gets filtered through and processed in your head and then you come up with these beliefs that go along nine domains.

So you process information and think about things on a cognitive and emotional level and illness perception, the good news is that illness perceptions are modifiable, the bad news is that it doesn't

always translate to changing the behaviour, so you might change your mind about something but that doesn't necessarily mean you're going to act upon it.

So a little example to make it a bit more salient. You have certain symptoms like headaches or dizziness and you attribute that to your APS, so the more symptoms you tend to attribute to your APS, that's causes ((?)) a stronger identity, so the more symptoms you attribute to that. Or the degree to which you think APS impacts on your life, that's again consequences, so the stronger the consequences the more significant the impact you think APS has on your life. It will all make sense in the next slide. So you can see the nine dimensions, these are all the illness perceptions, eight of them actually, and they were compared in people who took regular exercise versus irregular or non exercise.

As you can see the perceptions are significantly different between the groups. So people who tended to exercise regularly had less strong consequences so they believed that APS wasn't really significantly interfering in their lives. They had stronger personal control so they felt that they could do more things to control symptoms of their APS and they had weaker illness identities so they tended to attribute fewer symptoms to their APS and all these three were significantly different compared to people who took the regular amount of exercise.

So we went through that and then a bit of a breakdown to see how APS and its perceptions relate to people with lupus, type II diabetes and COPD. So they differ because illness perceptions are a big thing in chronic illness, there are similarities, but it doesn't mean that they're all the same, depending on the symptoms associated with the condition you get small differences. So as you can see for example APS patients and lupus patients think of their condition having more or less a similar impact on their lives while people with type II diabetes and COPD tend to think less so.

There were a few additional questions included in the study so people were asked whether they would like to increase the amount of physical activity or exercise they do and an astonishing 82% said they would like to increase physical activity, 14% said no and 6% were sort of in the unsure, I don't know region.

When asked how motivated they were to undertake physical activity 71% felt motivated or very motivated to do so with 18% being sort of in the middle of knowing and 12% feeling very demotivated, so you get quite huge numbers interested in increasing their physical activity, people are not against that, I think they just need to be shown the way.

And the third and last question was whether any of your doctors or healthcare professionals suggested participation in physical activity would help with your APS and only about a third of people had got that recommendation from their healthcare professionals while 60% hadn't really been told anything about physical activity being good for their APS, 7% weren't sure and 2% didn't really answer the question.

So you can see people are quite open to the idea of increasing their physical activity, it's probably a matter of getting more information, what they should be careful about and whether it would be good for their APS or not.

Now the questions that derive from this study are there's clearly an association between self-efficacy and illness perceptions in people who exercise regularly and not regularly, so people who have stronger confidence in their ability to do so tend to do more exercise and it's also associated with people who tend to think that APS is not really that big a factor in whatever they want to do in their lives.

So there is a dilemma, could we increase exercise self-efficacy and would that lead to people taking exercise or maybe should we target exercise in order to modify people's self-efficacy and beliefs. So usually in psychology you tend to go for the behaviour because that's easier to change, and once people engage in an activity they can see how it impacts their body and their disease and then that might change their beliefs regarding that.

In order to do that they need to look at barriers, so what prevents people from doing physical activity,

are they worried about their INR, about haemorrhaging, are they worried about making the symptoms worse, and of course facilitators want to make it easier for them to do so. So further research is needed. Now, as in every study in research you have a few biases and a few limitations, so most of the people who participated in the study were British and they were female and they were members of the Hughes Syndrome Foundation, that sort of limits generalisability of the results, they're not really a representative sample of all APS patients.

It was self-reported so there was no clinical data to confirm that people had APS and what sort of APS they had, whether it was symbiotic, obstetric and so on. And only one measure of physical activity was used so we could have asked more information about what sort of activity they were engaged in, how long for, things like that, and of course because of the nature of the design of the study it was cross sectional, which means you look at a specific thing across people at a certain time which could be different if you looked at that two months down the line. So you can't really say what caused what, you can just say there is a relationship between these variables.

And conclusions, it was probably the first study to examine associations between self-efficacy, exercise self-efficacy and perceptions and the frequency of participation and exercise in people with APS. Finding this association means we need more research and we've got something, it's not ground breaking but it's a first step towards doing more research and seeing how we can increase physical activity in people with APS. So thank you very much for your attention, if you have any questions Karen is very happy to answer emails. Thank you.

Professor Graham Hughes

Thank you very much Sofia. Our last speaker is going to talk about fatigue and you're very welcome, Karen.

Karen Smith

How to manage fatigue

Good afternoon. I find it interesting that fatigue is the last thing on the menu today, and I'm sure that you're desperate to get on with the questions and answers because there's been so many interesting presenters today but if you could just bear with me I'll hope that you'll appreciate that this is quite a practical session and that at the end of it you may take away just a few suggestions that you can try at home. You'll find that a lot of material that I have is in the back of your programme for today, so if you could just enjoy the presentation, maybe be impressed by my PowerPoint and maybe go away and think about some of the things I'm going to talk to you about today.

So I'm Karen Smith, I'm an occupational therapist, I have specialised in working with people with neurological conditions, oh, for a number of years and I've come today because I know people who are part of the Hughes Foundation and they tapped me on the shoulder and said can you come and do your bit, so I'm here this afternoon.

You may wonder what an occupational therapist actually has to do with people living with conditions such as your own, and I thought I might just tell you what occupational therapists do in case you've never met one, and you know, let's hope that you continue to live well and don't need to see people like me for a while.

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So I use people's activities that they perform every day that change when they become unwell as a consequence of illness or injury and I use activities in the context of their personal care or their leisure pursuits or even their work occupations and I look at what inhibits them, what gets in the way of them being independent or what gets in the way of a recovery. So I have an all-inclusive view of things, I look at the person, I look at their environment and I look at the tasks that they need to do in their daily lives. And then I use problem solving methods to look at limiting the obstacles in everyday life in order to maximise their potential, their abilities, and their potential to be as independent as possible.

Obstacles may be physical or mental but they can also be social and environmental, and they occur as a consequence of illness, injury or disability. So my role is to find ways to adapt tasks and introduce strategies that allow daily routines to be carried out in an effective and energy efficient way. So again I come back to the time of day and the fact that we're probably all feeling quite fatigued.

I thought I might talk about the challenges of time, I found this a little humorous when I was going through my material and someone's done this PowerPoint for me, so let's see if it works.

Those who are most active get most things done. Actually, this confuses activity with results; running around in a flurry usually accomplishes very little.

If I do it myself it'll be done faster and better than if anyone else does it. This actually results in the individual doing everything. Teaching others how to do certain things can actually lessen the burden on one person.

The harder one works the more work is done. Hard work alone does not ensure that things get done. Being well organised and working towards a goal is actually far more effective.

Another myth: Time can be saved. This actually isn't true. Time can only be better utilised through planning and organisation.

Time is against us. Well time can't fight us but people can actually fight by mismanaging time. So my general advice is really learning to say no is actually a very important part of taking control over your time and energy.

You'll hear the term fatigue management, energy conservation, work modification, lots of things actually essentially are all the same principles, so there are six identified principles to the management of fatigue or the management of your energy.

Balancing activities with rest, we've heard our previous speaker talk about the benefits of exercise and pacing yourself.

Prioritising activities, what is important to you. Planning ahead, that's not rocket science but it is good organisation and we do it more or less well or unwell in our daily lives. Organising the things we need to use so that we are energy efficient, we are organised whether that's in the kitchen, the bathroom or in the workplace.

Good posture. Good posture saves energy, if we stand well, if we sit well while we're doing certain tasks we can make our energy go further.

And leading a healthy lifestyle, taking exercise. We've heard several speakers today talk about diet and exercise and the benefits of that.

So what can we do? Well, the principles tell us how to make the best of our time and energy and when planning and organising your day or week it's important that physical and mental demands are considered. You might need to ask yourself how you would rate a specific activity, how tired is this going to make me, and you'll likely think about the physical effort you're going to take, whether it's something that needs a lot of strength or coordination, whether you're going to be standing or walking for a long time, if you have to travel, and overall how long the activity will take.

But I wonder, how often do you consider things like how much attention or concentration something needs? How many distractions are there? For example, noise, clutter, the business of traffic, the business of people, actually impact on how well we can pay attention, how well we can concentrate. And I've written here, 'especially on those brain fog days' because I understand that's something that people will understand.

If you're doing something new do you consider that learning actually uses more energy and is what you're going to do today something that's going to demand a lot of new learning. And does the activity require complex thought or problem solving? How tired are you before you start something? When are you going to do it? Is it at the start of the day or at the end of the day and how organised are you? These are things that I do all the time in the course of my work but I wonder when you're thinking about planning your day or planning your time do you also consider the mental attributes of a task as well as the physical ones?

So fatigue management principles, if I just go back to them, guide us in ways to use energy in a more efficient and effective way. So how could you plan? Well, you could look at something quite simple, a sheet of paper like this days of the week, you could divide it up, morning, afternoon, evening. A lot of us do this anyway if we have a calendar on the wall at home. So I use mine all the time, I also keep a diary, but if I'm doing this kind of programme with a patient I might actually take sheets of paper and ask them to write things down for me. So what I'm going to take you through in probably the next five minutes I might do with patients individually or in a group over six or seven sessions, so hold on to your seats.

Planning. Simple diary, sheet of paper, scrap of paper, it doesn't matter, you don't even have to fill it in, but it's just the way to make you think a little clearly.

What's important for you to do? I love this one, because I love to tell you what is essential for me, and what's essential for me is watching trashy telly. I love EastEnders I have to admit and I have been a lifelong fan of Coronation Street, and I will leave the washing up to sit and watch my favourite programmes, but of course for someone else that may be totally unnecessary, whereas I would put it in my desirable box. But for you it might be taking the children to school, popping round to your mum's to push her Hoover around, or in fact cleaning the car. So this is a very individual way or dividing up what we see as essential, desirable, unnecessary or in fact transferable, can someone else help me to do this?

This is a challenge and everyone carries out certain activities that could be shared, altered or eliminated from their daily routines, but it is worth noting that this process also involves the commitment from others such as your family, partners, or work colleagues, because sharing the burden often means sharing some of the priorities.

You might prefer a to-do list. You could just simply write down you've got to do shopping this week, visit to the opticians, maybe post some letters, and in the box to one side you can say what the priority is, numbers one, two and three, high, medium and low, it doesn't matter, whatever system, but making a note of things that's important to achieve over the course of a week can give you a little strategy to help it happen.

We talk about looking or feeling tired, we think about how that impacts on our day to day processes, but actually you could turn it around and look at your energy ratings. When you're doing something, particularly physical jobs, maybe in the garden, they can be very pleasurable but very demanding, so what you can do is test yourself, do it, get your sheet out, circle one of the numbers. Did it make you feel very tired? Did it energise you in fact? And by doing that you can have a better idea of where to place those tasks over a week so that you don't put all the heavy demanding high rated tiring tasks on a Sunday or a Saturday but you try and divide them up over the course of the week.

Maybe people prefer to think about how tired they are, so you can keep a fatigue diary. You'll notice on the screen it takes you through an average day from getting up in the morning to going to bed at night. If I was using this type of strategy in a treatment programme I ask people to complete them and I have

always found that people get very tired doing very little activity and by writing on a little sheet like this I can demonstrate to them that minimal activity actually exacerbates their fatigue. And what people tend to do is rest a lot.

Now by looking at what you do and how tired it makes you, you can then pace yourself and introduce rest periods into your day and hopefully by resting at certain times you'll find that your energy levels rise and by recording it on something like a fatigue diary you can actually see if there is a pattern to your day.

Organising things at home seems pretty obvious. There is a principle, as I say this again is all in your take home booklet, and organising things so that they're close by, things that are regularly used, things that you don't use very often you can store in high or low cupboards in the kitchen, but do also think that poor lighting at home increases visual effort, the more effort we use the more energy we use.

Good ventilation is important, if you get very hot you will tire more quickly, so if you're in the kitchen or if it's a very warm household do think about opening a window.

Energy saving equipment can be invaluable but it doesn't have to be expensive and it doesn't have to be bulky. One of my best tips is use a cooking basket inside a saucepan, you'd be surprised how easy that makes to drain vegetables over the sink rather than trying to struggle across a kitchen with a very large pot of boiling water if you're not having one of your best days.

Optimising your work space so that you can sit whenever possible for ironing, washing up. It seems fairly straightforward but how often do we think about what we do and how we do it? I would also say that you can carry these suggestions into the workplace and you could also if you are still employed ask for a workplace assessment. So ergonomic principles help us to understand our environments.

I haven't quite got to my thank you bit yet but if I could just reinforce the healthy lifestyle message, the right nutrients, drinking water, because it shows that our brain function improves if we are hydrated, large meals, alcohol and smoking can have a very negative effect on fatigue. Exercise as we heard is a positive approach to fatigue management and it provides muscle efficiency and strength as well as increasing stamina.

Exertion or deconditioning. Reduced activity can lead to deconditioning of both the cardiovascular system and muscles themselves, resulting in a less efficient use of energy and therefore the experience of more fatigue.

I would add that sleep is a very valuable commodity but it needs to be restorative so do consider how comfortable and how you can work to achieve a better quality of sleep. And finally, your emotional wellbeing, mood can affect motivation and it can make you feel lethargic. If you can find a way to share worries and fears it's important for your wellbeing. Rest and relaxation can help manage stress and anxiety which again can increase fatigue.

I'm going to whizz forward to my take home message because I think if you look in your booklet you can work your way through some of the things I've introduced this afternoon, but just to say it is important to optimise your energy expenditure, essential jobs can be broken down into manageable stages and tackled when fatigue is at the minimum. By following the principles of energy conservation and fatigue management you will develop an understanding of your levels of energy, your patterns of fatigue and what exacerbates it. It's important for friends, relatives and employers to understand your patterns of fatigue and the principles that you choose to follow. This will enable them to help you make the necessary adjustments to your lifestyle. And thank you for giving me a little slot this afternoon.

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Professor Graham Hughes

Thank you very much. Well I wonder if the speakers could come up here and we have questions, and we're limited to ten minutes so I'd like very fast moving questions and answers if possible. So if all the speakers would come up here.

Questions and Answers – Panel responds to questions submitted by audience

Professor Graham Hughes

Well, we'll start with one question that's been written down.

Q1: Is there a possibly that menopause symptoms are a lot worse with someone that has Hughes and Lupus Syndrome? So symptoms of Hughes Syndrome around the time of the menopause, any data on that?

Dr Hannah Cohen

Well, I'll take that. I think, well I see a few patients around the time of the menopause, they're usually referred to me because of thrombosis so I don't actually manage their menopause symptoms but nevertheless, I think, and I cannot quote you official data on this, I'm not really aware that there is, but one of the symptoms, or some of the symptoms that we see that are very profound in patients around the time of the menopause is just what's been talked about just now, fatigue. And then there's sort of various symptoms like sweating episodes, insomnia and paradoxically, also feeling very sleepy from time to time, so I think some of the symptoms clearly are some of the symptoms as you get in APS. So it is possible and it would be quite an interesting thing to look at.

Professor Graham Hughes

Thank you. Any other comments from the other speakers?

Professor David D'Cruz

The only other thing I would say is I see many patients with many different diseases like arthritis for example and often they say things got a lot worse at the time of the menopause. And part of that is that the menopause is a big change in your life and many things change around that time and many people who don't have any other illness at all feel worse at the time of the menopause so it may be a circumstantial thing, two things happen to you at the same time and so one looks for a link between those two things.

There's no experimental evidence to say that symptoms ascribed to antiphospholipid syndrome would get worse in menopause, there's no biology which would say that they would, if anything you might think they would get better, and the reason I say that is that it's an autoimmune syndrome, the immune system is overactive, and in general the immune system gets maybe a little less active at the time of the menopause. So you might think that the reverse was true if anything. But I think the most important thing is if you imagine I was sitting in my clinic with a lady of say early 40s with antiphospholipid syndrome and she said should I be worried that I'm going to get a lot worse when I go through the menopause I would say in my experience that doesn't happen to most people but I don't know what Graham would say.

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Professor Graham Hughes

No, I'd agree with that observation. Any other?

Dr Hannah Cohen

May I add one more thing please? One of the things that will arise then is the use of hormone replacement therapy for the menopausal symptoms, and perhaps that's a sticking point as well because women may be denied the HRT because of the perceived risk of thrombosis and I think what we know is that the tablet form of HRT is definitely something to be avoided in anyone who's at increased risk of thrombosis. The patch preparation, or the preparation that you rub in, the risk is much, much less, but I think one needs to look at that and see that the woman is able to get the treatment that she needs.

Professor Graham Hughes

Thank you very much. Any hands up in the audience? Two in the front row, the lady on the right and then the person at the end.

Q2: I appreciate that there's a memory loss issue or recognition with the early sort of symptoms of Hughes, if that memory loss is getting increasingly noticeable, even though you're being treated and everything else is fine and the symptoms are fine is that recognised? Is there any other link with other type of dementia or other kind of brain related diseases or anything like that?

Professor David D'Cruz

I think it depends what you mean by memory loss. So if you're talking about cognitive function, that is to say not just memory loss but loss of function in many other ways then there are actual psychological tests that can be done for that, you can measure that. So if somebody had tests which over say a six month or two year period showed a distinct deterioration on what they were doing on all the tests then I think most people would look for a reason for that. If it's just memory loss alone, somebody can't remember things that they could remember before that's much more difficult because there are so many causes of that, some of which are directly physical to do with things with the brain, some of which are not physical, so for example depression is a common cause of memory loss and so is poor sleep pattern, people who don't sleep very well and feel very tired all the time have memory loss. So there are many, many causes of memory loss so I think that a person whose main complaint was of memory loss, you would have to unpick it very, very carefully and take the history of what was happening in that person's life. And most of the time it wouldn't be to do with their autoimmune disease, whether that would be antiphospholipid syndrome, lupus or rheumatoid or anything like that, it would be something else.

Professor Graham Hughes

Can I say, I think this is a very important question because it's something we face in clinic every week. Let's take it that you've gone through those things and it is a patient with APS who's on say warfarin what do you do? Well the first thing is, is the INR good enough? You know, if it's 3.7 perhaps it could be 3.9, four, or 4.1 and it's such a difficult area because you have a hundred physicians on your back if you're trying to get someone to an INR of 4.1, but there are undoubtedly patients who find that slight increase in warfarin useful. There are others for reasons which I don't understand who get on the combination of warfarin and antiplatelet agents such as aspirin and maybe you can tell me why that is?

Dr Hannah Cohen

Well, get better on that you mean? Yes. I think it's because one is attacking the blood clotting mechanism from two different routes, so the warfarin will act on the blood clotting itself, whereas the platelets will act on platelets and it's platelets and clotting that actually work together to form blood clots. And so attacking both points might be potentially more effective. And one drug that I find very useful is the slow release Dipyridamole that seems, you know, we've had patients that anecdotally seem to do on that plus warfarin.

And may I say one more thing? I think in someone where there is any concern about the warfarin level and whether it's actually adequate I think one needs to think about doing some specialised assay which would be a factor ten which would give you a measure of warfarin activity that is independent of the INR, because as we've said the INR may be affected by the lupus anticoagulant.

Professor Graham Hughes

Thank you very much for that. And anybody else in the audience? The lady at the back after you.

Q3: Hi, Diane, you mentioned you were using an app to track your INR, which app was it?

Diane Eaton

It's an app called OAT Book, Oral Anticoagulation Therapy. It was actually on my slide, a little picture, but I didn't tell you about it. Literally you just get the app up, you can buy it, it's very reasonable, I think it's about £1.19 or something. We're delighted because it's actually been developed by a warfarin user, a young techie warfarin user who couldn't cope with the yellow book in his back pocket when he went out with his mates, he thought it was much easier to actually have it on a phone and that's why he went on with that piece of work.

But it's very simple to use, it's a calendar, you put your date in, put your result in, and you put your ranges in and it tells you even when you should be going to the clinic or reporting in, so it's very simple. I've got it on my phone if anyone wants to see it afterwards.

Professor Graham Hughes

Thank you. I can see a lady at the back. I can't see in that corner because of the lights, I'm sorry, so if you put your hand right up. Thanks.

Q4: Hi, I wonder if you can tell me if there's any research where people are using steroids for their APS? I was on steroids for that and for lung problems following PEs and subsequently I suffered quite severe avascular necrosis of my knees, my hips and other areas of my body and so they're saying I probably won't be able to use that to help me with my symptoms of APS.

Professor Graham Hughes

Yes, I think this is a subject dear to my heart. We did early on find in our lupus clinic that patients with positive sticky blood tests had more AVN and that in plain English is softening of the joints of the hips and the ankles and that's been proved now that it is a known risk factor such as deep sea diving and high cholesterol.

So you wonder in the case, I don't know whether your case is like this, where there's lupus give them steroids and have APS perhaps inadequately treated, it is more likely to cause avascular necrosis. I presume that you were treated with anticoagulants and that was carefully monitored?

Questioner

Yes, my INR was then at three to 3.5 but where they'd been finding I'm probably micro clotting it's now gone to 4.5 and I inject Fragmin if I go below 3.5.

Professor David D'Cruz

Sorry, it wasn't clear to me whether you had lupus and APS or just APS?

Questioner

I have confirmed APS but lupus type symptoms but not confirmed.

Professor David D'Cruz

Oh, the reason I stress it is that steroids are not a good treatment for APS, for APS alone without lupus steroids are very, very rarely used in APS alone. There are some special circumstances like catastrophic APS which is a very rare form of APS where it can be used, but for APS with no lupus the studies have shown that it isn't really a good treatment. Now in the scenario where you have lupus, or in your case a lupus like syndrome which responds to steroids then sometimes other symptoms can improve.

Certainly maybe 20 or 30 years ago people were having lots and lots of steroids and that did lead to adverse effects, of which avascular necrosis is one adverse effects and in general in most of these diseases, lupus included now, the gospel, the religion if you like, is to treat the patient with as low a dose of steroid as possible, get it down to the lowest that the person can tolerate while the symptoms are under control, to avoid these sorts of things, so that in a patient who was having steroid side effects and that just doesn't include avascular necrosis, it's things like for example cataracts, raised blood pressure, easy bruising, you might find the patient still needs some steroids, they can't manage without some steroids but you keep it as low as possible.

Now, as for the patient who already has avascular necrosis and still needs the steroids, of course there are surgical treatments for that, if there's avascular necrosis of the hip a person can have a hip replacement and we certainly at UCH had several patients who had hip replacements and then felt much better and of course you're always going to be worried about steroids in that patient in the future but it's not absolutely contraindicated. So my message here is it's a risk benefit equation, the steroids carry a risk but if the benefit outweighs the risk you keep the steroids and you deal with the risks, for example by an operation.

Professor Graham Hughes

Thank you. I can't see you so if you could put the microphone in her hand.

Q5: Good afternoon. I have primarily antiphospholipid syndrome and last year I developed lupus which affected my lungs and my kidneys so I just wanted to know, Dr Hughes, you've mentioned that the percentage is very little, but I had your symptoms exactly, I had primarily antiphospholipid syndrome and I had rashes ((?)) exactly like you and then one day I couldn't breathe so I phoned the mineral ((?)) hospital saying I can't breathe, come here and it was three months and they were treating me because my kidneys were really bad, I nearly lost a kidney and my lungs were full of water.

Professor Graham Hughes

So what you're saying is the APS came first in your case and the lupus later.

Questioner

Yes, my APS, and I had the same symptoms as the lady here.

Professor Graham Hughes

Yes, I accept that, I mean sure, the two arrows, but there are rare patients but it is unusual that story and many of our patients who think they've developed lupus have the test positive earlier in fact. I don't know if you have any comment on that?

Professor David D'Cruz

Well, I'll tell you a story rather than a comment and that is the message of this story is lupus doesn't start in a big bang, it's not the case that one day you haven't got lupus and the next day you have got lupus in general, it's something that happens over a period of time. And the story I'm going to tell you is about the United States Army, so if you were to join the United States Army which I don't recommend

incidentally that every year they would take a blood test and they would keep it in a fort somewhere in the Midwest, they have this fort where they keep blood samples from all US military personnel and they keep them there every year, so an enterprising researcher from Oklahoma asked for permission from the United States Army to test the blood of patients who had lupus for the years and years before they got the lupus.

So they were in the army, so all this blood was stored and say a patient got lupus in 2005 they could test their blood from '95, '96, '97, '98 and so on, and they found that the antibodies to do with lupus had developed in some cases ten years before the patients had had any symptoms. Furthermore, if you take the history of a patient with lupus you might well find that some years before they developed proper lupus they had sort of flitting symptoms which didn't bother them very much.

So your case is an extreme case because you were clearly very, very ill but many patients, when they look back they can see they were developing it for several years before they actually had it, so it may be that the antiphospholipid syndrome is diagnosed first because it's so dramatic, you have a clot or something, something really, really obvious, but at the same time there was a bit of lupus going on in the background that nobody knew about and it can be like that.

Professor Graham Hughes

I've got a really interesting one too actually. This is 32 years, now this is one of my patients from America, she has antiphospholipid…

Member of the floor

Is she in the army?

Professor Graham Hughes

I don't know if she's in the army, but she is 56 or something like that and she has APS and 32 years earlier she'd been turned down when she was a teenager for a job in a Wimpy bar because she had a positive test for syphilis. Now you may know that one of the antibodies cross reacts and messes up the syphilis test, so some of you poor patients who have APS, 5% or something, have been wrongly accused of having syphilis based on a false positive test. So this lady had APS or antibodies to APL 32 years earlier. Anyway, I think time is running out. Time for one urgent question, the gentleman at the back?

Q6: I was diagnosed with APS after provoked PEs following a cruciate reconstruction so quite poorly, off work for three months and the question is I'm adopted, I don't know anything about family history at all, my wife and I are beginning to think about the future of a family and is there any thinking on what percentage risk there is for me passing it on?

Professor Graham Hughes

Very low. I'll pass it on to the experts.

Dr Hannah Cohen

I would say the same, really, really low. I think we have got this one family we have for certain, and possibly two families in our practice at UCH where family members seem to have APS and SLE so it's not that it never, ever occurs, but you're worried that you have thrombosis and this may affect your offspring, is that the concern? Okay, and you've got antiphospholipid syndrome obviously. So I really don't think that should be a concern in terms of going ahead with trying to have a baby. I think though I would say I always take a broad view of thrombosis because thrombosis is what I call multifactorial, it's not just one factor, so we know that in individuals who have hereditary types of thrombosis where they find some factor we know that their offspring may be at increased risk of thrombosis, even if they don't have that specific factor. So I think we do need to take a broad view of thrombosis and I would simply say that if a parent has thrombosis then the child should be regarded to be at some slightly increased

risk of thrombosis and observe what I call 'simple' risk reduction measures, i.e. a sensible lifestyle, rather than going to town about it, but I think a broader view is good there. But certainly I would say there's no reason why you shouldn't go ahead.

Professor Graham Hughes

Thank you very much. I mean just to finish, it does raise the question which we get asked every week, I'm 40 and my daughter is 17, should she be tested and she's getting headaches perhaps, nothing else, and I'm in a minority of one I think here, I think the answer's yes, yes, yes because you need to know, especially for a future pregnancy that the person has a positive antibody. Of course you can't prove that you're right about this but clinically I think most of us would feel that.

Diane Eaton

Just briefly, I know my condition obviously isn't APS but I did know of the risk before we decided to have children, we got all the clinicians on board, they were absolutely fantastic, managed my pregnancy really well, and both my children were tested at birth, which I know isn't a trend for antithrombin now, but they were tested at birth and I had one child affected and one child not affected. I'm glad that we knew at that time because it meant that we didn't wrap our son up in cotton wool, we just knew and we made sure that he was kept well and looked out for anything that may have occurred. So we wanted the knowledge. I hope that helps.

Professor David D'Cruz

I don't completely agree with Graham to be honest, and I guess you'll probably have worked that out from my talk, I am worried about false positive tests but I don't think there's no one size fits all for people. I wouldn't recommend testing in somebody who has no symptoms at all, but that's not actually what Graham said, Graham said that the 17 year old in the story had headaches, so this is a person with symptoms, so then it's very tricky, and I think what you would have to do really is sit down with both the mother and the daughter and say look, we can do this test, very easy, I just write a blood form, we can do it. What will it mean? If it's negative does that mean you will never have any problems ever? Well, it could be that you could become positive in two or three years' time, we don't know, so you can have a negative today but it might not mean you're never negative. If it's positive what does that mean? So there are levels of positive, there's borderline positive, there's medium positive, there's high positive, so if it's just a borderline positive what are we going to do? We're not going to put you on warfarin, is that going to worry you for the rest of your life? When you start going out with somebody will you feel obliged to tell them you have this positive test? It may not be the right thing for the 17 year old to have the test, so what I would say and I hope Graham would agree, is that you have to take the individual circumstances into account.

Professor Graham Hughes

I do, I agree with that, yes.

Dr Hannah Cohen

May I say something? Okay, I think what is really important, rather than testing or not testing is that it sounds like there should be a dialogue with a haematologist, a personal face to face dialogue. I'm a tester, I have no problem with testing, because I think it's easier to do the test then it's out of the way and then you can deal with it because otherwise it's always hanging there, you know, that it's not been tested.

And in terms of whether it matters if it's borderline, the short answer is no, I think if we're talking about thrombotic risk I think the evidence is really quite good that you need to have a moderate at least high positive.

So I think it sounds like what is needed is advice and to do that that's a consultation I think and then the testing can be done or not done but the key thing I think is advice.

Professor Graham Hughes

Well, let me thank you all for a fabulous day and thank you all for coming and we hope to see you all next year.

Kate

Can I please just remind everybody, I know it's very tedious at the end of a long day, but we really appreciate any feedback. The last few years the feedback's been really helpful, we've been able to modify certain things about the day which we hope has improved it, so we'd be very grateful, on the table outside if you'd just leave your feedback forms we'd be appreciative. Thank you.

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