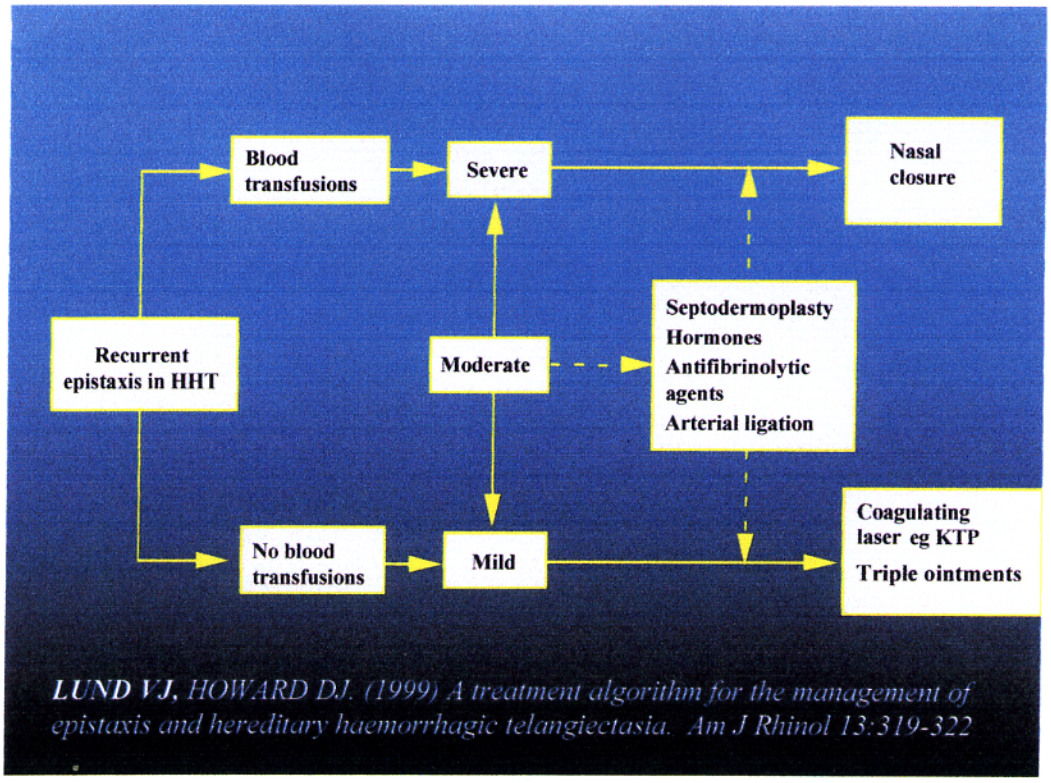
Observation of intensity, frequency and blood transfusion during a period of 4 weeks.					
Intensity of the bleedings (I)		**Frequency of the bleedings (F)**		**Blood transfusion (T)**	
0	None	**0**	None	**0**	None
1	Slight stains on the handkerchief	**1**	1-5 times	**1**	Once
2	Soaked handkerchief	**2**	6-10 times.	**2**	More than once
3	Soaked towel	**3**	11-29 times		
4	Bowl or similar vessel is necessary	**4**	Daily bleeding		

Epistaxis grading scale. *Al-Deen & Bachmann-Harildstad, Rhinology 2008, 46: 281*



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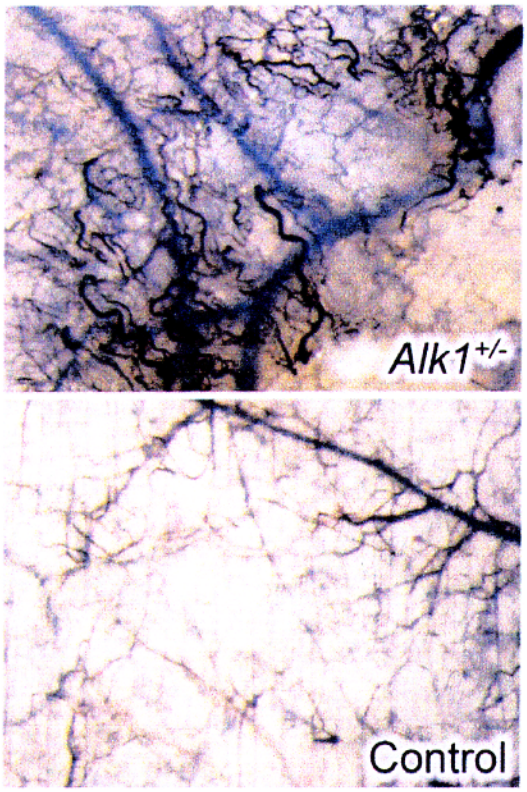
Recent Advances in Understanding HHT Through Studies of Animal Models

Over the last 10 years scientists in Europe, Canada and USA have generated mouse and zebrafish models of HHT with the aim of improving our understanding of the disease so as to better inform clinical therapies. So far, mutations have been introduced into the endoglin gene of mice to model HHT1 and into the Alk1 (also known as Acvrl1) gene of mice, and of zebrafish to model HHT2.
Four scientists presented work on *new* animal models of HHT in the recent HHT meeting in Santander in April 2009 and is summarised below.

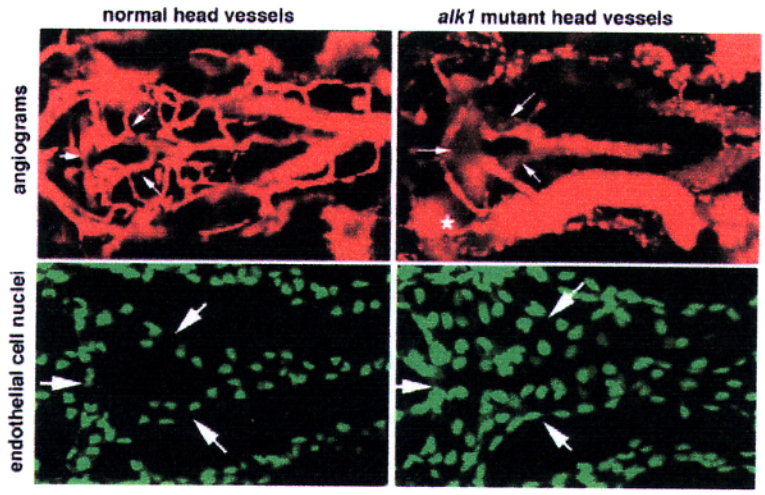
Dr Tsugio Seki (Medical College of Georgia, USA) presented his recent study of mice carrying a mutation in Alk1 that he derived with Dr Oh in Florida. He used an Alk1 heterozygous mouse (this is written as Alk1+/- to indicate one normal copy [+] and one mutant copy [-] of Alk1). It seems that most of the blood vessels in Alk1+/- mice appear to be completely normal, just like in HHT2 patients. However, Dr Seki wanted to know whether additional trauma would bring on symptoms of HHT. He used a magnetic system to apply repeated mechanical stress to the skin of Alk1+/- mice and control mice.



After 4 weeks of this treatment enlarged tortuous vessels were seen in the skin of Alk1+/- mice that were not seen in controls (blood vessels appear black in the images, left). This indicated that environmental factors such as repeated trauma could stimulate clinical symptoms of HHT2.

Dr Beth Roman (University of Pittsburgh, USA) presented her work investigating the development of abnormal blood vessels in zebrafish harbouring two mutant copies of the *alk1* gene. Zebrafish are a great model for studying vascular development because their embryos are transparent, making them accessible for continuous observation, and because development of their vasculature is guided by similar signals to those guiding human vessel development.

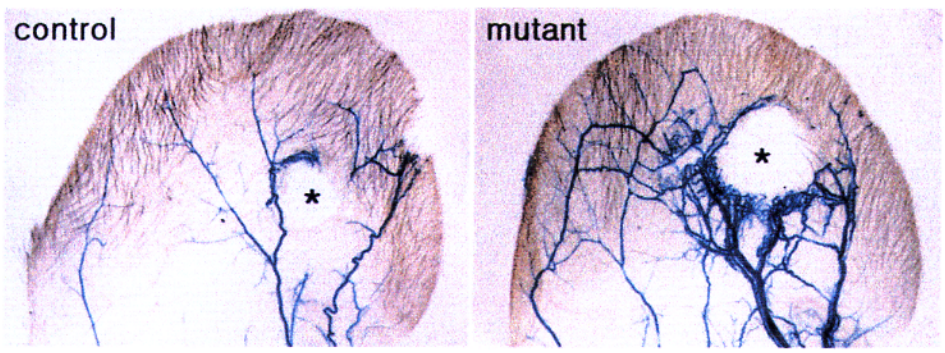
By using a microscope to examine transgenic zebrafish embryos that express fluorescent proteins in their blood vessels, Dr Roman is able to watch new blood vessels develop in live embryos, and to discern differences between *alk1* mutant and normal embryos (See http://www.pitt.edu/~biohome/Dept/Frame/Faculty/roman.htm). The 'HHT2' zebrafish embryos develop enlarged arteries in the head region that contain more cells than normal, and these arteries form shunts with neighbouring veins. Interestingly, stopping blood flow in *alk1* mutant embryos prevents much of the vessel enlargement and completely prevents development of arteriovenous malformations (AVMs). (Yes, you can stop blood flow in early zebrafish embryos with little ill effect, as these tiny animals obtain oxygen from the water via diffusion!) This work suggests that high blood flow through enlarged vessels plays a critical role in inducing AVMs in HHT, and may have implications regarding the management of blood pressure in HHT.



Some zebrafish arteries (eg those denoted by arrows in figure above) become enlarged in zebrafish *alk1* mutants (right panels) compared to wild type controls (left panels), and form abnormal connections to neighbouring veins (asterisk, upper right panel). The angiograms (top), generated by injecting very small fluorescent beads into the vasculature, demonstrate a dramatic increase in vessel volume in *alk1* mutants, whereas the lower images showing the nuclei of the endothelial cells demonstrate increased numbers of endothelial cells in the enlarged vessels.

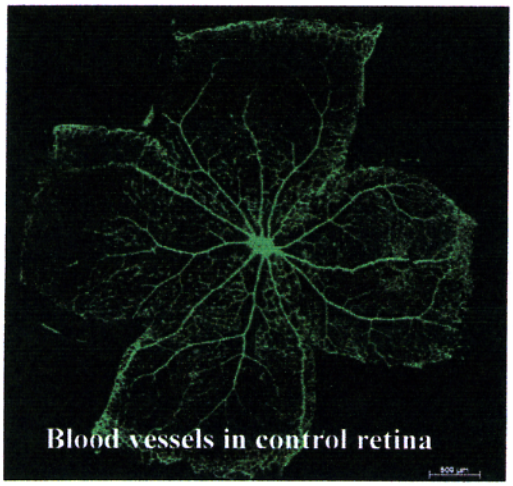
Dr S. Paul Oh (University of Florida, USA) presented his work on mice which had a conditional mutation in Alk1. This conditional mutation allows the Alk1 gene to behave just like a normal Alk1 gene until until the mouse is given a compound that triggers deletion of the Alk1 gene to take place. This occurs in both copies of the gene so the mice end up with no Alk1 activity. These mice die within two weeks with haemorrhages associated with arteriovenous malformations in the lungs, gut and uterus. Large number of arteriovenous malformations develop in the skin, but ONLY if the skin was given a wound.

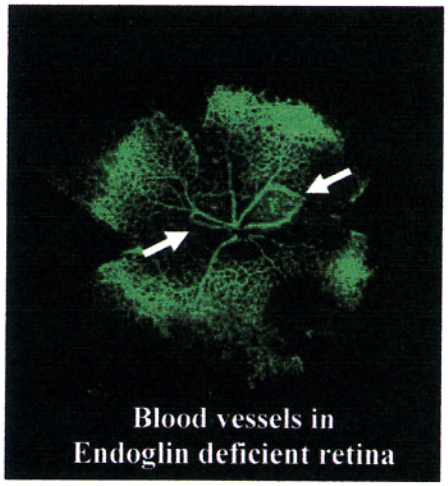
This work suggests that adult blood vessels in skin once formed behave normally even without any Alk1 present. However it also indicates that Alk1 is most needed for proper vascular connections when new blood vessels are forming (eg during development or during tissue repair), and these are also the times when HHT2 patients are most vulnerable to forming vascular abnormalities.



Arteriovenous shunts develop in the blood vessels of Alk1 mutant mice only in the vessels supplying or draining from a wound. In the images above injected latex dye is used to visualise AV shunts shown by double lines (both arteries and veins) in the mutant ear wound model. * indicates the site of the wound.

Dr Helen Arthur (Newcastle University, UK) presented her work on mice that carried a conditional mutation in Endoglin, the gene that is affected in HHT1. This conditional mutation allows the Endoglin gene to behave just like a normal Endoglin gene until the mouse is given a compound that triggers deletion of the Endoglin gene to take place. This 'controllable' mutation allows both copies of the Endoglin gene to be inactivated at a time of choice.





Dr Arthur focussed on the effect of endoglin loss on the formation of retinal blood vessels in mice. Mice are born unable to see and the blood vessels of the retina form in a highly organised way during the first week of life. The upper left image shows normal blood vessels in the retina of a 7 day old mouse. However, large arteriovenous malformations form in the retinal blood vessels in the absence of endoglin (see arrows; note also the densely packed vessels at the edge of the retina). If endoglin is removed in adult life, then no arteriovenous malformations are seen under normal physiological conditions. This indicates that endoglin is required during the formation of new blood vessels and that once the vessels are established then endoglin is no longer essential.

HHT Children's Clinic at Hammersmith Hospital

Children of parents with HHT can be seen in the child-friendly, purpose-built clinic at Hammersmith Hospital.

For the majority of children, this is a check-up to think about what HHT is and to learn about how to keep healthy.

For most children and young people, it is not possible to say definitely that you have or don't have HHT. The wisest approach is to consider the possibility.

There may be a test where a plastic peg is put on your finger to measure the oxygen in your blood. This doesn't hurt as the peg can read the oxygen levels through your skin!

It's important for everyone to look after their teeth.

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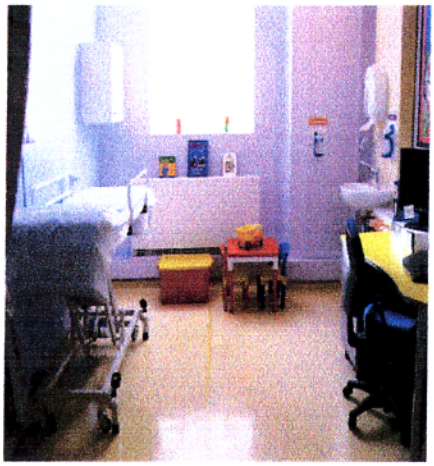
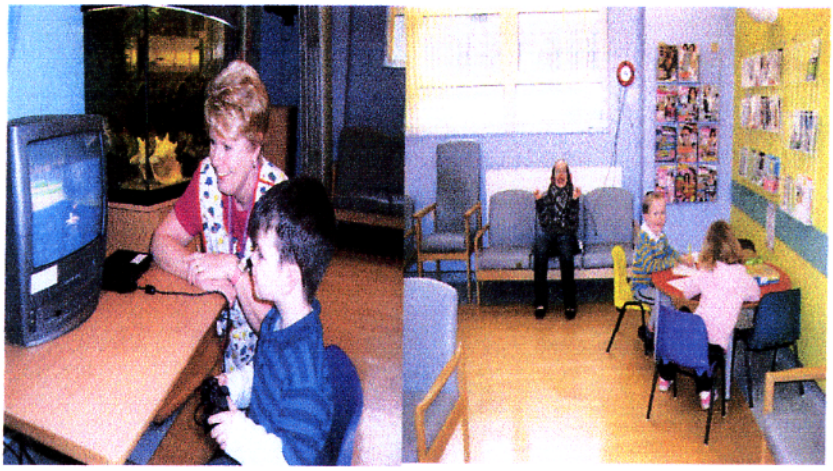
Clinic room in Children's Outpatients



Waiting area



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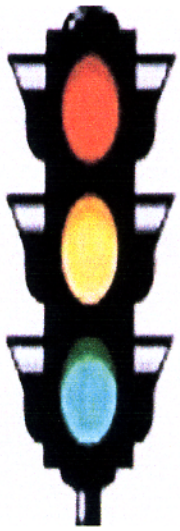

It is healthy to eat lots of green vegetables and fruit, especially oranges. Did you know that drinking orange juice with your meal can help your body absorb more iron?

If you have lots of nosebleeds, it is especially important that you eat foods which are high in iron such as meat, particularly red meat. Your body needs iron to make more blood.

Remember traffic lights – Red meat, Orange juice, Green vegetables.

Parents – remember to keep your iron tablets locked away.

Dr Nicky Coote
Consultant Paediatrician

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Recent Developments at the Hull HHT Centre

Close co-operation with Dr Jenny Thomson, Consultant Clinical Geneticist in Leeds, and Mr Paul Nix, recently appointed Consultant ENT Surgeon in Leeds.

The HHT outpatient clinics continue in Hull with Prof Alyn Morice. We have partial funding for a nurse specialist for the clinic which we hope will allow collection of detailed background information prior to attending the clinic and which should help streamline the process of clinic visits. Chest CT can be arranged the same day as clinic visit if we know this is required beforehand.

Successful introduction of day case embolisation for patients with fewer than 5 uncomplicated PAVMs and appropriate social circumstances.

Dr Graham Robinson
Consultant Vascular Radiologist
Hull Royal Infirmary

Here is the splendid team of Medical Specialists and Organisers at the 2nd HHT UK Patients Conference at Hammersmith on 28th February, 2009.

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