

Telangiectasia Self Help Group

NEWSLETTER NO. 16 - 2008.

Dear Member,

Once again I am pleased to send you our latest newsletter which includes a report from the recent HHT Conference in Capri, Italy. One of our members has written a personal account of her HHT experiences and this is also included. An update on the TSHG website has been provided by our webmaster and news of the HHT mutation database from the S.E. Scotland Genetic Service. My thanks go to Dr. Claire Shovlin and Dr. Helen Arthur for their informative contributions to this newsletter and also for their continued support for the Telangiectasia Self Help Group.

Wonderful news! A new HHT Centre has opened in Hull Royal Infirmary. Many congratulations to all concerned. I have reproduced an article about this HHT Centre from Direct Connection - the newsletter produced by HHT Foundation International, Inc. Dr. Robinson will produce an article for us and I hope to include it in this edition of the newsletter - or I will include it in No. 17.

Our membership is constantly growing and our website provides information on HHT to those who prefer to contact us on-line. Do let us know if you prefer to receive the newsletter in electronic format by sending us your e-mail address.

Thank you to all of you who have sent me feedback on your condition, treatment and experiences of HHT. One of our members would like to get in touch with anyone in our group who has a CAVM as she has recently been diagnosed. Another member has recommended the services of The British Association of Skin Camouflage, P. O. Box 202, Macclesfield, SK11 6FP, who successfully showed her how to apply skin creams to camouflage her telangiectasias.

Our 2nd HHT UK Patients Conference is still being discussed - watch this space .

With best wishes,



MRS DIANA LAWSON,
CO-ORDINATOR/ORGANISER,
TELANGIECTASIA SELF HELP GROUP,
39 SUNNY CROFT, DOWNLEY,
HIGH WYCOMBE, BUCKS HP13 5UQ
TEL: 01494 528047

email: info@telangiectasia.co.uk
website: www.telangiectasia.co.uk

Telangiectasia Self Help Group

Welcome to the website section of our newsletter.

The website has been in operation for some years now and has never been associated with any commercial ventures despite various requests. Frequent visitors may have noticed that we are constantly adding various items onto our website of which anyone that has web access can view.

As some of you may have noticed whilst surfing the net, there is a large amount of nonfactual (unproven) information out there. Our aim is to provide generic factual information for our members of which has been approved by a medical body.

Listed below are a few facts from our website:

The number of hits our website has received for this annual period was 32235.

16th October 2007 was a busiest day for hits which we received 187.

The busiest day for traffic passing through the website was 30th April 2007.

The following breakdown identifies where visitors access:

Front Page	45%
Fact Sheet One	19%
Fact sheet Three	14%
Fact Sheet Four	13%
Fact Sheet Two	9%

Our future plans for the website are, in-order to reduce our outgoings we propose to email our future newsletters to members who provide an email address, however we ask if all members who have an email address if they could email info@telangiectasia.co.uk stating their snail mail address and confirming that they would like to receive all future newsletters in this format.

Also as our aim is "to maintain a register of sufferers and to put affected families in touch with one another" could those members who are willing too email fellow members please confirm this in your email.

As a reminder our website address is www.telangiectasia.co.uk

Matthew Fletcher,
Webmaster,
T.S.H.G.

Telangiectasia Self Help Group

7th HHT INTERNATIONAL SCIENTIFIC CONFERENCE.

The 7th HHT International Scientific Conference was held in Italy on the island of Capri from April 25th - 28th 2007 at the Palazzo dei Congressi. The International HHT Scientific Conference takes place every 2 years and it provides an opportunity for Scientists, Physicians and Clinicians with an interest in HHT to meet and discuss their work. This 7th International Scientific Conference was hosted by the University of Bari Interdepartmental HHT Centre. There were 150 delegates in attendance - who had travelled from 11 different countries - and 61 Clinical abstracts were presented over the three days of the Conference. These conferences consolidate human and scientific relationships between the HHT Community and encourage new research into this disease resulting in the expansion and flourishing of HHT Treatment Centres around the world. It was particularly heartening to realise that many of the original 49 delegates from the very 1st International Scientific Conference held in 1996 in Edinburgh, Scotland were also present in Capri.

After an informal social gathering on the evening prior to the conference a full programme took place with continuous lectures and workshops running alongside each other in Clinical and Basic Research. A chance to look at the posters displaying the work currently in progress was taken during the meal breaks. The presentations were of a very high standard and some reports of exceptional research into HHT instigated animated debate and discussion. Dr. Claire Shovlin presented the results of the work funded by our own TSHG families (see her articles in TSHG Newsletter No. 16) and her findings were well received. In many countries it seems that funding or non-funding is the key to success as the necessary skills required for new research are available. It was also interesting to learn about the different funds available in some countries both from local taxation and from private sponsors. For example, in some countries funding is available for scans, so sufferers are seen and in some cases diagnosed quickly, whilst in other countries this diagnostic treatment is just not available. The Italian Research Programme was explained and 5% of the funds provided by their Government are to be used for Rare Diseases e.g. HHT. (A disease is considered to be rare when it occurs in 5 out of every 10,000 patients, but different countries have differing criteria, therefore treatments vary).

At this conference the involvement and treatment of nosebleeds was particularly focused on, but the specialists are still looking for answers in the research results so that a criteria can be achieved. This area of research will continue and will again be reported on at the next International Scientific Conference in 2009. Dr. Helen Arthur and Dr. Mary Porteous presented their work and their reports are included in this Newsletter. Prizes were presented by the University of Bari for excellence in Basic Science (Poster and Oral Presentation) and Clinical Science (Poster and Oral Presentation).

The future for HHT research is exciting and the HHT patient community worldwide is awaiting the results of the expanding volume of HHT research. We look forward to the future of science leading the way to eliminate HHT and "to wrest from Nature, the secrets which have perplexed philosophers in all ages, to track to their sources, the causes of disease....." (quoted by Sir William Osler at beginning of 1900s).

Many congratulations to the organising committee and to all participants for another very successful event. A special award of thanks to Carlo Sabba from the HHT Treatment Centre at Bari for his unfailing efforts to ensure that this conference was yet another triumph for those working so hard to solve the mystery of HHT.

Diana M. Lawson.

Telangiectasia Self Help Group

Dear Diana

Here is the write up on my condition,

HHT is part of my family history. My Mother and Grandmother had nosebleeds so when I too bled in childhood it was nothing to make a fuss about. At the age of 8 years I had keys dangled down my back by teachers at school during a bleed and various other old wives methods of stopping nose bleeds were tried.

At puberty the bleeds stopped and started again in my early 40's and during the menopause they became a nightmare I became very anemic and sought help. Over the years I was referred to 3 hospitals the doctors did not believe how badly I bled. My nose was cauterized with little effect.

In 1993 I was referred to R.N.T.N & E to see surgeon Mr. David Howard and my life changed. He understood the problem and started lasering my nose and palate to gain some control over the bleeding also I had blood transfusions to help.

Mr. Howard has now retired and Professor Lund now treats me and I can contact the hospital when I need help. I have had a skin graft to the inside of my nose and have had the graft added to as the original graft had shrunk. Treatment with the laser is still needed but only approximately every 10 -11 months.

My husband has made me a Large metal peg to stop outward bleeding and I have used Tranexamic Acid soaked on cotton wool as a plug for a heavy bleed (not needed as much now). I feel enormous guilt that I have passed on the condition to one of my sons and possibly my granddaughter. With the help I have received I can lead a relatively normal life.

Mrs. Ann Price.

N.B. Mrs. Ann Price is one of our members and this is her personal account.

If any member would like their personal account included in the next T.S.H.G. Newsletter I would be delighted to do so.

Hammersmith Hospital
London W12

21st December 2007

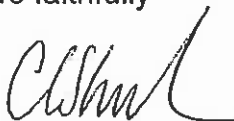
For the benefit of the many individuals who have written or phoned regarding antibiotics and dental measures for people with HHT and pulmonary AVMs, I am pleased to provide an update.

Due to the links between dental bacteria and brain abscess for people with HHT who also have pulmonary AVMs¹, we recommend excellent dental hygiene. You can discuss appropriate measures with your dentist or dental hygienist. Since pulmonary AVMs affect about half of individuals with HHT, we also suggest that all individuals in HHT families pay careful attention to their teeth. This is especially important for children who are developing their tooth-brushing habits.

In the past, we and others have also recommended antibiotic prophylaxis at the time of dental or surgical procedures, and have discussed potential issues with dental braces for children. However, this year I have become aware that many dentists are reluctant to offer antibiotic prophylaxis, even for individuals with one of our cards, as they are aware that antibiotic prophylaxis is no longer completely favoured for prevention of endocarditis (the heart condition which was why antibiotics were first introduced, but not a concern for people with HHT).

I was hoping to have definite recommendations regarding antibiotic prophylaxis and other dental measures to prevent brain abscess for the HHT community by the time this newsletter was sent out. However, discussions with senior British dentists which I initiated following our manuscript acceptance, have not yet reached a conclusion, and are pending publication of the NICE endocarditis guidelines. At this time therefore, I cannot issue our old cards to new patients, and ask that you remain patient while we try to resolve this important issue.

Yours faithfully



Dr Claire Shovlin PhD FRCP
Senior Lecturer/ Honorary Consultant Respiratory Physician
Hammersmith PAVM clinic

¹ Shovlin CL, Jackson JE, Bamford K, Jenkins IH, Benjamin A, Ramadan H, Kulinskaya E. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in HHT. *Thorax* 2007 doi:10.1136/thx.2007.087452

Telangiectasia Self Help Group

Dr Claire Shovlin is pleased to provide you with details of two recently published manuscripts about HHT.

The two manuscripts were published in November 2007 and provide the evidence for recommendations from the Hammersmith PAVM clinic.

We are so grateful to the people who participated, and to the families and friends of people with HHT whose donations made this work possible. Your donations are officially acknowledged on both manuscripts.

Imperial College Healthcare 

NHS Trust

Hammersmith Hospital, London

THROMBOSIS PAPER

Shovlin CL, Sufalman NL, Govani FS, Begbie ME. Elevated Factor VIII in hereditary haemorrhagic telangiectasia (HHT): association with venous thromboembolism. *Thrombosis and Haemostasis* 2007; 98: 1031-1039

HHT is obviously usually recognised as a bleeding condition. We were concerned that some people who we saw developed deep venous thromboses and pulmonary emboli. When this happens, blood thinning treatment with warfarin or heparin is needed, making control of nose bleeds or bleeding from the gut even more difficult.

In this paper, we studied more than 300 people with HHT. All were reviewed in the Hammersmith clinic between 1999 and 2005. Twenty developed deep venous thrombosis between the ages of 36 and 71 years. Some of these were already on transfusions for anaemia. Most of the thromboses occurred in people who were in hospital recovering from illnesses when preventative treatment for thrombosis is given. This was often not given because doctors thought it would make HHT bleeds worse.

We looked carefully at which individuals were most likely to develop thromboses. First, between 1999 and 2001, we studied the blood of healthy people with HHT, and their husbands, wives and our colleagues without HHT. Some of you may remember helping out at your clinic attendance, or on one of our weekend blood taking days. We compared proteins that caused the blood to clot. We found that clotting Factor VIII (FVIII, which when low causes the bleeding disease haemophilia), was actually higher in people with HHT compared to people of the same age without HHT. This was very important as high levels of FVIII is the most common risk factor for thrombosis, and this was also shown in 125 people with HHT with no recent ill-health, or intervention. We are currently examining why this happens in HHT.

Importantly, this study means that just because you have HHT, you should still be considered for preventative treatment against thrombosis at appropriate times, like everyone else, even if this makes nose bleeds a little worse for the few days involved.

STROKE PAPER

Shovlin CL, Jackson JE, Bamford K, Jenkins IH, Benjamin A, Ramadan H, Kulinskaya E. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in HHT. Thorax 2007
doi:10.1136/thx.2007.087452

Most people with HHT are aware that HHT can cause haemorrhagic strokes due to cerebral AVMs, but do not realise that the most strokes in HHT are due to pulmonary AVMs (PAVMs).

In this paper, we studied more than 300 people with HHT, and 219 with PAVMs. All were reviewed in the Hammersmith clinic between 1999 and 2005. Most of the individuals with PAVMs and HHT had no respiratory symptoms, and were unaware they had HHT when they were diagnosed with PAVMs. Fifty-seven developed a brain abscess or ischaemic stroke at some stage, usually before the diagnosis of underlying PAVMs/HHT.

We looked carefully at which individuals were most likely to develop these complications. *Brain abscess* was more than three times as common in men as in women. The bacteria grown from the abscesses at the time of surgical drainage, and the history of dental interventional procedures, indicated that the bacteria causing the abscesses usually came from around the teeth, and travelled to the brain in the blood stream. For *ischaemic stroke*, surprisingly there was no association with severity of PAVMs, nor with conventional stroke risk factors. We did identify an important marker of stroke risk- while we cannot use this yet to predict who will have strokes, or to prevent them, the marker is under further study and we hope will lead to new preventative treatments for stroke.

Importantly, PAVM treatment by embolisation reduced the risk of stroke/abscess. People with PAVMs were more likely to be referred for treatment, when their doctor recognised that PAVMs carried a stroke risk, and we are trying to inform as many British doctors as possible.

Telangiectasia Self Help Group

Dr Claire Shovlin is pleased to provide you with the most up to date information sheet from the Hammersmith HHT/PAVM clinic.

Imperial College Healthcare 

NHS Trust

Hammersmith Hospital, London

Hereditary Haemorrhagic Telangiectasia (also known as Osler-Weber-Rendu syndrome or HHT)

HHT is an inherited condition which leads to the development of abnormally wide and fragile blood vessels. HHT affects approximately 1 in 5,000 individuals. At present in the UK, most people with HHT are not diagnosed, but may be aware of nosebleeds, blood spots (abnormal blood vessels visible on the lips and finger tips), or anaemia. Arteriovenous malformations (AVMs) can also develop in internal organs (see below).

Simple general measures:

- Nosebleeds affect most people with HHT at some time in their lives. Nasal humidification regimes may help. Laser treatment is preferred to cauterisation.
- Anaemia may result from nosebleeds (most commonly) or gastrointestinal bleeding. Iron supplements should be prescribed, and efforts made to find an iron preparation that suits the individual, particularly if transfusions are required.

If someone with HHT has a particular problem, it is best for them to be reviewed by appropriate specialists who should be aware of specific HHT issues.

For people with HHT who are well, the key question is whether screening and treatment of abnormal blood vessels which are silent is appropriate. The frequency of problems caused by HHT is probably over-estimated because so many healthy individuals who have HHT are not known to the medical community. Nevertheless, data from thousands of people known to HHT centres around the world suggest that it is better to know about HHT, and take a few appropriate preventative measures, than to ignore it.

1) Across the world, screening and treatment of pulmonary AVMs is recommended.

- Pulmonary AVMs (PAVMs) occur in the lungs of up to 50% of HHT-affected individuals and are usually silent. Silent PAVMs carry risks of stroke and brain abscess later in life, and these risks can be reduced or abolished by embolisation which is recommended for all individuals, whether or not they have symptoms relating to their PAVMs. In view of the risk of brain abscess in people with PAVMs, and a link with dental organisms, we advise anyone with PAVMs to maintain scrupulous dental hygiene. Antibiotic prophylaxis at the time of dental procedures may be helpful. Further advice from the British dental community is awaited.

Telangiectasia Self Help Group

Imperial College Healthcare 

NHS Trust

Hammersmith Hospital, London

2) In contrast, in Europe and the UK, screening is not offered for other silent abnormal vessels, since there is no evidence that treating is better than leaving well alone for someone without any symptoms:

- Cerebral AVMs affect up to 10% of HHT-affected individuals and usually never cause a problem. In Europe (in contrast to the US), asymptomatic individuals are generally not offered screening because the risks of intervention are considered too high for their low risk of bleeding. Should an individual with known HHT develop epilepsy or sudden severe headaches (which may be a herald of a future bleed), we suggest an urgent neurological referral to exclude cerebral AVMs. Although the general advice is not to screen healthy individuals with HHT for cerebral AVMs, in families where two people have had cerebral haemorrhages, screening to exclude other non HHT-related vascular problems such as aneurysms is recommended, as if found, these would be considered for treatment. The advice not to screen for cerebral AVMs remains under review.
- Hepatic AVMs affect 30-70% of HHT-affected individuals and usually never cause a problem. Liver biopsy should be avoided in anyone with suspected hepatic AVMs. No treatment is recommended except on the rare occasions when severe liver disease develops, and therefore formal asymptomatic screening is not performed.

3) Pregnancy: The overwhelming majority of pregnancies in women with HHT proceed normally. However, there are small but definite risks of maternal complications. We have a pregnancy information leaflet for women with HHT, and recommend that this is shared with their GP, obstetrician and midwife. During pregnancy, haemoptysis should be considered a potential emergency prompting hospital admission.

4) Deep venous thrombosis: Although people with HHT have a haemorrhagic condition, they should not be denied preventative treatment against deep venous thrombosis at appropriate times, for example when immobile in hospital following an operation.

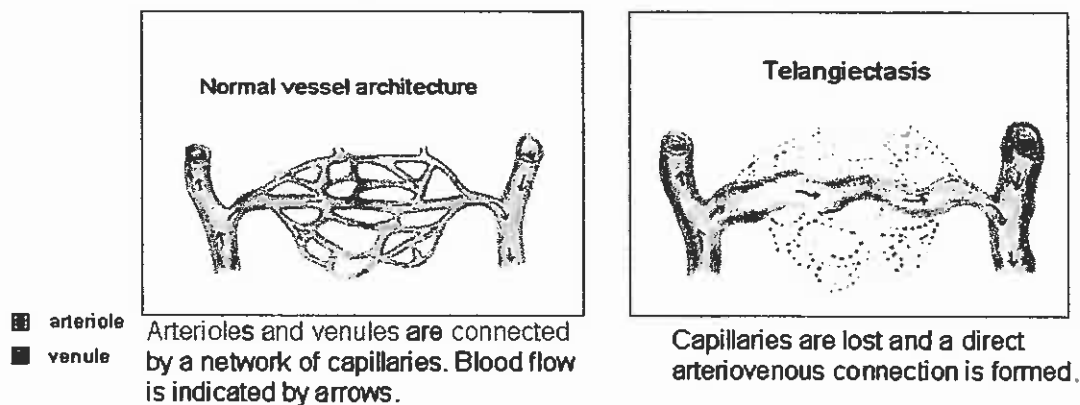
5) Children: HHT is a familial condition, passed from parent to child. Males and females are affected equally. Any child of an individual with HHT has a 50% risk of inheriting HHT. HHT is likely to present with nosebleeds during childhood, but cannot be excluded on clinical grounds even at the age of 30-40 years, when an asymptomatic child of an individual with HHT would still have a 1 in 20 chance of actually having HHT. For any child of someone with HHT, we suggest that 'Possible HHT' is added to their medical records to let future doctors know that the condition may be present. Our paediatricians can review as needed during childhood, otherwise we merely recommend that screening for PAVMs is conducted after puberty.

Dr Claire Shovlin, December 2007

HHT Research Update from Dr Helen Arthur, Molecular Cardiovascular Medicine Group, Institute of Human Genetics, Newcastle University.

My research on the role of endoglin, one of the genes that 'goes wrong' in HHT, began in Newcastle a number of years ago. In 2000, I worked with Dr Austin Diamond and Professor John Burn to derive a mouse model of HHT1, which carries a mutation in one copy of the endoglin gene, to mirror that of HHT1 patients. These mice showed some clinical features of HHT and greatly helped us to understand the role of endoglin in the cells lining the blood vessels. However, it was not suitable as a model to investigate how arteriovenous malformations (AVMs) developed over time. (The figure below illustrates a possible, but as yet unproved, mechanism of AVM formation.) In our first mouse model, HHT-like lesions sometimes took up to 2 years to develop, occurred in only a third of animals, and appeared in unpredictable locations (gut, ear, eyelid or abdominal skin). In order to use this model to investigate the development of vascular lesions, we would require a huge study involving many thousands of animals over a number of years - an unrealistic experiment on several counts, ethical, financial, and logistical.

Cartoon Showing Development of a Telangiectasis in HHT



To address this problem, I have now developed a vastly improved mouse model of HHT1 in collaboration with Professor Christine Mummery. This time the mouse has no endoglin at all - both copies of the endoglin gene are mutated. This is a bit tricky to do because if there are no copies of endoglin the mouse dies early during development and is never born. So we had to get round this problem by using some genetic tricks (known as Cre-Lox genetics) to allow us to remove endoglin after this vulnerable stage of development.

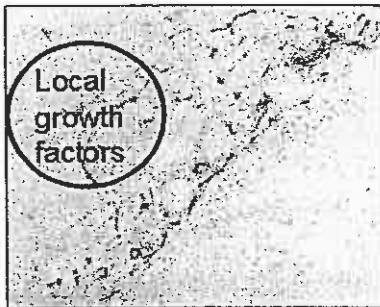
We have found that if endoglin is absent in adult mice, and dermal blood vessels are locally stimulated with growth factor proteins, the vessels dilate in a manner that is strikingly similar to HHT. Growth factor proteins are present in all higher organisms and without them cells will die. However, if we can identify which protein is the key trigger for stimulating vessel dilation we can aim to specifically block its activity.

The figure below shows a very thin (5micrometre) slice of mouse skin taken 2 weeks after stimulation with growth factors. The dilated vessels can clearly be seen in the HHT mouse, whilst they are absent in the normal mouse control. We are now generating 3D images of these arteriovenous malformations to monitor the extent of

Telangiectasia Self Help Group

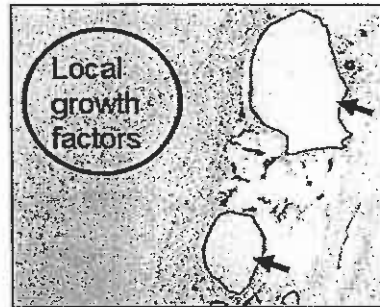
the malformations and the relative contribution of arteries, veins and capillaries. We anticipate that these 3D models will provide valuable information on how arteriovenous malformations develop.

Vascular Remodelling in New Mouse Model of HHT1



Normal Mouse Skin
Normal blood vessels grow in response to growth factors.

Blood vessels are stained brown



HHT Mouse Skin
Blood vessels dilate (arrows) in response to growth factors to form arteriovenous malformations

We are also using this mouse model to investigate which other proteins are altered in these abnormal vessels. In other words if endoglin is absent what other proteins are affected? We expect that this model of HHT will be sufficiently reproducible and controllable to allow us not only to analyse the steps involved in generating an arteriovenous malformation, but also to be useful for future drug screens for HHT therapies. A similar mouse model has been developed for HHT2 in Florida by Dr Paul Oh. These are exciting times for HHT research. With these advanced mouse models we now have the best possible opportunity to understand HHT and contribute to improved future treatments for this disease.

The HHT mutation database – an update

Paul Westwood Clinical Scientist SE Scotland Genetic Service

It is now over three years since the Edinburgh team initially set up the HHT mutation database as a set of simple web pages on behalf of the HHT Foundation. Since then, thanks mainly to an enthusiastic IT team from Heriott Watt University, we have been through two upgrades and now have a database-driven web application including search capability and an HHT-specific



variant submission form. We have also received a lot of very useful feedback which has vastly improved the database since it was first designed. At its conception in May 2005, the web list contained 112 mutations in the endoglin (ENG) gene and 83 in the activin receptor-like protein 1 (ACVRL1) gene. The current database now contains nearly 624 sequence variants (genetic changes) in these two genes, of which 539 are believed to be pathogenic (disease causing). Initially the database, which is run on behalf of the HHT Foundation by the Edinburgh team, was a set of web pages listing the sequence variants identified in the ENG and ALK1 genes. Then, at our last update, we had recently upgraded the site to a proper

database-driven web application. However, now we have just completed a second upgrade to the site which contains a much improved variant submission form, primarily driven by feedback from the HHT community. These changes include the ability to collect proper phenotypic information associated with each sequence variant and also for the first time we're beginning to accumulate observed (as opposed to only published!) variant frequency data as requested by many interested parties. Thanks very much to all the people who have been involved with feedback and ideas for the database. We're still very keen to keep improving the database and the best way to do that is to listen to the users.

HHT TREATMENT CENTER UPDATE

New Center Opens in the United Kingdom

A new HHT Treatment Center of Excellence has opened in Hull in the Northeast of England under the directorship of **Dr. Graham Robinson**.



Dr. Graham Robinson

Dr. Robinson is an Interventional Radiologist who has a long standing interest in HHT. He is a graduate of Oxford University, and trained in surgery in both Oxford and London before training in Interventional Radiology in Birmingham. It was during a year as a fellow in Interventional Radiology in Toronto at the Wellesley and St. Michael's hospitals that Dr. Robinson first met Marie Faughnan, M.D. (A respiratory fellow at the time, Dr. Faughnan is now the Chair of the HHT Foundation's Scientific and Medical Advisory Board.) Dr. Robinson also met Dr. Robert I. White, Jr. of Yale University during this period, and has maintained an interest in HHT ever since.

Dr. Robinson has gathered a multidisciplinary team around him, all focused on diagnosing and treating HHT patients. To contact the new Hull HHT Treatment Centre, please contact Mrs. Hillary Finnis at telephone 44 (0) 1482-674608 or email hht@hey.nhs.uk.

Hull Royal Infirmary, Hull, 44 (0) 1482-674608

Telangiectasia Self Help Group

HULL HHT CENTRE



Prof Alyn Morice (left), Dr Graham Robinson (right) and Mrs Hilary Finnis (front)

The Hull HHT centre was officially recognised by the HHT foundation as a centre of excellence in August 2005.

Consultant vascular radiologist Dr Graham Robinson, who is the centre director, trained at St Michael's and the Wellesley hospitals in Toronto where he developed a special interest in HHT and gained considerable experience in the techniques required to treat vascular malformations of the lung. During his time in Toronto he was fortunate to begin a close working relationship with Dr Bob White of Yale University, a world expert who was one of the founding members of the HHT foundation.

Respiratory professor Alyn Morice has a major interest in pulmonary vascular disorders of all kinds, and has experience of both the Yale and Toronto HHT clinics. Our centre is based between Hull Royal Infirmary and Castle Hill hospitals, the 2 major sites of the Hull and East Yorkshire Hospitals NHS Trust, and in line with other centres around the world draws on expertise from multiple disciplines. We welcome referrals from outside our local region and we do try as far as possible to coordinate

appointments to clinics and for investigations or treatment to keep visits to a minimum. We have a list of local accommodation for relatives and friends accompanying patients.

Team members are detailed on our website at <http://www.hey.nhs.uk/hht/>.

Our contact details are:

Centre coordinator Mrs Hilary Finnis
Centre director Dr Graham Robinson
Tel +44 (0)1482 674608
Email: hht@hey.nhs.uk