A Bedlington Terrier
Health Pamphlet:

(1) Copper and the Bedlington.
Copper and Bedlingtons

Bedlington terriers are by and large a healthy, long living breed. Those of us who are devoted to this breed know, though, to our cost that we have a problem called Copper Toxicosis (CT). Bedlington breeders have worked very hard to get rid of this problem, been very open about it, and so it is often thought of as “only” a Bedlington disease. However, more than twenty other breeds and some cross breeds have been reported to have CT so it is not just a Bedlington problem.

So..what is copper toxicosis?

Early Research. (the figures in brackets refer to references you can read to learn more)

In the 1970s a lady called Marianna Padula in America had a lot of Bedlingtons become ill with a mysterious liver disease, some of them died (1). She wrote that those which became ill had had something happen to them which caused them upset (stress), for example having puppies or being shown a great deal. She asked for help from some Veterinary scientists who investigated some of the dogs which died. They found that they all had a lot of copper in their livers (2) which had poisoned the liver, caused a problem called cirrhosis and killed the dogs.

Other scientists started looking at the Bedlington problem and found some dogs which became very, very, ill at about 2 to 4 years old and died. They also had a lot of copper in their livers and very characteristic changes in their liver cells.(2 and 3)

Next they took liver samples (a biopsy) from dogs which seemed to be healthy and found that some of these also had a lot of copper in their livers and from very little to a lot of liver cell damage.

In other biopsies of Bedlingtons they did not find any copper or liver damage.

All the dogs which had a lot of copper were called “affecteds” and those which did not were called “normal”.

In 1980 some scientists (4) mated a Bedlington they knew was “affected” (because it had been biopsied and found to have a high copper value and liver cell changes) to a Wire Fox Terrier (WFT), which they believed would not have the problem. They wanted to know if the Bedlington liver problem was inherited. They mated two of the cross Bedlington X WFT puppies together and then biopsied the puppies born from these cross breeds. They found that some had high copper when biopsied and others did not. They came to the conclusion that what had become known as Copper Toxicosis in Bedlingtons was inherited as a “recessive” gene (see below, genetics). They believed that a single gene (the unit of inheritance) had changed from the working “good” form to a non-working “bad” form. Only in dogs which had two “bad genes” was there a lot of copper in the livers. They believed all dogs with a lot of copper, even though they were not ill when biopsied, would later become ill and die.

What do we know now?

1. A high percentage of UK Bedlingtons biopsied in the 1980s and early 1990s (14) had greater than normal amounts of copper in their livers.
2. Of these we know a small but significant number died, between the ages of 2 and 4, from liver failure associated with copper poisoning, true cases of copper toxicosis.
3. As the surviving biopsied dogs which had had high liver copper levels and other signs which led to them being called “affecteds” reached old age, it became obvious that excess liver copper had neither killed them nor made them ill (as far as the owner could observe). They retained copper but it did not damage them enough to make them visibly ill or kill them, these could be called “copper retainers”. Significantly, many had not had the recommended medication which removes copper from the liver (5,6) nor were they kept on a low copper diet.

4. Of the Bedlingtons which have died of CT some have had less copper in their livers than those who have “lived with” much greater levels of excess liver copper.

So we can conclude that excess liver copper is not necessarily a death sentence even without medication and perhaps a great deal of misunderstanding and worry could have been avoided for people if the dogs with high liver copper but no symptoms of illness had been called “copper retainers” and ONLY the dogs which were ill &/or died of liver failure, with high liver copper, had been called “Copper Toxicosis cases”.

**What symptoms would suggest further investigation for possible CT?**

1. Excessive thirst.
2. Swollen abdomen.
3. Loss of appetite.
4. Yellow eye balls.
5. Yellow or very pale gums/mouth.
7. Depression.
8. Weight loss, with or without swollen abdomen
9. Behavioral changes, such as aggression, convulsions and standing staring as if in a trance.
10. Sickness and/or diarrhoea (not just an occasional “off day” but severe and not clearing up)

These are some of the symptoms regularly reported by owners of Bedlingtons who are sick as a result of copper poisoning their livers (true copper toxicosis). It is vitally important that if your dog shows some of these symptoms and appears quite ill, but you have been told your dog/bitch is “clear” or a carrier that you do not tell your Vet. “It can’t be copper toxicosis because mine is 1:2 (or 1:1)” because 1:1s or 1:2s CAN have CT. (see below for more details) and any delay in diagnosis and treatment can be fatal.

**What can I do if my dog is unlucky and is a Cu retainer or develops CT?**

First, do not panic! Many copper retaining dogs do not ever become visibly ill and live to a ripe old age even though they have very large amounts of copper in their livers.

Secondly, if your dog shows signs of liver failure and CT is diagnosed, the high standard of modern veterinary care and knowing what is wrong with the dog early in the illness will often pull the dog through even a severe liver crisis.
Thirdly, there are drugs available to remove the copper. Removing the copper stops the liver being damaged further and there is some reported evidence that once the liver is de-coppered some dogs do not build it up again (7).

Penicillamine is one drug used to remove copper from affecteds. This can have side effects which is why many dogs have been taken off it after a short trial. Owners opted for “a short life but a happy one”… but thankfully in many cases the dogs went on to live normal lives and to a ripe old age. To minimize any side effects the drug dose can be split up into smaller doses, trial and error is needed. Once the copper is well down Zinc may be substituted for the penicillamine. It can take about 2 years for very copper loaded livers to be brought down to a “safe” copper level.

Lastly, recent research suggests that copper damage to the liver can be greatly reduced by feeding low copper diets.

**How can I tell if my dog has excess copper and if there is liver damage?**

Many Bedlingtons with a lot of copper in their livers seem to cope with it and lead normal lives and live to a ripe old age.

If your dog is ill a blood test would show up any signs of liver failure.

It has recently become accepted that about twice the normal level (or greater) of a chemical called “ALT” in a Bedlingtons blood is a useful indication that the dog might have CT, even though there may be no apparent symptoms.(16) Bedlingtons of all DNA types can show excess ALT or other abnormal liver enzymes. Sadly the belief that 1:1 and 1:2, or no deletion 1 deletion Bedlingtons cannot have CT is wrong. The presence of abnormal levels of liver enzymes in the blood indicates the possible presence of CT though the “numbers” or “deletions” DNA results would suggest otherwise.

If the blood tests show the liver is struggling then you would need to follow up with a liver biopsy as this is the only completely sure way to tell if a dog has CT (13)

By definition an “affected” Bedlington terrier is one that has excess copper in its liver (>400μg/g dry weight); furthermore the copper must occur in particular regions of the liver, together with characteristic changes in the liver cells and liver structure- such changes are absolutely diagnostic and can not be confused with any other liver disease .(8) A liver biopsy would also tell you if the liver was being damaged by another disease such as Cushing’s syndrome, when there would not be the same kind of liver damage as found in CT cases.

**Genetics.**

All genes work in pairs, one being part of a chromosome from the dam and one on a chromosome from the sire. It was decided that there was one gene together with its partner on its paired chromosome which would lead to a dog developing CT if the dog had two non-working forms of this gene (4). The “non-working form of the gene” has been shortened to “bad gene” for convenience and similarly the working form of the gene has been called a “good gene”. Hence an affected dog would have two bad genes making up the pair, a carrier a good and a bad form and a non-carrier (or “clear” as it is often referred to) would have two good forms of the gene.

Usually the non-working changed form of a gene such as this is called a “recessive gene” and the working, original or normal form is a “dominant gene”.

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Dominant genes are bossy, if there is one in the gene pair it insists on the cell doing things its way and only if two of the recessive genes occur together, ie there is no dominant present, can they stop the animal working properly in some way.

When reproductive cells (eggs and sperm) are produced, only one of the gene pair gets into each egg in a bitch or each sperm in a dog, so a dog which has one good and one bad gene will produce sperm with either a good OR a bad form of the gene in them. When a mating occurs any egg will also only have one form of the gene until the sperm joins with it and we are back to having a gene pair.

If two bad genes are present in the Dam and Sire (i.e. they are “affecteds”) then all their eggs or sperm and thus all their offspring will have two “bad” genes and will retain copper.

If both Sire and Dam have only “good” genes (are “clear”) then all reproductive cells (eggs and sperm) will contain a “good” gene copy and thus the puppies they produce will all have two “good” genes and they will not retain copper.

If a dog or bitch has one “good” and one “bad” gene then it is called a carrier and about 50% of eggs or sperm will have a “good” gene and 50% a “bad” gene.

To work out the possible results of any mating a “Punnet square” is used. If only one gene pair is involved there are a small amount of possible outcomes from different matings. The most desirable mating is between two “clears”, followed by a carrier and a “clear”. A carrier to a carrier is not desirable, a carrier to an affected is undesirable as about 50% of puppies will be affected & mating two affecteds is highly undesirable.

However, these days it is widely accepted that more than one gene is involved and working out the possible outcomes of different matings where two or more genes are involved becomes very complex.

**How can I know my dog’s genotype, ie is it non-carrier, carrier or affected?**

1. **Biopsy** will identify an affected dog and thus the genotype of that dog, as it MUST have two “bad” genes otherwise it would not be affected!  
   Biopsy can identify non-affected dogs but cannot distinguish between carriers and non-carriers except when used alongside pedigree analysis and/or carefully controlled test –breeding. So biopsy is not a “perfect” test, but it is still the only way of knowing for sure if a dog has a lot of copper in its liver.

2. **The linked marker DNA test.**
   Aware that having to have dogs operated on was not an ideal situation, in the 1990s a scientists in the USA investigated what are called “DNA markers” as a possible way of eventually replacing biopsy. They obtained samples from many biopsied Bedlingtons and some whose genotype was known (eg all puppies of an affected dog must be at least carriers). They then looked for a DNA marker with two types, usually different length pieces of DNA. Each marker was investigated using biopsied dogs and their pedigrees, a useful one would track through the pedigree alongside known good and bad genes, complicated mathematics decide if the marker is useful or not. Luckily one was found quite quickly (9).

   The marker found was not perfect as the two forms were not always inherited with either a good or a bad gene so it is not a DNA marker, it is a DNA LINKED marker.
The two markers were called “1” and “2”, though it could have been e.g. “a” and “b”. What they found were the following combinations of “good” and “bad” genes and markers, deduced using the biopsy results for many animals in each pedigree used.

1:1 and two bad genes (affected)
1:1 and a good and a bad gene (a carrier)
1:1 and two good genes (a “clear”, or non-carrier)

1:2 and two bad genes (affected)
1:2 and a good and a bad gene (a carrier)
1:2 and two good genes (a “clear”, or non-carrier)

2:2 and two bad genes (affected)
2:2 and a good and a bad gene (a carrier)
2:2 and two good genes. (a “clear”, or non-carrier)

Using statistics they found that the 1 marker was most often found linked to a “good” gene and the “2” marker was most often linked to a bad gene but NOT ALWAYS.(9)

If one has a biopsied affected dog, it must have two bad genes. Therefore, if its DNA markers are 1:1 then both are linked to bad genes, both “1”s are bad gene linked.
If it is 1:2 then this dog has a 1 and a 2 marker linked to bad genes.
If it is a 2:2 then this dog has both 2 markers linked to bad genes.
Exactly the same applies to carriers and clears, they can be 1:1, 1:2 or 2:2.

As more information built up on dogs with virtually unquestionably known genotypes, the biopsied affected dogs and almost certainly known “clears” i.e. biopsied normal dogs which had also been carefully test bred, it looked possible to GUESS what the numbers mean with a reasonable degree of accuracy.
The AHT began to use the Americans’ test and looked at a sample of about 40 British Bedlingtons where some had biopsy results and some of known genotype (because they had been test-bred.) It looked as if to GUESS the linkage, based on this small sample, was about 95% likely to be right.(10)

However, surveys of dogs which have enough biopsy information to unequivocally show what their DNA marker linkage is suggest a much greater chance of “guessing wrongly”. The revised statistics indicate that the likelihood of wrongly guessing the linkage in the absence of biopsy information is in the region of 20%, this means about 1 in 5 of dogs with “guessed” linkages will have been wrongly identified as carrier, clear or affected. (5,6,8, Vetgen statistics sheets)

If there is biopsy and test breeding information a breeder has a very useful tool to work out the genotypes of their dogs/bitches and their subsequent offspring. If there is no biopsy or biopsy based test-breeding information then the breeder can make educated guesses, but they could be wrong for at least 1 in every 5 dogs.
SO..the linked marker test, though very, very, useful, is also NOT PERFECT.

3. COMMD1 deletion test.
A group of scientists in Utrecht discovered one gene (11) involved with copper processing in dogs which had a large piece missing in some dogs, this is called a “deletion mutation”, shortened to “a deletion”.
A commercial organization, Natural Fit, tried to produce a test based on “deletions”. The accuracy of the results was questionable and the test was withdrawn. Sadly this means that any certificates issued by Natural Fit must be ignored, they are not valid.

Several groups of scientists (12, 15, 18. Vetgen personal communication) have reported that COMMD1 does not identify the genotype of ALL dogs correctly. A team led by Dr Susan Haywood and a Canadian group are currently looking for another Cu gene or genes.(16, 17) Dr Haywood’s project is funded by a UK KC grant. More dogs are needed for this research (see below).

Some people tried to cast doubt on biopsy results when what they believed were “strange” DNA results turned up, e.g. an affected with a 1:1 or 1:2 marker type or less than two deletions. However, if biopsy was so inaccurate then the DNA test, since it was “discovered” by looking at biopsy results would cease to exist as a viable test, test matings would have to be discounted and so on. Biopsy results are essential for any dogs used in these various research projects.

Vetgen discovered and developed the linked marker test and give advice on using marker information on their website, www.vetgen.com Together with Dr George Brewer they are embarking on similar research for another CT gene. (17)

Until the full genetic causes of CT are worked out a combination of DNA testing plus blood testing and a biopsy if indicated is the best an owner can do to identify the state of their dogs’ liver. An initial ALT test will cost about £12. If the ALT is twice normal or higher, which shows there is liver damage but it does not show the dog has CT, ask your Vet to contact Dr Haywood at shaywood@tiscali.co.uk, have the full liver enzyme blood testing done and proceed to a biopsy if abnormal liver enzyme levels indicate the liver is struggling. Only a liver biopsy will show if the liver problem is CT or something else. Your dog could help rid the breed of this terrible problem but as soon as a foolproof DNA test is produced everyone will hear about it!

The role of breeders and owners.

Apart from the technological problems, progress towards a “perfect” test has also been hindered by us, the breeders and owners. Information available to develop new tests is scanty for three main reasons. Firstly, many dogs with high liver copper values often show no visible symptoms of CT during their lives and eventually die at a “normal” sort of age from other causes. Secondly, many owners and breeders steadfastly refuse to even consider liver biopsy. Thirdly, despite all advice and evidence to the contrary, many breeders and owners still have difficulty accepting the established fact that 1 markers can be found in CT affected Bedlington and that a second gene is involved.

As a consequence we simply do not know how many dogs there are in the breed today with high liver copper values.

How can you help get rid of CT from our breed?

Quite simply the best you can currently do is to help the search for the other gene. If you have a 1:1 or 1:2 (or no deletion 1 deletion) Bedlington get your Vet to do an ALT blood test, if it is twice normal or more contact Dr Susan Haywood and proceed to a biopsy if the liver enzyme testing suggests the liver is struggling.
Once Dr Haywood has all the affected dogs needed to find the other gene and the gene is found she will also need biopsied normal dogs as controls.

References
16. Various reports from Dr S Haywood and Roger Bannister on club websites and in club bulletins.

Useful Information.
1. VETGEN in the USA carry out COMMD1 and linked marker testing, both are done for one reasonable price. For testing kits phone Susan Santoriello at 01234 851647. Credit card payment is possible. Their website www.vetgen.com has some useful information pages.
2. The Animal Health Trust in the UK carry out COMMD1 testing. Phone 01638 751000 .
3. University of Liverpool. Conducting Kennel Club backed research for other genes. Carry out testing of biopsy and autopsy specimens for copper and histology, “a biopsy”, also give advice to Vets on how to obtain biopsy specimens from the liver. Contact Dr Susan Haywood, Dept. of Vet.Pathology, Faculty of Vet. Science, Univ.of Liverpool, L69 3BX