Hughes Syndrome FOUNDATION
for people with antiphospholipid antibodies

Professor Graham Hughes

Five patients' letters

Welcome everybody to this sunny afternoon here at St Thomas'. Before we start just two words of thanks, firstly to Kate and to Lynne for their hard work in setting this up, and for all your volunteers, many, many thanks for doing this. Secondly, we've got a little questionnaire, I hope you'll help us because it's just to see how many have family histories suggestive of the Hughes Syndrome. And anyone who can fill it in, if there's some questions you don't know about leave them out, and that's not just patients but your accompanying persons who happen to be the controls there if you see what I mean. So I'd be very grateful if you can. The bottom word is POTS, you may not know what that is, but you will hear a little bit more about it, I apologise.

So my first slide is here. In October it was the 30th anniversary of discovering the syndrome and every two years now there's a world conference on this and in October it was held in South America in Rio. I don't recommend Rio to anyone, it rains and I was there for a day and it's not nice, but the meeting was fantastic with 650 doctors from all over the world interested in this topic and I had to give the opening lecture. And what I'm going to do in the next ten or 15 minutes is give you a summary of what I talked about there. The title they gave me was what's happened in 30 years, what have we learned in 30 years? And the way I thought I'd do it at that meeting I'm going to do here, based on just five GP's letters, and that's what we deal with all the time, GPs ourselves and patients.

Just a quick background, it was 30 years ago in October that we published our observations on this syndrome in British journals, in The Lancet and in The British Medical Journal and for us as you can imagine it was a very exciting time because we knew this was going to be important.

A number of publications came in the next two years. This was one of the papers in The British Medical Journal, we called it Thrombosis, Abortion, Cerebral Disease and the Lupus Anticoagulant, which as you know is a very silly name for it. This is the young team that we had in Hammersmith in those days and a number of them, visiting fellows from overseas. In the top right hand corner as you look at it, Charles Mackworth-Young who was my registrar who is now at Westminster, and at the back the African gentleman with the big hair is now the Dean of the University of the West Indies, so he's gone on to far bigger and better things, but a fantastic team.

We then held the first world symposium. That was a grand title because it was at Hammersmith and we invited people from all over the world, and I got my secretary to do four desks with A to D, E to G and so on and 34 people came, so that was the first international meeting. We moved to St Thomas' here in 1985 and so we carried on the tradition and we had the second world conference here and since then it's not looked back, medically there have been these every two years world conferences.

These are some of the world leaders in this field, and it is very international. Top left, Nigel Harris, centre, Munther Khamashta who I think no introduction needed, he'll be speaking next. On the top right, sadly who died recently from cancer, Silvia Pierangeli, a great worker. At the bottom, two from Italy, and then Jean-Charles Piette, a good friend from Paris who did a lot of sterling work. He's given up hospital medicine and is now the medical doctor to Formula 1 racing cars.

So very quickly, as a clinician what is Hughes Syndrome? And I'm going to just briefly do five quick diagnostic letters from doctors. The diagnosis, the family, pregnancy, the heart sink patient and treatment hurdles.

So doctor's letter number one concerns diagnosis. 'Dear Dr Hughes, regarding Mrs Smith, although I suspect APS she's never had a thrombosis or a miscarriage.'

My first lesson is, and many of you know this, Antiphospholipid Syndrome is not just thrombosis or miscarriage, in fact many patients have had neither. For instance, some people get metatarsal fractures from jogging or break their bones while walking, there was a condition called march fracture which new soldiers sometimes got in the foot, and we see this in a number of patients with Hughes Syndrome, possibly because of poor circulation to the bone.

We see the heart involved with murmurs, many of our patients are found to have murmurs and very occasionally they get valve damage and need clotting valve surgery. They can get balance problems and ringing in the ears and we're getting referred now more and more patients from the ENT doctors, patients referred with swimming heads and so on, a very, very common presentation.

Ménière's is the label given to many of them, but perhaps the two commonest are memory loss, brain fog, and this when you ask the patient about it often is the number one overriding thing, 'doctor, I could not remember which exit from the roundabout when I was taking my child to school' or 'I'm the joke of the family'.

The skin is involved, this is what we call livedo; one of my patients called it corned beef skin. It's a cold circulation and we see it, but next to memory loss by far the most important common feature of this syndrome, number two is migraine. And it often starts in the teens, it often goes away and comes back in their 20s or 30s, often a family history of migraine and it's a terribly, terribly important and common feature of the syndrome. It's important because the migraine doctors who are here will know if you anticoagulate a patient the migraines often stop completely.

Multiple Sclerosis, some of our patients are wrongly labelled as MS because they have balance problems, visual disturbances and some of the features of MS, and we still don't know if you go to an MS clinic what percentage of those patients have not got MS but have Hughes Syndrome, whether it's 5%, we just don't know.

Doctor's letter number two, the family. 'Dear Dr Hughes, re Mrs Jones. Despite a history of migraines, low platelets and previous infarct all tests for APS are negative. Her sister who has APS has responded to anticoagulation. Should we follow suit?' Yes, yes, yes. This lady, Mrs Jones, was treated with first aspirin, then heparin, then warfarin, headaches are gone and she's probably in the audience and doing very well.
What is this patient teaching us? Well, this family is kind of interesting. She had four brothers and sisters. David is 50, had migraine, had a pulmonary embolus which is a major plot, but his test was sticky blood negative and migraine, pulmonary embolus, Multiple Sclerosis. Can you imagine that label? She didn't have MS but she was positive. Tina, memory loss and went to live abroad and died of a pulmonary embolism and actually whilst abroad was tested and found to be positive for the test for sticky blood. And finally headache DVT negative.

So this brings up this vexed question of sero-negative and Munther Khamashta and I wrote a paper many years ago saying that we are seeing patients who have all the features of the disease but where the tests are unhelpful or negative, exactly as we see with thyroid every week of the year, normal thyroid function with a patient with a lazy thyroid.

So does it exist? Well maybe not, it may be the wrong diagnosis. It may be that tests were positive and are now negative and occasionally we see that. I think what we all agree who are working with this subject is that we need more sensitive new tests.

Doctor's letter number three, pregnancy. And that's going to be talked about by Dr Khamashta who is here with his beard and with a good head of hair. And this has been the fantastic story, this has been the headline story of the Antiphospholipid Syndrome. The patient on the left had I think nine, ten miscarriages and is now well. She was treated with heparin during her pregnancy and this combined clinic which is haematology and obstetrics and lupus doctors. And that success rate now, under 20%, now over 90% success in pregnancy. 'Dear Mr Khamashta, re Mrs Smith. Mrs Smith had a stillbirth. Could APS be a risk factor?' Stillbirth, late pregnancy loss.

About six months ago The Times did a thundering column on the stillbirth scandal: Every day as many as three babies are stillborn. We now know that stillbirth is associated with Antiphospholipid Syndrome and this paper by Ware Branch who's a friend and colleague and Rob Silver in Utah in the United States showed a three to fivefold increase odds of stillbirth if you had sticky blood.

Now the bad news, and this comes from work from many of you in the audience working with the charity, is that pregnancy testing in the UK is still rather primitive. They looked at 11 UK trusts, five didn't include anti-cardiolipin assays and even in this hospital which is the centre of the world of APS if you like does not include ACL in standard screening, but does include syphilis for goodness sake, £16.

So I hit on the idea, maybe obstetric doctors should be taught to look for at risk patients because they do not test patients until there are three miscarriages and that will lead on to a very stormy issue here, why wait that long?

And the three simple questions are, have you had a thrombosis, are you a migraine suffer, and have you a family history of autoimmune disease like lupus, rheumatoid, MS or thyroid disease? And I'm sure that would pick out those on whom you could spend a tenner testing.

Doctor's letter number four, the heart sink patient. And every profession has a heart sink patient or a client and this is a terribly politically incorrect letter I received many years ago. 'Dear Dr Hughes, I'm delighted to tell you you've won Mrs Shuttleworth in our hospital draw.'

This is Mrs Shuttleworth, and this is what he sent me. These are her symptoms. Fatigue, headaches, blurred vision, short of breath, tummy pains, knee pain, cold feet, fainting, fainting attacks in school, poor memory, dry mouth, palpitations, hip pain. And you know as well as I do these are all very real, this patient was not just malingering.

This patient had Hughes Syndrome and POTS and I did not know what POTS was, but it's Postural Tachycardia, in other words when you stand up the heart goes the wrong way, it goes faster and you lose

your blood pressure and you faint. And my colleague who's in the audience, Jill, I don't know if you want to talk about this later, but has collected a dozen or so patients with the combination, fainting, fatigue, migraines, aches and pains. Jill Schofield, I think it's out you said, I haven't seen it yet, but it's 14 cases of POTS. Is this of any significance to us in the Hughes Syndrome?

Well we think it does have therapeutic implications. This is an email I received from a patient of mine, and we started her on anticoagulant for the Hughes Syndrome. It was very interesting, within 48 hours of starting heparin, headaches gone, tinnitus gone, stomach pains gone, that's gastric ischemia, numbness in the hands gone and so on. Visual disturbance, better, brain fog, improving. And what's very interesting is that these had not responded to conventional POTS treatment. So I think the ripples for the clinician keep on widening.

The last doctor's letter, treatment problems. I'm not going to go into details because many are covering this today, but the last doctor's letter, it says, 'Re Mrs Jones, despite being on warfarin her memory loss, headaches and balance problems have not improved.'

So what's this patient teaching us? Well first of all that failure is part of medicine and we see this all the time, and I've shown this before, but this cartoon drawing shows what we see with many patients with Hughes Syndrome on warfarin, that they're okay when the INR is high, in other words the blood flow is good and quick and thin, but when INR falls, for example in this lady below three, the headaches, the dysarthria, the brain fog comes down. And that's one of the reasons we're having a talk today on self-testing which to me is terribly important.

So I want to end with predictions, this I was asked to do for the World Lupus Conference and I didn't go but we sent some slides and they asked me what are my predictions for APS in the year 2050? Well the first one is the next conference won't be in Rio or London, it'll be on the moon at the Disney Conference Centre and you'll get there by rocket.

And these are my predictions. APL testing will now be worldwide. It'll be over the counter, there'll be kits available and we'll do away with the dreadful test, the lupus anticoagulant test. There will be new hope for migraine sufferers, and I know there are migraine doctors in the audience, but for me this is crying out to be studied in a very big way and there's no very good study as yet.

I believe that migraine is possibly linked with stroke through sticky blood and a very big paper in January from America showing some patients with a certain type of migraine had a higher risk of stroke, but unfortunately they didn't test for the antibodies.

I believe that the stillbirth scandal which is regarded by some people as the worst tragedy that can happen to mankind will be alleviated. If we could test those patients with recurrent miscarriages earlier or patients are risk we could put it off and maybe I predict cut the frequency of this tragedy. And chest pain I'm not talking about but many of our patients do get chest pains and it's just the heart not being happy with low oxygen, just as the brain isn't, and I think we are now beginning to hear from the cardiologists about angina, especially in younger women, being associated with Hughes Syndrome.

And finally the brain fog, that of course is the biggest study and it requires really careful study collaborating with psychologists, psychiatrists and so on. But I think that some cases of memory loss as you know in this

audience are very, very treatable.

So in summary, we've talked about psychiatry, it's touching on obstetrics for sure. I think this is a neurological disease more than any other and I think in future talks we'll have neurologists here, not just rheumatologists and haematologists. Gastroenterologists are becoming involved, orthopaedics I mentioned, fractures - I think Dr Khamashta has a lady with 52 fractures - and cardiology.

So I wanted to end by saying 30 years on the syndrome gets wider. We think there's a better understanding, although not fully understood, of the mechanisms, and I think that the concept of sero-negative Antiphospholipid is arguably the most important single aspect of this whole syndrome right now, and that's one of the reasons I want you in the audience to perhaps fill this in, because many of my sero-negative patients have come for one reason, that their sister, their mother, their aunt, has got the syndrome and they've looked it up on the internet. And genetic studies will be useless until they recognise all these wider features of the syndrome.

Back in 1983 in the BMJ I picked up this rather breathless quote actually but it was, 'for those of us hardened into nihilism by years of study of various auto antibodies in lupus there's a rare sense of excitement at the implications of the associations now being reported.' And I think 30 years on that excitement for us anyway is still continuing. Thank you very much.

I know that we're leaving questions until the end and if any of you who want to add to Kate's list of questions she's at the back there, but it's a great pleasure to welcome, Munther Khamashta, my colleague who I think most of you know; Munther.

Munther Khamashta

APS and Pregnancy

Thank you, Graham. Good afternoon. My usual task is to talk about Antiphospholipid Syndrome and pregnancy. Why is that? Because I run a pregnancy clinic and love running this clinic and have been running this clinic for 25, 26 years.

So I don't run the clinic alone, so the clinic is a multidisciplinary theme, we run it obviously with an obstetrician, we run this with a haematologist, it is a haematological disease and Beverley Hunt has been with us for now 20 or more years running it, and a neonatologist because occasionally the patients deliver prematurely, we need their support, and obviously an obstetric physician which is a unique speciality and there are only about six in the whole country. And Kathy ((Nilson Percy?)), she is in the photograph there, she's a doctor like me, she doesn't deliver babies, she doesn't know how to do it, she had four herself but she doesn't know how to deliver babies, but she's expert in managing pregnancy, preeclampsia, antiepileptic drugs and pregnancy, you name it, she's a physician dedicated to problems during pregnancy.

So it's a unique clinic we run here, very expensive but who cares, Mr Cameron has a lot of money, don't worry about that. But we run the clinic really in a very coordinated manner, we started with Graham Hughes with a small number of patients, now we see between us about 50 patients per week. And this is

why we are internationally known for this, our colleagues come from overseas to witness how we manage this unique clinic and to sit with us in the clinic and learn when they go back home how to manage this clinic.

What Graham said, the discovery of Antiphospholipid Syndrome was useful for something immediately, it was for pregnancy, because before the discovery of this syndrome and before treating these patients with aspirin and aspirin, heparin sometimes combination, the success rate was below 20%. Today in our clinic the success rate is above 85%, something to celebrate okay? An important advance in medicine.

But still, as Graham said, even in our own hospital the obstetric department didn't adopt the screening for anti-cardiolipin antibodies for all patients who fall pregnant, maybe it's not cost effective, we can discuss that, but it's not something that we will stop campaigning for, maybe in the future it will be a routine test, we don't have to wait until 2050, it will be too late for a lot of people, it has to be sooner than that.

As you can see, as Graham said, the syndrome is not only thrombosis, recurring thrombosis and miscarriages, it's much more than that, and over the last 30 years working with Graham Hughes here in St Thomas' Hospital we described many, many of the different manifestations of this syndrome. But my remit today is pregnancy loss, but before I go into treatment and management of the syndrome and pregnancy I'd like to call your attention to the overlap between lupus and Antiphospholipid Syndrome.

It's confusing to a lot of patients, I would like to go into the basics of that because many of the patients come to us saying 'dear doctor, could you see this patient who has lupus?' The patient most of the time they don't have lupus, they have lupus anticoagulant. It's one of the tests for Antiphospholipid Syndrome called lupus anticoagulant because when it was first described about 60 years ago it was described in lupus patients, most of the time nothing to do with lupus so there's a misnomer there. We tried to change this term in the literature but there is a huge market behind it and the haematologists were reluctant to change the term, it's still called lupus anticoagulant but most of the time nothing to do with lupus. You could have lupus but most of the time nothing to do with lupus.

The second thing to say is that some patients with lupus have Antiphospholipid Syndrome as well, you could have both diseases, they overlap. The majority of the patients with lupus they don't have the syndrome, they have the antibody but not the syndrome. So we have different groups of patients and as you will see the treatment is different, not all patients receive heparin, not all patients should receive heparin, and depending on the symptoms, depending on the background you will receive heparin yes or no and sometimes even will stop heparin and I will show you through the lecture when we sometimes stop heparin and why we stop heparin.

So when we did the study across Europe a few years ago just to see the prevalence, how much this pregnancy loss and different manifestation of the syndrome in one thousand patients and one thousand patients is a huge number of patients, as you see one third of the patients have pregnancy complications, so it's common. One of the major manifestations of this syndrome is pregnancy and pregnancy loss.
Now miscarriages might occur early in the pregnancy or might occur late in pregnancy, the problem with early pregnancy loss in the first trimester you have many, many causes of that, not only Antiphospholipid Syndrome is responsible for early miscarriage. One in six pregnancies end up in miscarriage so it's not rare to have one miscarriage and this is where cost effectiveness, if we screen everybody who has a miscarriage for anti-cardiolipin antibodies for example it will be nice but might not be cost-effective. And more

importantly than that, what do you do next? If the test is positive will you treat next? It's not clear yet. If you have two maybe it's different, two early miscarriages.

The problem is not with two early miscarriages, the problem comes later. If you have foetal loss. In the general population foetal loss is rare, foetal loss after 12 weeks of pregnancy, after the first trimester. It might happen, there's other causes than Antiphospholipid Syndrome but usually the obstetrician should think of Antiphospholipid Syndrome if you lose later than 12 weeks. And I'll show you the figures, where they come from, it's not even from our unit.

These figures come from St Mary's, they have a recurrent miscarriage clinic. If you have three consecutive miscarriages the chance of having antiphospholipid antibodies is 15%, so it's not 100%, it's 15%. If you have second or third trimester loss, i.e. once you pass the first trimester, this is not frequent in the general population, 20% have Antiphospholipid Syndrome. This is why you don't have to wait for two, three, four miscarriages to test for this, straight away you should be tested for antiphospholipid antibodies if you have foetal loss.

If you have foetal loss and the baby wasn't growing nicely inside the womb, i.e. intrauterine growth restriction, the chance of having antiphospholipid antibodies is even much higher, 40%, that might cause stillbirth. One of the questions that Kate asked me, do stillbirth ladies, when they have stillbirths, they have any tell-tale symptoms to tell you you might have a stillbirth? If you have intrauterine growth restriction obviously it's a good sign for that, you are at risk, but unfortunately sometimes you don't have that sign, it just happens out of the blue, the pregnancy is going fine and suddenly a stillbirth happens.

So it's not clear why, we thought in the beginning it could be clotting, but sometimes studying the baby and studying the placenta you don't show clots there. So coming back to the question, not always you have manifestations to tell you that you might face a stillbirth, it might happen out of the blue, after a normal scan just a stillbirth.

We are, as I mentioned before, a very expensive service, we have a multidisciplinary approach, we have obstetricians, we have clinicians, we have rheumatologists and we have haematologists and obstetric physicians, but the most important thing is not medication which I'll share with you in a minute, how we treat and when we stop medication and so on, but I think timely delivery.

So some of you are my patients anyway, you come to St Thomas' Hospital, you know that it's not practical to keep dragging you to St Thomas' Hospital, but if you are at high risk and we think you are at high risk I always try to persuade you to be looked after at St Thomas' Hospital, not because our obstetricians are better than your local hospital, they just have more experience in the management of this syndrome than other obstetricians around the country. So I prefer that you be looked after with specialised physicians who see these patients in and out every week.

When it comes to medication I'm not obviously trying to go through all these medications, I highlighted four drugs which are used frequently in Antiphospholipid Syndrome. This is the good scenario that many of the drugs we use to treat lupus are believe it or not compatible with pregnancy which is good, it allows for pregnancy to go ahead despite having lupus and perhaps Antiphospholipid Syndrome as well. We use Azathioprine, we use steroids, we use cyclosporin, tacrolimus, which are immune suppressant drugs which have a safe record in pregnancy.

But let me stick to the drugs that we use routinely, low dose aspirin, and one of the questions that Kate got me is about is there any difference between 75 and 150. Well I lived in Spain and practiced medicine in Spain, in Spain low dose aspirin was 100, in Portugal believe it or not it was 125, in the United States it's 81, in this country 75, all of that low dose aspirin, nobody bothered to compare the two, whether 150 is better than 75. I think 75 is enough, the aim of the aspirin is not to thin the blood, it's to make the platelet less sticky, so I think there shouldn't be any difference between 75 and 150.

Hydroxychloroquine is a drug we love, if I left it to Graham he would put it in the water for everybody to take. It's a very good drug and unfortunately frequently, frequently the GPs stop this drug. When the patient falls pregnant they panic, they open the book, the formulary, the formulary says don't use in pregnancy. Okay, most drugs they say that, don't use in pregnancy, and the patient comes without this drug. This drug is safe, to the best of my knowledge never, ever in the world's literature in any language has it been reported to damage the eyes of the baby.

So there is no data to support that and if anything it might even be useful to prevent miscarriages in Antiphospholipid Syndrome. With Professor Hunt, she'd just coming in, we're trying to set up a trial to use hydroxychloroquine in Antiphospholipid Syndrome as well. So it's a useful drug for lupus, it might prevent miscarriages and even those with low antibodies it might prevent ((heart block?)) in the baby so it's a very good drug to use in pregnancy.

Heparin and low weight heparin ((?)) come to that which is a safe drug to use in pregnancy and those who take warfarin they are aware that this drug should be stopped early in pregnancy, as soon as the patient knows she is pregnant she should stop that, especially between the six and ten weeks of pregnancy which is the window of toxicity, so you should swap to heparin and carry on throughout the pregnancy and once delivery occurs we go back to warfarin.

Breastfeeding is another major issue about the use of drugs, the drugs we are talking about are hydroxychloroquine, low dose aspirin, heparin, including warfarin, are safe in breastfeeding, so don't panic about that, you should be able to and allowed to breastfeed as you wish while you are taking these medications.

Regarding specific management of Antiphospholipid Syndrome these are the different scenarios we have, okay. Many patients come to us with no previous history of thrombosis, no previous history of miscarriages, maybe they have lupus or a lupus like illness, they were tested for antiphospholipid antibodies, and they come saying 'okay, what do I do now, I am pregnant? No previous history, nothing, what do I do?' There's no evidence we should do anything in truth but in practical terms we end up always giving aspirin. And that's because there is some data to suggest that maybe baby aspirin reduces the risk of miscarriages and especially late pregnancy complications such as preeclampsia. Aspirin low dose is safe in pregnancy, we'll end up giving it, most of the time, although there is no evidence we should do that at all.

What happens to those that have had previous thrombosis as I mentioned before? The majority are on warfarin, that should be stopped as soon as possible once pregnancy is confirmed and we give long term heparin throughout the pregnancy and a few days after delivery and if they wish they can go on warfarin after that back to their level before the pregnancy.

I put in red those who have recurrent first trimester miscarriage, this is a very controversial area despite

there are four trials to suggest aspirin and heparin is superior to aspirin and everybody should be treated with aspirin and heparin. We at St Thomas' Hospital were not convinced with that and we think many of the patients can get away with aspirin alone and do very well. And I'll show you in a minute why it's a controversial area and why people come to us already injected with heparin and it's very difficult to convince a lady who had three miscarriages and she was told to take heparin to stop heparin.

And what we do with our group, or at least what we decided to do, those who are adamant to keep on taking heparin to stop it at 20 weeks when we do a special Doppler scan for the uterine artery to see the circulation to the uterus and if it's normal it's reassuring and at that stage we try to convince many of our patients perhaps you can live through the remainder of your pregnancy without these injections, they're awful injections anyway, you might not need them.

The last group have never been subjected to clinical trial believe it or not, the stillbirth ladies, those ladies who have pregnancy loss at a late stage, the typical Antiphospholipid Syndrome when you have no doubt about Antiphospholipid Syndrome, never been subjected to clinical trial so in this subgroup of patients we always give heparin and aspirin throughout the pregnancy and when I say heparin it's usually low molecular weight heparin. We use Clexane and Fragmin in our hospital.

Just to show you what I mean by the Doppler scan, to the left the uterine artery Doppler scan, this is how it looks, normal, and you see a notch there and this is the notch what we call resistant to the flow and these patients at 20 weeks if we notice that, that pregnancy is at risk. Not necessarily that patient will lose but that patient will be at risk and this patient we carry on giving heparin but if it's normal at 20 weeks there is no reason, if the person has only first trimester miscarriages she should carry on taking heparin. So we try to, some of you maybe came across this and we tried to persuade you to stop heparin because your uterine artery Doppler scan was normal at that stage and we didn't see the value of injecting yourself for another 20 weeks.

Now this is my last slide, so don't worry, I'm finishing on time, what do we do with those who we fail? Our success rate is not 200% and will never be, we are about 85%, 87% according to the latest statistics we did in our unit. Well we sometimes try to convince the patient try again, do the same thing, and most of you say no, I want to do something different. If we lived in the United States, we don't, they give them IVIG, intravenous immunoglobulin, a very expensive drug and there are four trials to suggest it's not superior to heparin and aspirin alone.

I don't know why they carry on doing that because anecdotal data suggests it might be beneficial, but we don't do that, firstly it's expensive, secondly it is not proven to improve the outcome. What we did with Professor Hunt is to cheat, I call it cheat because we give low dose steroids, ten milligrams, not 40 or 50 or 60, ten milligrams, plus aspirin, plus heparin the first 14 weeks of pregnancy. Once you pass the first trimester slowly, slowly stop steroids and keep the patient with aspirin and heparin. And our success rate with this unusual regime I call it, it's a cocktail regime, it's 63% and we publish that in an important journal called Blood to call it to the attention of other colleagues in the world.

You see the word hydroxychloroquine there. We believe, Professor Hunt and myself and others working in the field, this is a fantastic tablet to be tested and so we are discussing how we go about this. Patients with lupus take this routinely but if you have primary Antiphospholipid Syndrome i.e. recurrent miscarriages and no lupus symptoms you're unlikely to take this tablet, but we think in the future we might be giving these

tablets routinely and I think Professor Hunt is doing that in most of her clinics in patients with primary Antiphospholipid Syndrome offering hydroxychloroquine as well.

We sometimes use immunosuppressant drugs in occasional cases but not routinely, so I leave it there for questions. Thank you very much.

Professor Graham Hughes:
Thanks very much, Munther.

It's a great pleasure to welcome Beverley Hunt who's Professor of Haematology here, and a big topic really for all of us, are the new oral anticoagulants any use at all? Beverley.

Professor Beverley Hunt

Update on blood thinners

Hello everybody. I do this talk every year and I'm going to try and keep it as short as possible because I know lots of people have questions. I've got some questions that I was asked by email so I've tried to put them in the lecture as well.

So, what do we want out of an anticoagulant? We want something that works, which we know that warfarin does in Antiphospholipid Syndrome without a doubt in 99% of the patients, but we want it to be safe, and ideally we all have to live our lives, we're meant to push our diseases behind us and live our lives, not let our disease dominate our lives, so we want it to be convenient.

And the coumarins which we use in this country, mainly warfarin, were discovered 60 years ago to the next few weeks actually, they were discovered in Wisconsin, and what had happened was a load of cows had gone into a field of spoilt clover and they developed bleeding disorders and a lot of them died. And the scientists went back and looked at the clover and they isolated this warfarin and in fact there's an academic meeting in Wisconsin very close the field that the cows were in in a few weeks' time.

So what do we know about coumarins for you? Brilliant, they work, but the problem is that you have got to monitor them, they don't have what a medic would call predictable pharmacokinetics, which is a glorious way of saying that if we all took ten milligrams we'd all have a different INR result and they would have a different effect in every patient.

Not only that but they're altered by what you eat, what you drink and any other medication. And it's quite complicated how the warfarin levels are reached, they have to be metabolised in the liver, it depends what your liver enzymes are like, it depends on how much alcohol you've got in your blood, lots of different factors will affect what dose you need.

And you, if you're on warfarin, know that is not ideally convenient because you have to monitor the blood levels, we've had a longstanding history in this country of anticoagulant clinics, there are over a million

people taking warfarin in Britain, so we have this big system of anticoagulant clinics, but of course we now have home monitoring which NICE have or are about to approve for use, so you can be freed up from that system.

Soon after warfarin heparin came along, it was discovered by a medical student at John Hopkins and they gradually developed it, we can only use the original heparins in a pump and we have to inject it. Again, they've got unpredictable pharmacokinetics which means that everyone needs a different level and really not convenient because you've got to have it through an IV drip.

So in the '70s someone had the bright idea of breaking down all the heparins into little tiny molecules, the little tiny molecules, they actually have predictable pharmacokinetics which means that if we all had an injection of one we'd all have the same blood levels. So what am I talking about here? I'm talking about Fragmin, Clexane, Dalteparin, Enoxaparin, Innohep as well, and they were a major advance, but the problem is they're not convenient, there's no oral form, if you actually ate heparin your stomach acid would break it down, so we have to inject with subcutaneous injections.

Then the other drug, just to mention, because there's usually a few people who are taking this one, this is Fondaparinux, Fondaparinux is synthetic heparin, and if we just go back to heparin it's derived from pig mucosa and mainly comes from China, it comes over to Europe and gets processed in factories over here, and you have to think my goodness in 2014 one of our main anticoagulants is coming from a pig in China, it's sort of crazy.

So Fondaparinux, someone had the bright idea, let's make synthetic heparin, so this comes out of a vat, it's a beautiful molecule, it's just that little bit of heparin that has an anticoagulant effect. You can inject it, it has predictable effects so you don't need to monitor it, the trouble is it's very expensive compared with using a lower molecular weight heparin, so if you come into hospital for an operation and you have a daily shot of Fragmin or Clexane it's a pound a pop, if you have an injection of this it's about £6 and it's just too much for the government to pay for. But really a major advance, much safer than heparin with virtually no side effects.

So most of the patients with Antiphospholipid Syndrome are taking warfarin. Just a little note about keeping a stable INR, remember warfarin works by stopping vitamin K from making clotting factors so in order to keep a consistent INR you need to keep a consistent intake of vitamin K, because if you didn't have any vitamin K one day the warfarin could really get a grip of your blood and make it runny for the next few days. If you had a big splurge on broccoli or something like that then the warfarin couldn't get to work and for the next few days your blood would be very sticky.

So it's about eating the same amount of vitamin K, I see lots of people in the clinic, I take a dietary history which is a glorious way of saying well actually I ask what you have for breakfast, most people have cereal or toast if they're Brits and then they have a sandwich at lunchtime and then they sit down in the evening and somebody in the house cooks a meal.

And that's the time of day when you're having vegetables, so whoever cooks in the house I usually say to them please would you cook and put on the plate the same amount of green vegetables every day. It could be nothing, it could be a mountain, it could be a teaspoonful, it could be a tablespoonsful, it could be a cupful, it doesn't matter, but it has to be done every day and then you've got a consistent background of vitamin K for the warfarin to work on. Just remember carrots are red, they don't have any vitamin K in. And

the other thing is that cauliflower is white but it breaks the rule, it does have vitamin K in.
So the real excitement now is we've all had enough of monitoring anticoagulants, it's a huge industry, and all the drug companies knew that there was a massive commercial market for them out there if they could find a drug to replace warfarin. So we've got two that we're already using in this country with many more on the way, they're itsy-bitsy tiny little molecules and they have a direct effect on the coagulation pathway and we class them as either having an anti 10A effect against molecule factor 10A or they have an anti-thrombin effect.

And the joy of them, and I speak passionately here, because I'm fed up of anticoagulant clinics too, is that they have a predictable dose response, you don't need to monitor them and you don't need to adjust the tests and they don't get affected by food and they don't get affected by alcohol. And they have a very limited number of drug interactions like warfarin, you just have to take an antibiotic with warfarin and you're out of control. There's just two classes of drugs where there's interference, so fantastic.

And more than that they've been widely trialled now, they've been given to hundreds of thousands of patients in huge clinical trials and what they have shown surprisingly, now this is a very scientific summation of all the trials they did of patients of atrial fibrillation who need to be on warfarin, that's the bulk of the patients in the anticoagulant clinic is they are better, they give better anticoagulation than warfarin for that group of patients, and they have a lower risk of bleeding. And they have a lower risk of bleeding particularly in the head, because we're always worried about intracerebral haemorrhage, so they are more efficacious, they work better, and they are safer. And by goodness they are convenient too because we are talking about one or two tablets a day.

So where have we got to? So this is just saying where all the trials have happened. We've got Rivaroxaban, Dabigatran, Apixaban, Edoxaban, they're all abans, there's other abans coming through, and Rivaroxaban is the one that's been accepted in most number of areas, so we use it for preventing clots after hip and knee surgery, we use it in patients at risk of stroke with atrial fibrillation and we use it also to treat deep vein thrombosis and pulmonary embolism.

Dabigatran has been out a little bit longer, a bit slower, actually this is now wrong because the week before last it got a licence to treat DVT and pulmonary embolism, Apixaban is about to get the same. Exciting.
So we're all moving over to them. So this is the protocol for the docs on how to manage a deep vein thrombosis or a pulmonary embolism if they come to our accident and emergency department. I don't want you to know the details, I just want you to see that we now use Rivaroxaban as our first line, no more injections of heparin, no more tablets with warfarin.

And the shock horror for lots of people is, it's cheaper. So NICE have looked at using it in deep vein thrombosis and pulmonary embolism, they do some very complicated results, but basically what this says is it you have a DVT or you have a pulmonary embolism it's so much cheaper to use Rivaroxaban for the first three months. And even if you continue to use it, someone needs to have it long term it's still an acceptable price to pay for that, it's slightly more expensive than warfarin.

So of course they are exploring other areas. So what have we got going on here in combination with UCL? Well, Professor Khamashta and I are leading on a study on leading with Rivaroxaban in Antiphospholipid Syndrome. Now the problem is all of the studies have only looked at people who are running an INR target of two to three, no one knows what dose to use if you're running an INR target of three to four, so we can

only really try it out in those with an INR target of two to three and those who have previously had a deep vein thrombosis or a pulmonary embolism. So we are recruiting a reasonable rate and we are going to find out about its safety.

Now, for those who have got cerebral or brain Antiphospholipid Syndrome I'm afraid you're going to have to wait because we don't know what dose to use and I suspect from what the patients are saying in the clinic, some of them are getting headaches and things, that this dose isn't enough and does it work in the right way to help people with cerebral APS because warfarin is amazing because it does work so well. And the other word of caution is there was a big trial where they tried Dabigatran out in people with artificial heart valves and they have to run their INR between three to four and they had to stop the study because so many people had thrombotic complications, it didn't work. And we don't quite understand why it didn't work, but just a word of warning, it will be fine for people running an INR with between two to three to go into a study but we aren't ready yet for those running an INR between three to four.

So it really is the dawning of a new age in anticoagulation, but we must be cautious, we want to be safe, we're not switching anyone over unless we think that it works and that it is safe, clearly it's convenient. And the other thing that's happened is we've suddenly realised actually warfarin is a bloody good drug and although it's got some problems it's also got huge advantages. Thank you very much.

Professor Graham Hughes:
Thank you very much indeed, Beverley, I'm sure there'll be lots of questions, and again we've been asked to keep them to the end, but it's a great pleasure, I'm not sure if Anisur is here, to welcome Anisur Rahman from University College Hospital who's going to update us on what's possibly new and futuristic in the management. Many thanks for coming.

Professor Anisur Rahman

Prospects for innovative treatments in APS

Thanks very much, Graham, and it's a pleasure to be invited here once again as a guest artist in this St Thomas' show, I'm the only one who's not from St Thomas' here.

So today I want to talk to you about the future, and the reason I'm talking to you about the future is I think about the future a lot these days and the reason is that one of my jobs at UCL is I run the medical student teaching, so every year we get 120 students in groups going through our department in UCL and I was thinking about them, so the people who start medical school this year, their career as doctors will run from 2020 to 2060. So what's life going to be like for them? How are they going to be managing this syndrome? And my prediction is this. The future will be different, the future will be better, and above all the future will depend on patients, and I'll explain to you why that is, there's a central reason why what happens to this syndrome in the future will depend on patients.

So before we talk about the future let's say what we have at the present, so what drugs do we use to treat this syndrome today. So we use warfarin, we use heparin, we use aspirin in some cases, and I've got

hydroxychloroquine in brackets because of what Munther Khamashta says, many people think that this would be a good drug for use in APS but it is not generally accepted, it's not part of a standard management, you won't find a textbook which says you should treat patients with this drug. So this is one which is kind of on the edge of being accepted and those are the sorts of drugs that we have at the moment.

So lots of people, probably people in this room, are being treated with one or more of these drugs, so you might say so what's wrong with that, why does the future have to be different? So why isn't it good enough? Why aren't the drugs that we have now good enough? Well one reason is side effects, they have side effects, and one of the main side effects is bleeding, people can bleed on these drugs. The need for regular monitoring which Beverley has described eloquently, all these regular blood tests, INRs, it's a pain in the neck, you have to watch out about what you eat, you have to watch out what you drink, you have to watch out if you're on antibiotics, that's irritating. If you're on heparin of course it means you have regular injections and that's not very nice either.

Evidence, is there evidence that these drugs work? Well there is evidence that these drugs work, and in fact Munther and Graham were some of the first people to publish that evidence and after that many other people published it as well, so you wouldn't go anywhere in the world and find somebody who says it doesn't work, it does, we know it works. Heparin has evidence as well, there isn't very good evidence for aspirin and hydroxychloroquine except for in pregnancy with aspirin. So although they're used it's very hard to say that they're definitely backed up by good evidence.

The next two things in my list are actually contradictory to each other, so one of the reasons why the drugs aren't good enough is that they don't always cure all the symptoms. So some people are on warfarin and yes, it stops them having clots or strokes or whatever but it doesn't get rid of a lot of the other symptoms like joint pain for example and fatigue and livedo reticularis and things like that, so we have these treatments and they're great, they stop you having a clot, they stop you having a stroke, but do they make you feel well?

Well that's not always the case. The contradiction is that there are other people who feel perfectly well, so they're feeling perfectly well and they're on this drug every day for years and years and years, they have to take this drug, and why are they on it? To prevent something. To prevent something which might never happen. So you're on this drug, you have to take it every day with all the inconvenience that that has and it's to stop you having a clot or a stroke. So if you say to your doctor, 'so will I have it if I stop the drug?' they can't tell you for sure that you'll have it. You're on something to prevent a thing that might not happen, so it's a risk management thing.

It's like when we wear a seatbelt, we wear a seatbelt every day to prevent ourselves from being injured in a car crash. Well you might have a car crash, most likely you won't have a car crash, wearing a seatbelt isn't terribly inconvenient, taking warfarin every day is much more inconvenient, so you have to factor that in. What sort of drug do we want to give to people who don't feel ill and they have to have it as a preventative agent?

And lastly, anticoagulation is not a specific treatment for this syndrome, anticoagulation blocks all clotting, both the good and the bad. Clotting isn't always bad, if I cut my arm today I want to clot, I want my blood to clot, that's a good thing for me. If I'm on warfarin, yes it will stop the bad clotting but it also stops the good clotting. So I want something which will leave me with my good clotting and just get rid of the bad stuff, the

stuff that happens with the Antiphospholipid Syndrome. So for all those reasons the treatment that we have, good as it is, is not perfect, and that's why we need something better.
So what do we want? Here's my wish list, you might add to it if you want. We want I think drugs that work just as well as what we've got at the moment, at least as well, maybe better. We want to be able to use them long term and without any symptoms, we want them to be acceptable because they haven't got any side effects for people to take for years and years and years, even though they're not feeling ill.
We want them to have fewer side effects than anticoagulation. We want them to treat all the symptoms, not just prevent clots and strokes. And so all of this are uses for something which is targeted, it's not just a general blocking of coagulation, it just targets the things which are going on with the Antiphospholipid Syndrome.

I liken it to a society where you have some vagabonds, some terrorists, some bad people running around in a society. So one way to stop them is to run a police state, you repress everything, you repress everybody's freedom then the bad people can't do any crimes, but it's not very good for the good people either. That's what having warfarin is like, warfarin suppresses all your clotting just so you can stop that bad clotting which might or might not happen.

It's much better to target the bad people, to go and get those people, stop them doing bad things and leave everybody else free to lead their lives, that's what we're looking at, something which is targeted just at the Antiphospholipid Syndrome. So how are we going to get there? That's the question in the future, and I think there are three steps.

Number one, understand the biology of the syndrome, how is it happening. Two, develop drugs based on the biology, and three, prove that the drugs work by doing clinical trials. So can we do it, how far are we along? And I hope to show you that actually we're surprisingly far along the road to doing this.

So this is the biology of the Antiphospholipid Syndrome. It's an autoimmune disease, that means that it starts with these antibodies, antiphospholipid antibodies or APL, which instead of fighting against bacterial viruses attack things which are in your own body. That's what's going wrong, you've got all these antibodies which are attacking something in your own body and the something in your own body is called an antigen. So the first step is that the antibodies attack the antigen and when they do that then the antibodies and the antigen together go and attack cells in your body in various parts like the blood vessels in the womb and that in turn leads to thrombosis, clots and miscarriages. Now what we're doing right now is we're just attacking the bottom of the diagram, anticoagulants just attack that right at the bottom. All that stuff at the top, all that stuff which is to do with the antiphospholipid antibodies themselves is not being addressed by our current treatments.

So how can we do it? Well the first thing I said was it all starts with the antibody and the antigen, so what's the antigen, what's the thing in your body that these antibodies are attacking? And the thing in your body what most of these antibodies are attacking, not all of them but most, is this. It's called Beta-2 Glycoprotein 1 and it's a protein which is present in every one of us, we all have it, it's a normal thing for us to have, it's not a disease, we all have this.

What do we know about it? Well it's in everybody, it's divided into five parts, so it's a protein which has five domains or five parts like beads on a string, I've shown them here. Now, domain one which is at the top is the one which the antibodies attack and domain five at the bottom is the one which attaches to cells.

So you've got the antibodies at the top, the attachment to cells at the bottom. So what happens is this, I've shown it in steps, step one you've got the antibody binding to domain one, and you can see it acts like a bridge. Every antibody molecule has two arms so it can attach two molecules of Beta-2 Glycoprotein 1, so it makes a bridge, it makes a bridge of two molecules.

And that thing, that Y shaped thing I've shown then attaches itself to cells by means of its other end, the domain five end. And when that happens the cells react, they get switched on and by switched on I mean that there are these things floating around on the surface of cells which I've shown by the dark blue trapezium, those are called receptors. Those receptors are not triggered normally, when this antibody antigen complex attaches to the cell they get switched on and that in turn switches on things inside the cells which are called signalling molecules which causes clots and pregnancy loss.

And that's how it works, that's the biology of the Antiphospholipid Syndrome. So if we know that, and we do, there's lots and lots of research showing that, does that mean that we can invent some treatments? So you can see logically there's lots of things we could do, we could take away the antibodies, we could give a treatment which gets rid of all the antibodies. Or we could give a treatment which stops the antibodies from attaching to domain one, or we could give a treatment which stops the domain five attaching to cells.

All of these things I'm showing in red circles are interruptions of this pathway that I've shown you. Or we could do something which blocks the receptors so even if the antibody tries to switch them on they won't be switched on, we're blocking them. Or we could block the signalling molecules, so that's five different places where there could be drugs to block this process, none of which are anticoagulants, all of which would be new to the syndrome. So this is a possible future.

So you might be thinking now well this is pie in the sky, he's talking about stuff which is 30 years away. So here are some surprising facts for you. All those things, all five things that I've just talked about, there are already things, chemicals, I could bring a bottle of the chemical and show it to you, if I could afford it, and they exist, they're in the world today.

Furthermore there is a place in America, in Texas, where they have mice with Antiphospholipid Syndrome. Well I put it in inverted commas as you can see. They don't exactly have Antiphospholipid Syndrome, what happens is they give the mice blood samples from human beings with Antiphospholipid Syndrome and the mice get clots, so it's what's called a mouse model. And so what you can do is you can say in those mice if you give them these agents do they not get clots anymore? And all five of those things that I've told you about work in the mice.

Now, drugs which target those things are already available, drug companies have made those drugs, they have given them to people, not people with Antiphospholipid Syndrome in general but other syndromes, so they're already available, some of these drugs. Not for all of those things but for some of them. For one of them, the one where you get rid of all the antibodies, there's a drug called Rituximab, and Rituximab is a drug which kills the B lymphocytes which makes antibodies. And Rituximab is a well-established drug, it's used in cancer, it's used in rheumatoid arthritis, it's used in lupus, it has been given to probably thousands of people around the world, it already exists, and a group in New York has tried it in people with Antiphospholipid Syndrome, have actually done a trial in people with APS.

The results were not particularly promising, it's not the case that all of these will work in Antiphospholipid

Syndrome and the results of that very small trial weren't necessarily promising, but it just shows you that what I'm talking about is not pie in the sky, it's not in the far future, there's actually no reason why these things can't happen. These drugs could be made, but here's where the patients come in.

Let's say we make these drugs okay, can we use them? Is it okay to use them in people with Antiphospholipid Syndrome? And the answer is it's only okay to use them, they will only be licensed, it will only be allowed for them to be used if clinical trials prove that they work in people with APS and they are safe, and - and the last one is a controversial one - oh sorry, this isn't controversial, the next slide is controversial - so we can use them if they work, we can use them if they're safe and having clinical trials depends absolutely on patients, doctors cannot do trials without patients, it is impossible. And that's why the whole future of this depends on patients.

Okay, so let me tell you how a trial works, and it's possible that some of you may have been in a trial already but many of you won't have been, and in very simple terms it works like this. You have a number of patients with an illness, I've called it a thousand for the sake of argument, a thousand people with Antiphospholipid Syndrome, and randomly, it has to be randomly so there's no bias, they're allocated, half of them go to one treatment which is the standard treatment, in this case warfarin, half of them go to the other treatment which is the new case, the new treatment, we'll call it drug X, this new agent. So half and half.

Now right at the top there's a decision and the decision is made by the patient, somebody like myself or Professor Khamashta or Professor Hughes will come to you and say look, there's this trial, would you be willing to take part? You might say okay, what's in it for me? What's the risk? What's the benefit? And then someone would explain to you, they'd say this is the drug, we think it will work, we think it will be better than warfarin, we'd like you to change from warfarin to the new drug, but we can't tell you for sure, you've got a 50/50 chance.

A computer will work it out and you might be on warfarin, you might be on the new drug, you won't know because I'll make tablets which look just the same, nobody will know, but you, the patient, are taking a risk. And at the end of it they'll work out whether it works by counting up the number of clots in the warfarin group and the number of clots in the drug X group and the side effects.

So drug X would be considered to work if the number of clots is much less than in the warfarin group, the side effects are not as severe and at least no more common, and, and this is the controversial one, drug X would work if it was not so expensive that the country couldn't afford it.

So if you had a drug which worked but it cost £20m per patient you couldn't use it, it wouldn't be possible to use it. So that does factor in as well. So what are the problems with doing this? So think of it from the point of view of a patient, warfarin is a very good drug in many cases as Beverley Hunt has said. So you have a group of patients and not many of them get clots. Let's say you have a hundred patients and you would expect two of them to get clots on warfarin, so how much better can drug X be then? It can only be one or zero but that might happen through chance alone. So really you're going to have to do a thousand patients and show that 20 get clots on warfarin and ten get it on drug X because only then will you believe it's a real effect. So you're going to need huge numbers of patients.

Beverley showed you all those trials of Dabigatran and Rivaroxaban and so on and all those trials had

thousands and thousands of patients, she said that, that's not an accident, they had to have thousands of patients. They had to have thousands of patients because in the warfarin group the number of clots were so small already that to prove that the other drug was better you had to have thousands of patients. And who has thousands of patients with APS, not even St Thomas' has thousands of patients with APS.

The big thing here is would patients want to take this risk? I'll come back to that in a minute, and you might have to keep the trial going for a long time because the only way you know if it works is if some people have clots, and it's hard to say it but the only way that you know if one is better than the other is if you can count the number of clots, so some people have to have clots. That might take a long time so you might have to go for a long time which will be expensive and so on.

NICE, the National Institute for Clinical Excellence, is the body in Britain which decides which drugs can be used. You've probably read about it in the papers, drugs which have been rejected by NICE because they don't believe it's value for money, so they have to agree too, but this is the critical one, would patients take the risk? And to be honest, I don't know, the one thing that I can't say or Professor Khamashta can't say or even Graham Hughes can't say is what is it like to be inside the head of somebody who actually has Antiphospholipid Syndrome? What is it like to be the person who is actually taking the risk?

If I'm a person who has been kept free of strokes for ten years on warfarin and I change to a new drug that's a risk I'm taking, and it's not the same as doing a trial of rheumatoid arthritis, if I go into a trial of a rheumatoid arthritis drug and it doesn't work very well, the new drug, I'll have very painful arthritis for a while, but you can rescue me, the doctor can rescue me by changing me back to the old drugs. I'll be back to where I was before. If I'm a patient with Antiphospholipid Syndrome and the new drug doesn't work and I get a stroke how are they going to get me back to where I was before?

So there's a risk and would I take the risk if I was a patient? I don't know the answer to that. Somewhere along the line patients are going to be asked to make this choice and that's why the whole thing is dependent on patients. Munther will remember a trial that both of us were involved in about ten months ago which he might tell you about later which was much less controversial, it was about two drugs which were known for years, aspirin and warfarin and patients had to choose aspirin or warfarin, it was very, very difficult to recruit people to that trial, very difficult. And I sympathise with the people, why would they want to choose warfarin when they were doing fine on aspirin. So it's not a small thing.

So lessons from lupus. Now, lupus is a disease where we have done trials of new agents and here are some lessons. Rituximab, the one I told you about, has been trialled in lupus, big trials, and what happened was the trial said this drug doesn't work, it's not any good for lupus. In fact it probably does work but there was a reason. One reason was, just like I said for warfarin, warfarin is very good for APS, so how are you going to prove something else is better? Similarly in this trial of lupus the Rituximab group did pretty well, lots of them got better, but the people who were not on Rituximab also did very well because they were on other drugs which made them better. So you couldn't show Rituximab was better, both groups did well. That could happen in these trials too. And the other thing about the Rituximab trials is they didn't have enough patients, they had about two hundred patients in the trial.

Belimumab is a different drug, and in that trial they had eight hundred patients, much more. Because of that they managed to show that the drug was better than the alternative, so you'd think fantastic, halleluiah, we've got there. NICE will not let British doctors use Belimumab for lupus because they made a calculation

that based on the cost of it it was too expensive for the country to bear using it in such a rare disease as lupus. So even though it works, nobody disputes that it works, British doctors can't use it.
So those are some lessons from lupus. So what could be the solutions? Number one, if these trials happen they will be huge, they will be very big trials and no single centre can do it alone, I don't think any single country can do it alone, I think it has to be international collaboration, so Nigel Farage, if you're in the audience, I'm sorry, we're going to have to work with Europe on this one, it's going to have to be working with some of the people in the picture that Graham showed.

I think the answer is to be cleverer. Yes, we can measure the number of clots, but do you remember my first slide where I said we want something which does other things? I think we need to find another way of measuring the other effects on the patients. Does their migraine get better? Does their fatigue get better? Does their livedo get better and does the new drug do that better than warfarin does? If we can measure more subtle things like that then it may be easier for us to see that the new drug is better than the old drug.

Now, that business I told you about, would you take the risk? If you're happy on warfarin would you take the risk of being on a new drug? If you believe that actually people wouldn't take that risk then one answer is well we'll only try it in the people that can't manage warfarin. There are people who hate warfarin, they can't tolerate warfarin, warfarin does not work for those people, so you think those are the people we're going to try the new drug in because they don't have an alternative those people, they're the ones. And lots of drugs in lots of diseases are tried in those people first, the hardest cases of all go on to the new drug. But you can see the flaw, it's like the old proverb, hard cases make bad law, if you try the new drug in the most challenging cases first then it may very well fail, because you gave it such a hard challenge and then you'll throw it away, even though it might have worked in the people who weren't as hard to treat. And that's a big danger because that can happen. So it's very difficult in that way.

So I don't want to give you a hopeless message because I started off with all that stuff about there are new drugs, we can develop them, the science is there, the drugs are there, the question is how is it going to be translated from the science to actually giving it to patients. And critically, I want to leave you with this, it will depend on patients because in the end the patients are the ones who are making the choice and taking the risk. Thank you.

Professor Graham Hughes:
Thanks very much, Anisur. Anisur's got to leave afterwards so we'll break with the previous rules and ask you two questions right now.

Beth:
So these are two questions that have come in in advance. The first one is:

Q1: Fatigue is listed as a low grade symptom of APS and yet once an appropriate anticoagulation regime is established it generally becomes an APS sufferer's prime consideration. At present hydroxychloroquine is the only medical treatment prescribed, what research is currently being carried out and is being planned for the future with a view to studying fatigue in APS patients and thereby broadening the treatment available to combat it?
Professor Anisur Rahman:

Okay, it's a simple answer because it's not a very good answer, and the answer is fatigue is one of the most difficult symptoms to deal with, not just in APS but in lupus and in most autoimmune rheumatic diseases. Sometimes people with lupus are treated with high doses of steroids and everything gets better except their fatigue, the truth is we don't have a good grasp on what causes fatigue in these patients.

Now, David D'Cruz who's sitting in the audience, about 15 years ago now did a very interesting study in patients with lupus in whom he said that exercise was the best treatment. So we got patients with lupus to do a relatively low level of exercise and they felt less tired, they didn't have side effects, but the downside, and I'm sure David will confirm, is that a year later they weren't doing the exercise anymore. And that was proper research, a proper trial, which proved that, and nobody as far as I know has ever followed it up because it's very difficult to do trials like that.

We don't know what causes fatigue in patients with lupus, sometimes it's related to other things like poor sleep, stress and so on, which all feeds in, it's multi-factorial, and a drug, a single drug, probably isn't going to be the answer. So it's not something which is easy to study. David D'Cruz has probably done the best study, or one of the best studies, so he might be a good person to answer it. So people try but it's not easy.

Beth:
Okay thank you. And the second one we have for you is:
Q2: Why are rheumatologists reluctant to treat mildly and moderately affected patients, especially secondary Hughes patients more aggressively, for example, introducing steroid or immunosuppressant treatment?

Professor Anisur Rahman:
Is that about secondary APS?

Beth:
Well, it says secondary Hughes or mildly and moderately affected patients.

Professor Anisur Rahman:
It's about risks and benefits is the bottom line and it just comes back to my point about who is assuming the risk here, is it the doctor or is it the patient? And in general if you give people aggressive drugs with side effects, let's take steroids as an example, would I personally like to take 15 milligrams of steroids a day every day? I would not, because I know the side effects of those drugs.

Most drugs that we use aggressively, aggressive treatments, have lots of side effects. So the question is does the benefit of using the drug in a patient outweigh the risk of using the drug in a patient? And that depends on how cautious you are as a doctor. And many, many doctors are quite cautious about that; before they're going to use a drug they're going to want very strong evidence that it will work. If you have a patient who we're going to call mild, in inverted commas, because their blood tests are fine, they don't have swollen joints, big rashes and so on, but they have lots and lots of symptoms, we don't have very good evidence that giving those people lots of drugs or high doses will make them better, and we do have quite a good evidence that giving people those sorts of drugs over the long term will have side effects.

So the reason people are cautious is because the risk benefit ratio looks as if it's going more towards risk and less towards benefit. It's an individual decision, I certainly have had patients who all the blood tests are

always normal, but you work out over a number of years that actually when these patients get particular symptoms they do respond to a short dose of oral steroids and that's what they need. So it's a patient by patient thing, but over the whole range of patients doctors are cautious and I think it's appropriate because the first principle of medical ethics is this: first do no harm.

Professor Graham Hughes:
Our last speaker before the break is my colleague, David D'Cruz, who's going to talk about this and about the brain I think.

Professor David D'Cruz

APS and the brain

Thank you very much, Graham. Just to extend the question session from the previous, ((Lyndsey Beard?)) who's in the audience and I are looking at fatigue in Antiphospholipid Syndrome and as Anisur said, this is an incredibly difficult area to look at, but we're going to be doing some qualitative research which means what are the factors that drive fatigue in APS patients before moving on to clinical trials if we have.
I advise all patients with Hughes Syndrome and lupus to take regular exercise, and the other bit of research that we did some time ago was actually weight loss, we did a study of calorie controlled diet versus a low carb diet, and we showed that just by losing weight fatigue improves, so these are simple things that can be done.

So I'm going to talk to you about the brain and Hughes Syndrome, you've seen this slide already, thrombosis, venous and arterial and pregnancy loss and really Graham should be given full credit for describing this syndrome and it's with all our support that it's called Hughes Syndrome.

And I entirely agree with Graham, this is a brain disease, it's a neurological disease, and here's a very sad patient that I looked after many years ago when I was still at St Bartholomew's Hospital. She was a 35 year old nurse who came along, she'd had a stillbirth and three previous miscarriages and during the last pregnancy before the stillbirth she had something called HELLP Syndrome where your platelets drop and your liver function tests go off the scale.

And she came in with a stroke, and you can see here that the baseline brain scan when she came into St Bartholomew's was normal, we made a diagnosis of Hughes Syndrome, we started treatment with anticoagulation but despite treatment she went on to have two more strokes and then she bled into those strokes and she sadly died. So this is a really serious complication and fortunately we don't see so many of these severe patients but it illustrates the point very well.

There's a whole spectrum of symptoms and syndromes that you see with Antiphospholipid Syndrome. Headache Graham has mentioned already, it's very, very common, especially migraine, and cognitive dysfunction, Graham put up a very nice slide showing that these patients have memory problems, brain fog, they forget friend's names, they forget where they're going, they forget why they went into a room, this is very, very well described. It's also a feature of lupus and trying to distinguish what cognitive dysfunction is

due to lupus and how much is due to Hughes Syndrome is almost impossible.

Strokes have been mentioned and I'll come back to those. There are other types of thrombosis in the brain as well, as well as arteries in the brain they are veins or sinuses and they can clot as well.

Seizures are a major manifestation of Hughes Syndrome and movement disorders. I saw a 14 year old a couple of weeks ago who I discussed with Beverley Hunt, who suddenly developed massive chorea, these severe shaking disorders. And then there's very controversially the Multiple Sclerosis like syndromes and I'll try and touch on these in the next ten minutes or so.

So cogitative dysfunction has been studied a great deal, there's a strong association with memory disorders with Antiphospholipid Syndrome, in lupus cognitive dysfunction results in reduced attention spans, reduced ability to concentrate and you're unable to process information, you do it slower than other people. Headaches and seizures. So Graham Hughes many years ago made this observation, that if you had a patient who had headaches and a previous history of seizures, they then had a blood clot, a deep vein thrombosis or a pulmonary embolism, you start them on warfarin and immediately the headaches disappear. Not only do the headaches disappear but the seizures stopped. In many cases the seizures stopped and you were able to take these patients off their anti-convulsant, their anti-epileptic medication.

So many years ago Maria Cuadrado with Graham's direction decided to look at this, we decided to look at headache in the Antiphospholipid Syndrome, and this was a proper controlled study, a randomised controlled study, looking at getting patients with bad headaches to fill in a 56 questionnaire every day and that's enough to give you a headache anyway, every day, but they did this and wonderful patients, as Anisur said, patient involvement is critical, but these were well motivated patients.

So these patients were given heparin injections, filed in the questionnaire with the headaches, stopped all treatment for two weeks and then went on to a dummy treatment and just injected themselves with a dummy and nobody knew which was which. The problem is everybody got better including the placebo patients, the dummy patients. And this was very disappointing to us but it tells us the power of the placebo, just simply injecting yourself is a very powerful thing to do and people got better. So we're a little bit no further on from that point of view.

Seizures are dramatic, they occur in lupus patients, the prevalence is 10% to 15% in this particular study by Appellenzer and seizures in lupus are a feature of cerebral lupus on its own without Antiphospholipid Syndrome but seizures in lupus are especially associated with the presence of strokes, and that makes a lot of sense, you've had a stroke, you damage brain tissue, that brain tissue, the electricity is disturbed and then you can get seizures with it.

Antiphospholipid antibodies, a very strong association obviously with strokes and then with seizures. And then heart valve lesions, Munther Khamashta and Ricard Cevera were the first to show that heart valve lesions don't just occur in lupus, they are a feature of Antiphospholipid Syndrome. This old label, Libman–Sacks endocarditis, these funny vegetable like things on the heart valve are a feature of Hughes Syndrome and you can get little blood clots sitting on those damaged valves and they can break off and give you these splinter haemorrhages, they can break off and give you mini strokes. So seizures are definitely a feature and certainly in this context with antiphospholipid antibodies in strokes one would have a very powerful case for anticoagulating somebody like that.

Now this is a really controversial area, so a lot of patients come along with lupus or not, they have a lot of headaches and sort of minor neurological symptoms so the next logical thing to do is to do an MRI scan. So you do an MRI scan and back comes your report showing these white matter lesions and we don't really know what they are, they could be areas where the blood is flowing more slowly, they could be mini strokes, we don't know what they are, but we do know from big studies in the Netherlands that if you take elderly patients in their 60s and 70s who do have these lesions, this is the Rotterdam scan study, these patients have a higher risk of developing strokes in the future, in their 80s, sort of ten years down the line.

So the question here, the big question for us as clinicians is if we see a patient with minor symptoms maybe and these lesions what do we do? This is a very controversial area. I think there's no controversy, if somebody has had clear symptoms of a stroke, or signs of a stroke, they have to be anticoagulated and warfarin I think would be the first line treatment. But if they have no symptoms or minor symptoms if you like it's very hard to justify putting somebody on warfarin for the rest of their lives if they've not had a proven thrombotic event.

So what do we do in practice? We put all of these patients on aspirin even though there's absolutely not a shred of evidence that it does help, it's probably treating us more than the patient, but we think it does help. And again many people have mentioned the hydroxychloroquine, patients with lupus will be on hydroxychloroquine anyway, but if they're not on hydroxychloroquine because hydroxychloroquine does have a weak blood thinning action we would certainly consider adding hydroxychloroquine to aspirin, but again there's no evidence in this area.

Where there is plenty of evidence, not just in lupus and Antiphospholipid Syndrome but in the general population is we must reduce the standard cardiovascular risk factors and this is common sense stuff, get your weight down, stop smoking, get your cholesterol down, this is fairly standard stuff. And actual as rheumatologists we've been fairly poor at addressing these, we tend to ask the GPs to do it, but in fact actually there's been a sea change in our attitude to reducing cardiovascular risk factors and we're much more proactive now at addressing these in the clinic.

So we come to this study, published in a big journal, JAMA, Antiphospholipid Antibodies and Subsequent Thrombo-occlusive Events in Patients with Ischemic Strokes, the APAS investigators. Now I'm going to keep Munther away from the stage because he'll come here and he'll start fisting me. This is a very controversial study. Briefly these studies started off looking at stroke in the general population and it's a very important question, if you have a stroke should you put a stroke patient on warfarin or just leave him on aspirin, this is completely independent of Antiphospholipid Syndrome.

So they did exactly that, they randomised large numbers of patients to either warfarin or aspirin and you can see that there was no difference in either arm and I thought it was a reasonable conclusion that there's no benefit. If you had a stroke without Antiphospholipid Syndrome there's no benefit to adding warfarin to these patients. They then made a very controversial sub study and they looked at patients at the beginning of the study who happened to be tested for antiphospholipid antibodies, just on one occasion, and they concluded amazingly that routine screening for Antiphospholipid Syndrome in stroke patients was not warranted; that's my exclamation mark.

Now many years ago when I was a registrar I used to go to these ((Bajar?)) conferences and people would stand up and ask a question and they'd preface their question with, 'with due respect, Professor D'Cruz'

that means they don't believe you. When they say 'with the greatest respect' they say Professor D'Cruz is talking a complete load of rubbish. This, with the greatest respect, is a complete pile of rubbish, this study, and actually Munther stood up at the American College of Rheumatology with 15,000 rheumatologists and said exactly that. So when we say critique we mean this is a load of rubbish, this study. And I'm not going to go through this but essentially there were so many problems with this paper it was a miracles, I've no idea how it got into such a big journal as JAMA. This is definitely not a treatment trial of stroke in APS and as far as I'm aware there's never been a treatment trial taking patients with Antiphospholipid Syndrome and randomising them to warfarin, heparin, and I think that probably would be unethical to do now.

This is a very important study in The Lancet and this was looking at the predictive value of this terrible name, the lupus anticoagulant, as people have already said it's nothing to do with lupus, it's not even an anticoagulant, but it is a powerful risk factor, it's one of the sticky blood antibodies. And what they showed was that the odds ratio, if you're a young woman who is lupus anticoagulant positive and you've had a stroke that risk is massively increased by smoking and being on the pill or even both.

So it's very clear that the lupus anticoagulant, one of the major sticky blood antibodies, is a major risk factor for stroke, the risk is increased by having other risk factors, like smoking and the pill as I've mentioned already, and the clear message is that if you're a young woman who's had a stroke these patients should be tested for the Antiphospholipid Syndrome. And in our view that should be all three antibodies, Beta-2 Glycoprotein 1, cardiolipin and of course the lupus anticoagulant.

So I'm stretching even more controversially difficult areas, so we know that Multiple Sclerosis is an autoimmune disease, it's an autoimmune disease that particularly causes inflammation in the brain, it leads to neurological signs and symptoms, people end up in wheelchairs. We also know that if you do prospective studies of Multiple Sclerosis clinic patients attending a neurology clinic and you test them for a bunch of antibodies some of those patients will have antibodies, including lupus antibodies or antiphospholipid antibodies.

The question is, is this what we call an epi phenomenon, is it just bad luck, is it because they've got an autoimmune condition and that's why they've got these antibodies and they're meaningless, or is it a real phenomenon, are these antibodies actually causing Multiple Sclerosis? This is very controversial, we have a large number of patients here at St Thomas' Hospital, over a hundred now, who've clearly got Multiple Sclerosis who clearly have Antiphospholipid antibodies.

So the first question is should all Multiple Sclerosis patients be tested for Antiphospholipid Syndrome? I don't think so, I think routine screening of MS patients I think is very controversial, I don't think I would do it. Where I would consider antiphospholipid antibody testing is in patients who have what the neurologists call atypical MS, so it looks like MS but there's lots of features that don't fit for it.

And certainly in our standard patients with lupus or patients who've got Antiphospholipid Syndrome this may well be what we call demyelinating syndromes, in other words, MS like syndromes may occur in patients and certainly somebody with lupus who's developing Multiple Sclerosis like syndromes I would definitely test for Antiphospholipid Syndrome.

What you do about it is a bit more controversial, and the question here is do you anticoagulate these patients or not and again there's no evidence at all in this area, there are a few patients who do benefit

from being on anticoagulation, in my personal experience and Graham may differ here, most don't because these patients have suffered inflammation in the brain and that's left damage and scarring and no amount of anticoagulation is going to improve that damage.

This is Sneddon's Syndrome which is livedo reticularis in recurrent stroke. In fact the vast majority of patients actually are Antiphospholipid Syndrome or Hughes Syndrome patients.

So treatment. So cerebral APS is what we call it when it affects the brain. I think it's very clear, a patient who's got moderate to high levels of antiphospholipid antibodies, persistently high, who has clear evidence both clinically and radiologically, they've got cerebrovascular ischemia or stroke like syndromes I don't think anybody would argue that these patients would need to be on warfarin. And we would argue here that patients with arterial events like strokes need to have a higher target INR of three to four. And what we also need to do obviously is to eliminate all the other cardiovascular risk factors, improve blood pressure, get rid of diabetes, get your cholesterol down, stop smoking and lose weight, these are all equally as important I'd say as anticoagulation.

So my final slide is Antiphospholipid Hughes Syndrome is a common and treatable cause of neurological syndromes, especially ischemic syndromes, and the other message I think for neurologists and emergency physicians is that if a young woman comes in with a stroke you need to ask them about symptoms for lupus, you need to ask them about a previous history of miscarriages, and you need to screen patients for Antiphospholipid Syndrome. Thank you very much for your attention.

Professor Graham Hughes:
Thank you very much, David. I'm sure you'll all agree, I certainly have enjoyed this first part of the meeting, if I could just make two domestic comments before we break for tea. First of all we have exhibition stalls, both here and I think down the stairs as well so please do visit them and they have been supporting Kate and her team.

Secondly for those who may have come late there's a questionnaire and I'd really be grateful if you could have a go at it, both patients and non-patients because that gives us what we've been hearing about this morning, the controls, and the reason for this questionnaire is to see the strength of family histories in this syndrome and it will give us I think very important information. So now we break for tea and come back here in 15 minutes or so. Thank you very much.

Hughes Syndrome FOUNDATION
for people with antiphospholipid antibodies

HSF PATIENTS' DAY: WEDNESDAY 14TH MAY 2014
Session 2

Chairperson (Professor Graham Hughes):
Welcome back, and it's a great pleasure to introduce the next speaker, Mette Toft, whom I've known now for two years I think, and I think she'll tell you more about it, but she's won a major international prize for the things she has written from the patient's point of view. So it's a great pleasure, welcome from Denmark, and welcome to sunny London.

Mette Toft:

Secrets for healthy ageing with a chronic disease

Hello everybody! First of all, I'd like to thank Kate for letting me speak here today. It is truly a great honour and quite a bit scary, especially following all the doctors, but I have to tell myself that I don't do this for a living and I've only given half of the speech once before. And as you can tell, I'm not a native speaker of English, my mother tongue being the exotic Danish language spoken by only a handful of people, so please bear with my pronunciation and other linguistic shortcomings.

What I'm going to talk about today is Secrets for Healthy Ageing with a Chronic Disease. That is I'm going to read to you my winning essay in last year's Stene Prize Competition, and that is EULAR prize - and I'll get back to that – the EULAR Stene Prize Competition on this particular subject. But before we begin, let me give you a very brief introduction to what EULAR and the Stene Prize are.

As some of you might know, and some of you might not know, EULAR stands for the European League against Rheumatism. Members of EULAR are scientific societies and corporate members, which means pharmaceutical companies I suppose, as well as health professional associations and patient organisations.

And this constellation underscores the importance placed by EULAR on combatting rheumatic diseases, not only by medical means but also through a wider context of care for rheumatic patients and an understanding of their social and other needs. And each year, around 15,000 people, mainly doctors and researchers from all over the world, attend the impressive EULAR congress in one of the major cities in Europe for four days of scholarly presentations and socialising. Patients, by the way, can register for only 35 Euros, so maybe you should consider going sometime!

EULAR has established a programme of special awards that are granted each year: The Young Investigator Award, The Abstract Award, The Meritorious Service Award, etc. The Stene Prize for Patients is a prize bestowed on the winner of an essay contest. You should consider participating in that once, too, because you get invited as a VIP guest to the congress and it's a unique experience.

Patients with rheumatic diseases are invited to write a two-page essay on a subject chosen by EULAR, and last year the Patients Organisation from 19 European countries participated and each chose their own national candidate for the international competition. And, by some amazing stroke of good luck, my essay

was chosen as the winning essay of the Stene Prize 2013. Now, let's get started.

The subject chosen by EULAR for The Stene Prize competition 2013 was the one that you see here. Not the most elegant title perhaps, but it did inspire me to write the following essay. And here's my essay:
When the World Health Organization (WHO) was established in 1948 under the auspices of the United Nations, it was, of course, necessary in its constitution to define what health actually meant. And they came up with the following grand statement: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".

This definition has since been criticised, not least for being unrealistic, but also for defining happiness rather than health. I find that for those of us who have been diagnosed with an illness it is particularly problematic and annoying that, according to WHO, we cannot – by definition – be healthy because we are sick.

The topic for this year's Edgar Stene competition clearly takes a different definition of health as its starting point – one where health and illness are not opposites, but where health is something we can strive for whether we are sick or well. I couldn't agree more. Of course it is possible to be healthy even if you are ill, just as someone can be unhealthy even if, on paper, they are well. So here are a few of my tips for how to make the journey from cradle to grave in reasonably fine fettle in spite of chronic rheumatic disease, or chronic disease of any kind.

Health secret number 1:
Don't worry – be happy!

I'm sure you all know this song and that many of you will agree to the idea that in every life we have some trouble, but if you worry you make it double. So this is not such a big secret anyway I guess!

"Tell me, how can you sit there smiling when you have all those illnesses to contend with?" a neighbour asked me recently when we were having coffee together. She meant no offence; she was genuinely mystified. I was totally stumped. How could I answer her? "Sorry, that was wrong of me. I won't do it again!" or "Well, you know, that's just a brave face I put on when I'm in good company!" No. After a brief pause I could only tell her the truth: "But that's just the way I am!"

Once again, I was reminded how lucky I am, because I am, at heart, a happy soul. However, I also think that a positive outlook on life is something you can consciously choose and try to hold on to, and that it pays to do so because it makes life so much easier, whether we are sick or well.

That cheerful disposition stood me in very good stead when, in the autumn of 2005, I came down with what I thought was a bout of flu. From then on the diagnoses began to rain down on me. I was 48 when, all of a sudden, I went from being fit and healthy to sick and wretched. And as you can see, it was in 2008 that I was diagnosed with Hughes Syndrome, and the diagnosis was made by Professor Hughes, so I think we have known each other for a little more than two years, and it's a pleasure!

Systemic lupus erythematosus was the first interesting diagnosis I had to get acquainted with, and a handful of additional diagnoses followed in swift succession: Sjögren's syndrome, Hughes syndrome, steroid induced osteoporosis and discoid lupus, among others.

At that time, when I was at my most ill and exhausted, and unable to do much else, I hit upon the idea of putting myself through a kind of laughter therapy. It didn't come naturally to me to laugh out loud at any old thing the way some people can. Instead, I sought out funny books and films and TV series, determined to laugh long and loud if anything was even the remotest bit amusing. I laughed like a madwoman – and had to reassure my husband, who was initially alarmed, that it was deliberate.

Does it work? It certainly does. Try it yourself sometime and see. It is very hard to brood on things and remain tense when you are laughing out loud. But it doesn't even take as much as that. Try just a big smile. Please everyone! Actually, I saw on television a study where they ask people to have a pencil across here, and that means you have to smile, and something happens in the brain, I think, when these muscles go up, so it is more or less scientifically proven that this helps. And if these three lovely ladies can't make you smile, I don't know what can! So I hope you are feeling better already!

And that brings us to Health secret number 2:
Health recommendations only help if you follow them,

And here it is no big secret either, I suppose, but easy to forget sometimes. I wonder if I am the only person who is tired of listening to all the talk about health and slimming. Tired of TV programmes about people who need to lose weight, instead of proper entertainment that makes us laugh. Tired of the glossy pictures in women's magazines of beautiful, well-turned-out people eating correctly and exercising properly in smart outfits, showing us how it should be done.

Honestly, this is just too feeble and excessive. Grown adults who need a personal coach in order to eat sensibly, and other grown adults who devote a large number of their waking hours to keeping fit and looking good. Don't we have more important things to achieve here on earth in the short time that we are here? I think we do.

We have heard all the recommendations, ad nauseam. Whether we take them on board is up to us. Whether you are sick or well, you are sure to be able to find plenty of excuses for your hard luck. But one thing is certain: health recommendations only help if you follow them, and no-one can do that for you. Not your mother, not your doctor, and not your Aunt Nellie! They are busy elsewhere, as you can see.

If you want to stop smoking, just make up your mind and do it. If you want to eat a healthier diet, only buy and eat healthy food. If you want to lose weight, just eat less and check your weight morning and evening. And if you want to put on weight, just eat more and check your weight morning and evening. And if you want to exercise more, and we just heard that exercise is very good for you, just get up off the sofa and turn off the television and log off from Facebook, and get going!

Enjoy your healthier lifestyle instead of feeling sorry for yourself – and then use all the new energy this gives you to do some of the things you want to do. And above all: do something that makes you happy! Thank you.

Chairperson (Professor Graham Hughes):
Mette would like to put a question to the audience. How about that!

Mette Toft:
I'm not a doctor! Okay, so I wonder if there are any questions, and if that's not the case, I have a question for you in the audience, because I would like to ask you what is missing in this essay? Because I was only allowed to write two pages and actually one very important secret is missing here. I wonder if you can guess what that could be? Or I'll just tell you that the third secret to healthy ageing that I would like to add is make sure you get yourself a good doctor! And I know I have, and he's standing right over here and I couldn't live without him, literally!

And just one more thing. In case you are curious about this EULAR and essay competition thing, you can Google EULAR Booklet 2013 and this will come up and you can read my essay and an interview with me, along with nine other of the essays submitted for that year's competition.

Chairperson (Professor Graham Hughes):
Thank you. It's a great pleasure to welcome back Caroline Fisk who is going to update us on the very important topic, still, despite the new drugs, of INR patient self-testing. Thank you for coming.

Caroline Fisk:

INR and patient self-testing

First of all, I would like to say that in the typical Hughes' style I do suffer from the brain fog, so please forgive me if I forget what I'm saying or repeat myself.

Before I would start, I would like to emphasise that this talk is purely about my own experiences of self-testing INR and other people will have different experiences to me. I would also like to emphasise that I self-test through the help of my local anticoagulant clinic; I do not self-monitor, purely self-test.

I'm 61 years old, I've been married for 34 years – that's my husband sitting over there – and I have two adult sons. I am a retired literacy support teacher. In 1998, whilst undergoing a minor operation, I had what appeared to be some kind of stroke, but I managed to get back to work after a break of six months, and then, after another 18 months of my teaching job, it became clear that I couldn't carry on. I had extensive neurological examinations in 2000, and I'm very glad to say that an alert and astute neurologist referred me to see Professor Hughes and I was diagnosed in 2001 with Hughes Syndrome. Initially, my condition was managed with Aspirin, and then a combination of Plavix and Aspirin, and then, in 2008, I had a three month trial of Heparin, which was a great success and I felt better than I had in months. In fact, within a couple of days I was literally swinging from the lights I felt so good.

I then went on to Warfarin, and I was then still a patient at St Thomas', and my INR range was set between three and four. It was suggested to me that self-testing would be a very good option for me, and I'm glad to say that I have a very supportive GP and a very supportive anticoagulant clinic and there was no problem with my surgery agreeing for me to do this. My INR range, as I said, is between three to four.

My dosage is mainly four to five milligrams, although that can vary. I self-test every week, and I know there's

a lot of controversy and some people say it's too much, but I feel happier doing that because I have periods when my INR is unstable. I also know when it's dropped below three because I have migraines, memory loss, lack of concentration, balance problems, intense fatigue, and feeling generally unwell. I'm sorry to say it was self-inflicted a few weeks ago, and I don't know what happened, but I forgot to take three doses of Warfarin and my INR dropped to 1.4, and I could truthfully say somebody could have set a bomb off behind me and I wouldn't have noticed, I was just completely out of it. I was told by the anticoagulant nurse, after I'd had a telling off, that I must go and get some Heparin straightaway. And it's only a short walk but my husband drove the car – I wouldn't have driven the car – my husband drove me to the chemist and all I can remember is walking round to the chemist and I literally couldn't walk in a straight line, it was like I was drunk. So at that point it really made me aware what Warfarin does for me.

The pros and cons of self-testing. Well, the big pro, of course, is the flexibility. If I'm not well or I have to have antibiotics or more painkillers than usual, or any other kind of mediation, I know that I can test myself, test my INR, to see it's affected it. I know now from experience that most, particularly painkillers, will take me above and into a higher INR range, but I have also experienced one particular drug that I was given, that in actual fact dropped it quite considerably the other way, so I always test then. I can test when I want, 24 hours a day, seven days a week, any time I want to, and if I've got any concerns I can test myself. It gives me a real feeling of control, and I think that's the main thing for me, it gives me a feeling of control over my condition, because I know that I can test myself and I know that I can phone up for assistance if I need it.

And the one thing I'm conscious of throughout this is that Warfarin is a dangerous drug. I think it's too easy to become complacent and think, 'Well, I've been on it for years,' blahdy-blahdy-blah, but I'm very aware of the dangers of Warfarin and that's why I'm very careful to try and keep my INR. To be honest, it would be so tempting to let my INR go up to five/six or whatever, because then I just feel absolutely fantastic, but I know that it's dangerous to do that, so I'm pleased to say I don't do that!

It's also very helpful when I need additional monitoring. A couple of years ago I had to have a tooth extracted and my dentist told me what INR he wanted me to be. I phoned the clinic and they told me what dosage to take. I was then able to test myself the day of the extraction, and I'm pleased to say that I had the tooth taken out, I didn't need a stitch, I didn't have any bleeding, I didn't have any trouble at all.

Similarly, when I've had to have one or two tests done, and also when, unfortunately, I've had to have four shoulder operations since that time, since I went on Warfarin, and again I was able to monitor myself, stop the Warfarin, and on the day of the operation I was able to say to the hospital, 'This is what my INR is,' and it was within range for the operation, so that again gave me a feeling of control.

As I said earlier, the flexibility means that I don't have to be tested within the clinic times. I am very, very lucky with the services that are provided at my local surgery. There are, in actual fact, anticoagulant clinics available at either of the partnership surgeries three days a week for patients to go in and be self-tested, but obviously you have to get there within those times and there can be quite a queue of people waiting to be tested.

It's interesting, actually, when you do go into the clinic, although I'm middle-aged I feel very young because most people are 80 plus! And the clinic nurse is available at those times for me to speak to her, and I had a problem yesterday, I'm sorry to say I did it again and forgot to take my Warfarin, and I was able to phone her up even though it was a different day and speak to her, so that is very reassuring.

The con, of course, is the cost. The machine is expensive, and that's the initial outlay, and then there're the testing strips, a very contentious issue. Initially, I was prescribed the strips on prescription, and about 18 months ago that policy changed and I was informed that I could only have 12 strips on prescription per year, on the basis that 'one size fits all' and this was fine for the people who only need to test themselves once every four to six weeks. So I weighed it up and decided that although they're extortionately expensive, it was worth buying them, so I'm now doing this. The GP who's in charge of the anticoagulant clinic will not budge on the issue and I know that my CCG will not budge on the issue, so, unfortunately, I have to accept that at the moment, with the present economic climate, there is nothing I can do about it, but it does outweigh, as I say, having to go to the clinic every week.

My anticoagulant clinic is very clear that I have to sign a contract and if I break that contract in any way they will not allow me to self-test. They're very adamant on that, which, as I say, given the dangers of Warfarin, I think is understandable.

Under the terms of the contract, I have to attend the anticoagulation clinic every six months and I have my machine tested against theirs to see if my machine is working properly. And I'm pleased to say that so far it has tallied with the clinic machine and it's been fine. Also, under the terms of the contract, I'm given a specific time, date, at which I have to phone up with my latest result to be told what dosage to take, and I do that.

And the only time - which has been very, very seldom - I have broken that rule is perhaps when it's been a weekend. The Yellow Book, of course, is a godsend, and I then look at that and see what dosage I took when my INR was within that range. And obviously any support or changes or anything, then I can easily speak to my clinic, but as I say, I think that's where I know I am very, very lucky.

And then tips for success! Well, I was a teacher and one of the things we drummed into all our children was 'Read the instructions, read the instructions, read the instructions.' There's a very good DVD that comes with it, there's a very good manual, and my advice: if you've got a memory like mine, keep the manual and the machine together in the same place, never move it, leave it there all the time, and you can't lose it. And then you need patience, it takes a long time to get used to it. I thought I would never do it, but I managed in the end and now I can do it in my sleep.

And then finally, you obviously can't put the test strips and the prick test needles into the bin, so you'll have to get in touch with your local council to see what they do for disposal. The bin my council gave me was that size, which took up a large chunk of the room, so I just go to my local Sainsbury's and buy one of these little bins that's about £2, and then when it's full I phone the council and ask them to take it away.
That's all I've got to say, but I hope it's of some help to those thinking of doing it.

Chairperson (Professor Graham Hughes):
Thanks very much indeed and it's nice to get the practical side of it like this. Thank you very much for coming.

Our last speaker is Ann Sumra from the London Support Group, who is going to tell us how to work with your health professionals.

Ann Sumra:

How to work with your health professionals

Thank you. Right, as it says in my brief, I've actually seen this from both sides, because I am a paediatric physio, although I've had to give up work, and I'm also a physiotherapy teacher, so I've seen this from both sides, both as a health professional and as a patient, which has been a very interesting journey.
I'm just going to say a few points that I feel are pertinent and I hope they'll be useful to you, and if not, there we go.

Doctors and health professionals want to do their best for us, but are not gigantic computers and cannot know everything. It's important to consider how they feel when we come with our possibly superior knowledge of Hughes Syndrome. Although I am using the word doctors, please take it to mean all health professionals.

Ten years ago, when I was first diagnosed, I was confused. I had no idea how I was going to manage this condition. This was before there was much knowledge around. Although under the care of a haematologist, I had been referred back to my GP. I had a look at the list of names in our clinic and picked one. I walked in and said, 'I have been diagnosed with a condition called APS, do you know about it, or can we learn together?' She has been fantastic supporting me, as we did learn together. But then she went on maternity leave. When I saw a new doctor I did the same. She said, 'That's alright, I come from Southwark and I have been to Professor Hughes' GP seminars.' So the awareness campaign is making progress.

So how can we help ourselves to have good relationships with those who care for and about us? One thing I would like to point out is that doctors get frustrated too, if we don't improve or if things don't seem to be falling into place, and I think that's something that perhaps as patients we forget, that the doctors get just as frustrated as us when they can't make us better, because that's what they came into medicine to do, and I think we sometimes don't appreciate that.

All the points on your sheet – you've got a Hughes Syndrome Foundation sheet here in your pack – are very relevant and do help communication. Many of the points here actually help us to gain information, whereas I think sometimes the most important thing is for us to be able to give the right information to the doctors.

I know we do get emotional in clinic situations, GP situations, I know I do myself, it's par for the course, but in my experience from both sides of the fence, we can get better results from our appointments if we can be factual rather than emotional. For example, give your doctor a brief, clear description of symptoms, rather than saying, 'Well, I think this, I think that.' Say, 'I have this, I have this. This is how long it lasts for. This is what's going on.' Also, the tone of your voice and your body language are really important, because if you come in with a very aggressive approach it can make a doctor really defensive before you've even started having your appointment. I find it's also helpful to use 'I' messages rather than 'you' messages. For example, 'There is no way you can understand how bad I feel,' could be stated, 'I am not feeling well. I need some help,' which is a much less aggressive form of going in.

I found this quite useful. This is what we learnt on our Expert Patient Programme: think about PART, P-A-R-T: Prepare, Ask, Repeat and Take Action.

When you're preparing for an appointment or a meeting with a health professional, you need to prepare. You need to be specific, have your information and questions ready, and the most important at the top, because you may have a list of 13 questions, even, and sometimes we have, but you want to have the ones that are most important to you at the top so that you can get the answers that are most important.

Don't always expect to cover everything on your list, and you may, if you've been told to take printed off sheets from the Hughes Syndrome Foundation, leave them with the doctor to read, don't expand your results, don't expect the doctor to suddenly have a pile of papers thrust at them and then be able to immediately understand what's going on.

Try to give them time and say, 'This is the information. Can I come back in a week?' or something like that, to give the doctor time to look at what's going on. Some GPs give double appointments. My surgery certain does and if I'm ringing up for an appointment, I say, 'Can I have a double appointment?' and they say, 'Fine,' and then that's all right. Or else they may accept that you need more than one appointment and that's fine too.

So then having prepared, when you get into your consultation, Ask is the next one. And again, be specific, know what you want to ask, not a vague idea, 'Well, I'd like to know about this,' but actually know what it is you want to ask and what you want to do. And then when the doctor's spoken to you and given you information or you're discussing your case, repeat back to him or her, or however it is, what you think they've said. I think this is a very useful tool and some people call it reflecting, in counselling, or like a mirror.

This gives both of you a chance to clarify or correct information which he may have said in jargon or you may not have understood. If you reflect it back to him then there's a chance that you can get things right. And then finally, Take Action, T. Decide with your doctor what your next move is, whether you're going to have blood tests, medications, physio, anything like that, so that it's very clear exactly what you are going to do, what the doctor is going to do.

And then finally a word on anticoagulation clinics, which our previous speaker was speaking about: I found, in my experience, it's very hard for nurses in the clinic to understand us Hughies with our high INRs. They're so used to dealing with other medical conditions where INRs are much lower and blood is much more stable. They also find it hard to understand how we fluctuate. I actually self-test and often when my INR is going like this, they'll say to me, 'What have you done? What have you done? What have you done differently?' And I'll say to them, 'Actually, it's the way it is, there's nothing I can do about it and it's just the nature of the beast.' But I do believe that they want the best for us too, just like our health professionals. Education from us is vital here and requires gentle techniques. Try to be human and have a laugh and get them on your side.

When I ring up with my results and they say, 'Oh yes, Mrs Sumra,' I say, 'Hello you kind people who are keeping me alive,' and then I always get a laugh and a smile, and then they remember you and you cease to be just a name and a number on their list, 'This is so and so,' because they have so many people. In the clinic, and when giving blood, I always try to greet them and the technicians with a smile, because it's fairly demoralising when they're just going through the clinic like this, taking blood, taking blood, and everybody just stomps in, and I think the previous speaker was saying about smiling, and I think that's very important, if you smile at people they generally smile back at you, even if they don't realise they're doing it, and that will give their day a lift.

And finally, and I think perhaps most importantly, if you get a good appointment, or find a good health professional, please do comment on it. People are so quick to criticise, in my experience, and are not so ready to praise. When I was working in Physio I used to love it when I got a thank you and some affirmation that I had helped someone. Everyone loves and needs praise and we need to be grateful that we have a health service, even if it falls short of expectations more often than not. It is made up of people, after all, and they have their own lives too.

I just hope this has given you some food for thought and I wish everyone well in their Hughes' journey.

Chairperson (Professor Graham Hughes):
Well, thank you very much indeed. We've got to pack in some important questions now in a short space of time, so what the team have done is to put together some questions to start with, but if any of you have questions that you're itching to ask, grab Kate or any of the team.

So let's start. I'd like the other speakers to come up if they will, or if we can call on any of them. So, would you read out? Beverley, come on up. Okay, the first question?

Question and Answer Session:

Kate:
So we've got a selection of questions that were sent in in advance, so we'll address those to the panel and see who takes them. So, to start with:
Q1: Are there any precautions which you would recommend for those with APS when undertaking endurance sport?

Professor Beverley Hunt:
Do more of it! Sport is fantastic because it does stimulate clot breakdown, but the most important thing about endurance sport is people don't tend to drink enough, and outside of Antiphospholipid Syndrome we've had a run of runners and cyclist who've been going more than six to eight hours, who just haven't drunk enough, and they've had a clot, they've had a DVT, or even a really high clot in the inferior vena cava. So please, if you're going to do sport, and you're fit enough to do it, will you please drink enough. You're meant to drink at least half a litre an hour if you're doing endurance sport. I see lots of people nodding – good, it's great!

Kate:
Moving on:
Q2: Is there any further ongoing family research in terms of families with Hughes Syndrome and zero negative Hughes Syndrome, taking into account the other diseases in the wider family, such as Lupus, Sjogren's, thyroid problems, etc?

Chairperson (Professor Graham Hughes):
A good question. So family studies, there are lots of family studies going on, and a lot of them very poor, very poorly thought out, but I think people are recognising, amongst our trade, that this often a familial disease, and in the family you may not just have someone with Hughes Syndrome but someone else with another autoimmune disease like low thyroid or MS or Lupus. And that's why I'd be very grateful again if all of you who can fill in this questionnaire, because it will give us a little bit of insight and I promise you, if we get any statistics out of it, we'll come back and let you know what we've found.

Professor Munther Khamashta:
About three years ago, when we became interested in the sero-negative concept, we had ethical approval from St Thomas' Hospital to bleed some of you and keep the blood for genetic study as well. We did the testing, so far, but we didn't do the genetic studies, so the fridge is full of plods with some genetics to be done. Okay, it will be done.

Kate:
Another family-related question:
Q3: Should we test our children?'

Professor Munther Khamashta:
No, if you don't have symptoms there is no evidence that testing the children is going to help, unless there are symptoms. This applies to Lupus as well. One in five patients with Lupus, the children will have antinuclear antibodies but that doesn't mean they have the disease, so I don't think we should screen the children and we don't do it routinely, unless there are symptoms. Do you agree, Graham?

Chairperson (Professor Graham Hughes):
No, I don't agree. I don't agree! I think we underestimate the worries that parents have about their teenage children. I think you're absolutely right on the statistics, that it is not so common a thing, but I think if the patient genuinely has, and particularly a girl rather than a boy, because of the worries of a future pregnancy, when the periods start, in the old days that's when we used to test for Lupus, because it's rare to get good positives earlier than that. So I think if you have a daughter who is 13 and is starting to develop severe migraines or features that Mum has got, I think there is possibly a reason to be more positive there. I don't really disagree.

Kate:
Moving on:
Q4: Is it okay to take Melatonin?

Professor Munther Khamashta:
I don't have experience with it. Beverley, Melatonin?

Professor Beverley Hunt:
I don't have any experience on it.

Chairperson (Professor Graham Hughes):
No, I don't. I know pilots use it for sleepiness, but if you look at Melatonin, the bottle, many of the bottles say don't take it if you've got Lupus. Now I've never understood this, and many of my Lupus patients take it

quite happily if they have sleep problems.

Kate:
One patient says:
Q5: During my research into APS, I discovered something called Harris Standards. Could you explain what this is and how it relates to APS?

Professor Munther Khamashta:
Nigel Harris was the, I call it the architect in the laboratory. Graham was at the bedside with the patients and Gharavi and Harris were in the laboratory. His background is biochemistry, so before becoming a physician he was a biochemist. And working in the laboratory with Graham, they standardised this test, Anticardiolipin. Antibody test in 1982, '83, '84, and he distributed from our laboratory to around the world, this wasn't only to the UK, around the world, standard for people who would like to test for this, in Chili or the United States or Japan, to use a standard to distinguish between positive and negative, and has become known as Harris Standard, and still called Harris Standard in some publications. So he is the ((?)) and has now moved away from Antiphospholipid Syndrome but it's still called Harris Standard. It is Graham Hughes Standard as well!

Chairperson (Professor Graham Hughes):
I'll tell you, these two people in my lab were, like many of our research fellows, the crème-de-la-crème, they came on minimum salary, they were motivated, and they were different. Nigel Harris was a poet and wrote poetry, and Aziz Gharavi, who is a Muslim, actually brewed the beer in our laboratory!

Professor Munther Khamashta:
He was a good Muslim then!

Kate:
Q6: Is there a link between and what triggers APS to become catastrophic APS, if at all?'

Professor Munther Khamashta:
This is a very severe form of the Antiphospholipid Syndrome and it affects only less than 1% of the population with APS. In the data available so far, nobody has a large amount of patients. Beverley and us, with Graham Hughes here, maybe we have, over the last 30 years, one per year, maybe we have 30/40 patients. If it's a severe manifestation, clotting problems in the brain level and lungs and kidney at the same time, in a short period of time, and the patient ends up intensive care and unfortunately 50% of the patients die if we don't act quickly.

So there are triggers and there is a register for this disease and it's very rare, there're about 300/400 published around the world. So there is a registry held in Barcelona, one of our fellows, ((Silbera?)), Graham put his photograph there, and he's holding the registry and so far he has about 400 patients, and 50% of those patients who have that syndrome have triggers, and the trigger is usually infection, or, for some reason, the Anticardiolipin was stopped to do biopsy, to do dental work, or whatever, in the past, and the syndrome has happened. There is a trigger in about 50% of the time and infection was one of the major triggers for this.

Kate:
Q7: Severe infections, not a cold?

Professor Munther Khamashta:
No, no, severe infections.

Chairperson (Professor Graham Hughes):
Thank you. Can I just add one question here actually, to Beverley?

Q8: I very much enjoyed your talk on the new anticoagulants, and can you give us just a little insight into how often you change someone, you swap them over from Warfarin to one of the new oral anticoagulants? Is this a regular thing that you're doing now, or is it the occasional patient only?

Professor Beverley Hunt:
So we are putting people in the RAPS Trial, and if they're not eligible for the trial but they have Prepis Venous Thrombosis disease, under the NICE guidelines they actually can go on Rivaroxaban and we need to get permission from their local CCG, and then we can switch them. So quite a lot of the teenagers – and there are lots of teenagers with APS – who can't cope with the Warfarin, it's too much for them at their time of life with all the other pressures, we are switching to Rivaroxaban. So, small numbers, but growing, and it's been fantastic for most of them.

Kate:
One patient asks:
Q9: What do statins do besides lowering my cholesterol levels, and do I need to take them?

Professor Munther Khamashta:
Statins and Antiphospholipid Syndrome is a new field and we think they have a role to play, not only to lower your cholesterol, so if you have high cholesterol you take statins to lower cholesterol and perhaps to reduce the risk of a heart attack. Statins have been used in Antiphospholipid Syndrome in animal models - which was mentioned here by many people - and this showed that you can reduce the size of the clot and the frequency of the clots in animal models. In humans, we have very little data on it, although in the laboratory, giving statins to patients, and maybe you participated in some of the trials, suggest you might reduce that clotting by reducing tissue factor, and this is the Beverley work, by interfering with some of the coagulation and the coagulation cascade.

There is no specific trial ongoing, to the best of my knowledge, in statins in Antiphospholipid Syndrome today. We are using it more and more, more and more. We don't use it in pregnancy because of the fear that it might be toxic, although there are two clinical trials ongoing to show that maybe statins are good to prevent preeclampsia. We have to wait for the results of these specific trials to prove the concept that they might reduce the chance of preeclampsia, but in patients, especially Antiphospholipid antibodies and no clot yet, as you know, we use Aspirin, sometimes ((hydroxyl?)), and maybe in the future we should add statins to reduce the risk.

We don't want you to have the first stroke or heart attack or deep vein thrombosis and then remember to give it to you. So it's not only to lower the cholesterol, to interfere with the coagulation cascade, and maybe reduce the risk of clotting. Maybe in the future we should use it more and more, and Beverley is hinting to

me she's using it more in her clinics.

Professor Beverley Hunt:
So, when they introduced statins they did huge trials, 20,000, 30,000, 40,000 people went into the trials and they showed they reduced mortality from heart attack and stroke. And then they went back and had another look over the next few years, and they showed it reduced the incidence of venous thromboembolism, deep vein thrombus, and pulmonary embolism as well. So they really are very good, and it's not dependent on reducing the cholesterol, it's something else that's happening, and we think it's because it calms down the lining of the blood vessel. And in Antiphospholipid syndrome we're wondering how much the lining of the blood vessel is important in causing the clotting. So we know it has that same effect, well, in the laboratory anyway, doesn't it?

Professor Munther Khamashta:
Yeah, so it's a good question.

Kate:
Q10: Are angina symptoms attributed to APS?

Chairperson (Professor Graham Hughes):
Yes, very definitely. Angina, as I said in my talk, it's been under-emphasised, I think, over the last 30 years, and we've always recognised it, and the book some of you have bought is by a patient, 'More Sticky Blood' I think it's called, and it's by Kay Thackray, and I think it's the best book of all on the sticky blood syndrome. And she, in her book, tells how she had all the neurologic things were prominent, but missing all the time the fact that she had quite nasty angina, which really messed her up going to the shops, this, that and the other, and it's totally gone since she's been treated.

Professor Munther Khamashta:
Can I ask Beverley a question?

Q11: You mentioned NICE is changing and there are guidelines coming for self-testing at home. Are you tackling the ((?)) patient and Antiphospholipid Syndrome? Because the prospect you say is don't use it if you have Antiphospholipid syndrome, the prospect of that self-testing.

Professor Beverley Hunt:
((I know it works very well?))

Kate:
Q12: Can you become tolerant to Warfarin so it's ineffective over a long period of time?

Professor Beverley Hunt:
Not normally, no. So when you start Warfarin you usually need a certain amount, and you'd continue to need. So if you'd got an INR of 3 to 4 with a level of 10 milligrams, you might find if you used other drugs you might need a little bit more, a little bit less. As you got older, you might need more or less, but you shouldn't become tolerant to it, no.

Chairperson (Professor Graham Hughes):
Q13: Can I follow up on that and ask both of you a very difficult thing that we sometimes face, that patients face, is that they are on Heparin, as you've heard today, and do fantastically well, feel sharp, move over to Warfarin, and not so good. And you've got a collection of patients like this, and what do you do in this situation as a doctor in a clinic?

Professor Munther Khamashta:
Graham and myself, at least, we do frequently, both at St Thomas's Hospital, in the private sector, and London Bridge, those patients that we are in doubt whether we should give them Warfarin to start with, we do a short trial, three or four weeks, to try with Heparin, and if they respond well, and usually the response is overnight, quickly, and the following visit, two or three weeks later, they say, 'I feel better.' Then that patient will come to the clinic, saying 'What do I do next? I'm not going to inject myself for the rest of my life.' So we move into Warfarin. The problem I observed, and Graham Hughes observed as well, that some patients respond better to Heparin than Warfarin. Obviously they work differently, and we don't understand why. Now, I have a few patients who wanted to remain on Heparin, and say, 'Well, Warfarin wasn't good for me,' and they keep them with Heparin.

One of my patients comes from Israel, she comes from overseas, you know the patients, and her husband is a haematologist, and she still comes over from Israel to see us, and she had Heparin for 15 years. I'm not saying you should do that all the time, but I tell you the truth, she refused to stop it. I know it's an anecdote and it's not something I recommend, that you take Heparin every day for 15 years, but something we did before, I don't know why some patients respond better to Heparin than Warfarin. Obviously the mechanism is different, they work differently, and some patients are sensitive to Heparin but not Warfarin. Do you have anything to add?

Professor Beverley Hunt:
I absolutely agree. I think most patients are better on Warfarin, but there are a minority, about 2% or 3% that do better on Heparin. I don't know why. And the issue about long-term Heparin is it causes bone thinning, so people need regular – and I'm talking every two or three years – bone density scans. And the other issue is you can switch them over to Fondaparinux, which is the drug I mentioned in my lecture. But again, that doesn't always work as well as Heparin, so it's a bit of trial and error.

Kate:
Q14: Has there been any success treating visual disturbances associated with APS? What treatments were used and did patients respond?

Chairperson (Professor Graham Hughes):
Visual disturbances are common in APS, especially when the patient has not yet been diagnosed or started on treatment. It's a brain thing, it's a neurologic thing, and certainly, anecdotally, the majority improve with visual disturbances when their INR is higher, and some patients are absolutely clear about that.

So the first move is to make sure that the patient is being fully treated, as you would with any other neurologic features. I should mention Plaquenil, as Munther did. Plaquenil is not ocular toxic and the British Society of Ophthalmology say you don't need regular testing on Plaquenil. But the Americans start people on Plaquinil, three a day as a loading dose – I think they're doing it less now – which I think is terrible. What happens, you get a temporary lazy eye, a slight double vision, and the patient says, 'My God,

I'm going blind,' and you lose their confidence, but that's a separate issue.

Kate:
Okay, that's from our pre-arranged sheet. I think if we have a couple of urgent ones in the audience we'll get to them quickly. If you want to raise your hand and we'll dash about to you.

Q15: If you have taken anticoagulants for a long time, does the thinning or less sticky effect reduce the furring up of blood vessels? So are people with Hughes Syndrome more likely to develop circulatory Alzheimer's? Have you seen evidence of this? Is this a licence to eat butter?!

Professor Beverley Hunt:
It's a difficult one. And the actual evidence is that people on long-term Warfarin still get the narrowing of the arteries, they still form the porridge substance called atheroma in the lining, so they still have heart attacks and strokes eventually. Is that enough, or do you want me to say more? It's a difficult subject. But it doesn't guarantee you from that you won't have the build-up of narrowing of the arteries, as you see like furring up inside the kettle.

Q16: I just wanted to ask about Mepacrine. I did try Plaquenil in 2001, but developed the most horrendous reaction to it, and I've been on Mepacrine ever since. I know it's a very, very old drug, but is it safe to keep taking it?

Chairperson (Professor Graham Hughes):
Yes, it's a very useful drug and it's one of the antimalarials. Plaquinil is the best because it's 99% acceptable to people, but rarely you're allergic and that has to be stopped. The second choice is Mepacrine, which is a very old drug and it's quinine, it's horrible it's bitter, it's yellow, and in a high dose it can affect the skin, but in a low dose we use it a lot, especially in patients who've had hair loss or Cutaneous Lupus. But it's getting rather specialised that we often use a combination of two antimalarials to keep the doses of each down. Further question: The reason I'm fed up with it is because I get these horrible black marks and my nails have gone black.

Chairperson (Professor Graham Hughes):
Your nails go black yes. I couldn't answer that. Yes, reduce the dose, don't stop it, do things gently.

Any last questions? If not, I'd like to thank the speakers for today's wonderful meeting and to thank the audience for being so positive and on time.

Thanks a million.