Iatrogenic Disease in Haematology

GPTV

Presented by Dr Alan Green.
Introduced by Dr Paul Grob.

University of London Audio-Visual Centre, 1975.
Made for the British Postgraduate Medical Federation.

Medical Editor: Dr Paul Grob.
Produced by David Sharp.

Black-and-white
Duration: 00:26:27:23

00:00:00:00

<Opening titles>

<Dr Grob to camera>

Last year, we wrote about 280 million prescriptions for our patients and I'm sure the vast majority of them were benefitted from our therapeutic intervention, but a small percentage were considerably harmed by the drugs they took. And the subject for today's discussion is to look at the small percentage and examine some of the iatrogenic disease we may have caused. Now I'm joined in the studio today by Dr Alan Green who's a haematologist and, as well as providing haematological services for a large area in the South Coast, also has a special interest in the sort of problems that may beset the general practitioner.

<Dr Grob and Dr Green are seated for discussion. Camera alternates between the two speakers>

<Grob>

If I may start, Alan, quite a lot of your work is concerned with GP work.

<Green>

Yes, we do about 15 000 blood counts a month in our lab and I should think 5000 of those are directly from GPs.

<Grob off screen and then narrates over illustration of a man facing question mark symbols>

I see, so that's quite a lot. Well, let's open up the discussion. Here's a little chap beset by question marks, isn't he?

<Green continuing narration over illustration>

Well, I think all doctors must feel like this, perhaps most of the time that we're confronted by what seems to be a simple problem, but, in fact, there's a multiplicity of question marks, some big and some small so that in any disease process if we, say, get a blood count back, there will be the major problem of, say, the disease and then the smaller problems of what effect is the treatment having on the count and this sort of thing.

<Grob to camera>

I see. Well, lots of chemicals – and drugs are really no exception – can affect cell metabolism, can't they?

<Green to camera>

Yes, and I think there are so many that it's probably worth breaking them down into three groups because I think this sort of division helps you think about it,…

<Grob off camera>

Fine.

<Green>

… more important remember it. The sort of drug that will cause a direct toxic effect, the sort thing like halothane jaundice, phenacetin kidney, chloramphenicol aplasia of the marrow. Then there's the question of drugs interacting; many drugs will interact with each other. Warfarin is no exception; many drugs will interact with warfarin. And then I don't think we should forget that some drugs can directly affect the laboratory test result.

<Grob>

I see. Well, let's look a little bit more at what's happening at the bone marrow because this can cause aplasia if it's effective.

<Green off camera>

Yes indeed.

<Grob narrating over photomicrograph of bone marrow>

I think we've got a picture of a normal bone marrow. Take us through that.

<Green over photomicrograph, using indicator>

Yes, this is the normal bone marrow. All you really need to see – I think the thing that strikes you is that most of it appears to be nothing. These are fat spaces and

sinusoids by which the cells get out into the blood. And this sort of starry sky, spotted effect in between is the multiplicity of cells actually making the circulating cells of the blood.

<Grob to camera>

I see, so this is a normal bone marrow. I know you've got a picture of someone who, perhaps, has been on something like phenylbutazone where the bone marrow is affected. Let's see if we can see that.

<Green narrates over photomicrograph of bone marrow affected by phenylbutazone>

Well now, in these overall aplasias, where Butazolidin has destroyed the proliferating cells, you can see mostly nothing. It's quite horrifying really that this is just a fatty marrow, with a few blood vessels. And you can see the odd nucleated cell, which is just a stem cell probably. But this is why these people have virtually no circulating cells.

<Grob to camera and then over slide showing number of phenylbutazone prescriptions written in 1970>

Well, I know you're worried about phenylbutazone, but how big is this as a problem? I know we've got some figures about. It's almost 4 million prescriptions, aren't there?

<Green over slide listing statistics for haematological toxic effects, 1964 to 1971>

Yes, in fact, I will only see perhaps 1 a year of toxic complication. The point is that of that nearly 4 million prescriptions, only this many produced a toxic effect. But, of course, they're dreadful toxic effects as you see.

<Grob over slide>

You mean to say, that's a 149 people died.

<Green over slide>

That's a lot of people. And probably the others were in hospital for a long time with perhaps crippling effects.

<Grob>

I see. Now, if phenylbutazone affects the marrow, it does so pretty severely and is this reversible?

<Green>

Well, I haven't personally seen one come round.

<Grob>

I see, so what would your advice be? I mean, should all patients on phenylbutazone have regular blood counts?

<Green>

I think with 4 million prescriptions, this would be a bit difficult. I would sooner approach it from the very practical other end that you only use the butazone group of drugs if you really have to, if you really need that sort of strength of drug, and that you should use it for a very finite time, not to go on beyond it's necessary course.

<Grob off camera>

So not one of the repeat prescriptions going on and on?

<Green>

Well, one would hope not. And if you do have to repeat, I think most laboratories would accept a check every month or sooner if they get a sore throat or blood spots or something.

00:05:25:24

<Grob>

Well, that's a particularly serious sort of aplastic anaemia, but there are other drugs that can cause aplastic anaemia too aren't there?

<Green>

Yes, the commonest drug effect we would see would be, say, a transient thrombocytopenia from a thiazide drug.

<Grob off camera>

Diuretic?

<Green>

Yes or, say, the neutropenia coming on in NeoMercazole treatment, this sort of thing.

<Grob off camera>

Yes, the antithyroids.

<Green>

The antithyroids.

<Grob off camera>

And anticancer drugs can cause…

<Green>

Well, unfortunately, of course yes, no anticancer drug is specific for cancer. It will go for any rapidly developing cell, and the marrow, of course, is rapidly developing. But I usually find people are rather surprised that we don't worry too much about anticancer therapy and this is because they're very rapidly reversible, generally.

<Grob>

I see. Penicillamine is a new one that's on the market, this is causing problems, isn't it?

<Green>

This is a new one. It seems to have a tremendous effect in the rheumatoid arthritis that won't respond to anything else, but it does seem to have something like a 10% toxic effect on the marrow.

<Grob>

So we should be really aware of this possibility?

<Green>

I think this is the main theme throughout this, isn't it, to be aware?

<Grob>

I see. Well, let's move on to haemolytic anaemias.

<Green>

Yes. Well, this is a very wide group and again I think you can bring them down into three. There's this drug methyldopa.

<Grob off camera>

Which is a hypotensive.

<Green>

A widely used hypertensive drug, hypotensive drug. What we find is that occasionally it will give you a downright haemolytic anaemia. And it's a very interesting one because it will mimic autoimmune haemolytic anaemia. Somehow or other, it seems to make lymphocytes produce an antibody to your red cells.

<Grob off camera>

So you really are destroying your own red cells.

<Green>

Yes and you will have the antibody around the red cells. Now, we find this either as a patient who develops the symptoms of anaemia while being treated for hypertension, but quite often we find that this is a completely chance finding, say, in a cross-matching procedure in the blood bank.

<Grob off camera>

He's come in for something else?

<Green>

Come in for something like a hernia or prostate something, we will find incompatible blood and at this point, it would save us a lot to time if people remembered to tell us.

<Grob off camera>

Sure, you'd like to be told the sort of drugs they're on.

<Green>

Yeah.

<Grob>

Well, there are other people who are particularly prone, aren't there, to haemolytic anaemias? I know you were mentioning before this enzymic deficiency.

<Green to camera and then over photomicrograph of red blood cells from patient with favism>

Yes, I think up to now, we've more or less dealt with drugs that affect some people at the moment haphazardly, we're not quite sure why. There are two groups of people who will get into trouble, for sure. Well, now this is a, I hope you're not getting fed up with blood pictures, but I think it helps to see what I see down the microscope. Now, this is a mixed picture as we'd say. There's a normal cell with a little pale bit in the middle and these little round chaps are from a patient with an enzyme deficiency of red cells. It's called favism. They generally come from Mediterranean areas. The point about them is that their cells can't withstand oxidation challenge. So if you put them on certain drugs, they for sure, as we said, will get haemolytic anaemia.

<Grob>

What sort of drugs?

<Green>

This sort of drugs: sulphonamides, phenacetin. There's a very wide range of these drugs. And I think the answer really is that once diagnosed, these patients must be told what they've got, exactly – told the sort of drugs to avoid and probably be given a card or a medical bracelet, or this sort of thing.

<Grob to camera and then over photomicrograph showing sickle cell anaemia>

I see. Well, you did mention there was another group that – sickle cell anaemics.

<Green over photomicrograph>

Yes, this is the other group where they will certainly get trouble under certain conditions. Now again, we see the normal shape of cell and this one, quite obviously, is a sickle cell. It's distorted when the haemoglobin becomes deoxygenated and it actually takes up almost a crystalline form within the red cell.

<Grob over photomicrograph>

I see. Now, what happens to these people when they sickle?

<Green over photomicrograph>

Well now, if you can imagine this sort of cell trying to get through a capillary about 3 mu across, it will literally get stuck in the side of the capillary and then another one will come behind it and you'll finish up with a sort of logjam effect and then you get anoxia, ischaemia, pain and so on.

<Grob>

Right. Now, what ethnic group have these?

<Green>

Well, this is generally people from West Africa, wherever they've gone – the West Indies, South London, wherever.

<Grob>

Right. Now, these people, you can screen for sickle cell?

<Green>

Yes, it's a simple test.

<Grob>

Easy?

<Green>

And, in fact, in Portsmouth we have an arrangement with the school dental officers that any person from this ethnic group is tested at their grammar school or secondary school dental health check.

<Grob off camera>

Why the dental officers?

<Green>

Well, we find that every school child goes through the dental officer at some stage and its, probably, the greatest challenge is dental anaesthetics.

<Grob off camera>

Because of the anoxia?

<Green>

Well, unfortunately, we shouldn't say this but any form of anoxia, even in full operating theatre conditions, you need to put a very high degree of oxygenation to avoid acidosis, to avoid stored blood, for example.

<Grob>

I see. You mentioned acidosis. Now, that can be caused by other things apart from…

<Green>

Well obviously, and the worst combination would be pneumonia. Pneumonia in a child with anoxia, with acidosis, will give a sickle crisis.

<Grob>

OK, so these people should be screened, identified and warned of their deficiency.

<Green off camera>

Yes.

00:11:14:12

<Grob>

OK. Well, let's move on to megaloblastic anaemias. Certain drugs can cause this, can't it?

<Green>

Yes. Now, I think again, sorry to keep grouping things, but to my mind there are two groups here. There are those in which absorption of either vitamin B12 or folate is blocked. An example of this would be hydantoin therapy.

<Grob off camera>

The antiepileptic, yes.

<Green>

Now, that over any length of time will block folate absorption and, using a term loosely, will give you a sort of doctor induced pernicious anaemia.

<Grob off camera>

I see. Do you give them folic acid or … ?

<Green>

Well, there's some controversy about this. I think, generally, most neurologists would or possibly folinic acid. There is some people feel that it might increase the fit rate, but generally our neurologists give them folinic acid.

<Grob>

I see. Now, trimethoprim, that's another one.

<Green to camera and then over photomicrograph showing effect of blocking folate absorption on red blood cells>

Now, this is the other type of drug – I don't know if you know but trimethoprim works by blocking folate absorption in many bacteria. It will block folate absorption in any cell, red cell precursors being no exception, and I think we have a picture of the sort of thing that goes on if you block folate absorption. What happens is that…

<Grob over photomicrograph>

What is this, this is a megaloblast?

<Green over photomicrograph>

No, this is a developing red cell, which has gone bad in a big way. Its nucleoprotein, i.e. chromosome metabolism has been blocked. That nucleus hasn't divided properly. The poor old cytoplasm seems to be trying to divide into four. It's completely the communications have gone wrong. This cell, in fact, will die and the blood will lose probably something like 64 or 128 formed red cells and this is why they get anaemic.

<Grob>

I see. Well, it seems that quite a variety of drugs can cause this sort of picture. Clinically, what is, how is the patient going to present to us?

<Green>

In that terribly vague way that anaemia patients do.

<Grob off camera>

Sort of fatigue.

<Green>

Fatigue, loss of breathness, I mean loss of breath. But I think it's worth bearing in mind a neuropathy, or a peripheral neuritis out of the blue, should alert you, particularly in people on the antiepileptics.

<Grob off camera>

What about jaundice, does it?

<Green>

Well, in the favism group, yes, jaundice is the thing. They behave like the congenital acholuric jaundice. They will suddenly get an attack of jaundice which will be quite benign.

<Grob off camera>

So, any patient presenting with the change in their normal, hopefully, good health should be rechecked by the lab?

<Green>

Yeah, yes.

<Grob>

So far, Alan, we've been talking about things which are essentially rare complications, but one of the constant worries I, and I imagine other general practitioners, always have is our patients who are on anticoagulants and we're thinking they present with something else and we ought to give them something for it. Alternate therapy.

<Green>

And the trouble about this is that so many drugs can affect warfarin dosage in a very dangerous way. I think one really can split it down to three major sorts. One is protein binding. Most drugs, or many drugs anyway, are protein bound and only a small amount is active in a pharmacological sense. Warfarin is one of these. The second group will be those which affect the absorption of vitamin K, which is necessary for clotting synthesis, and if there's less vitamin K, we will need less warfarin for an effect. And the third group is that group of drugs which will actually alter the rate of catabolism of warfarin…

<Grob off camera>

I see.

<Green>

… so that a drug may increase the breakdown rate of warfarin and therefore you need to give more warfarin for a given effect and vice versa.

00:15:09:10

<Grob off camera>

Well, let's focus a little bit on the first cause you mentioned, protein binding.

<Green>

Yes.

<Grob off camera>

I know you've got some rather nice animations of how this actually works.

<Green to camera and then narrates over series of diagrammatic slides illustrating warfarin binding to proteins>

Yes, fine. If you take this as plasma protein, with the black ovals being mostly albumin. If you give a dose of warfarin, then something like 90% goes straight on to that protein and is not pharmacologically active. It's only that one little white sausage which represents warfarin, which will go to the liver, suppress clotting factor synthesis and then anticoagulant.

<Grob over diagram>

That's the crucial part, the free?

<Green over diagram>

That's right.

<Grob over diagram>

Right, OK.

<Green over diagram>

Now, drugs vary in their protein avidity. Some are more avid for protein than others. So let us suppose we give something like phenylbutazone, which is more avid for protein than warfarin. As you see it displaces the warfarin.

<Grob over diagram>

A sort of pecking order.

<Green over diagram>

Yes. Now, all that free warfarin will promptly go to the liver and increase the anticoagulant effect. There will be more clotting factor suppression.

<Grob over diagram>

Right.

<Green over diagram>

The patient will therefore become overdosed.

<Grob over diagram>

Sure. What's the next step, then?

<Green over diagram>

Well, obviously, to reduce the amount of warfarin given by mouth.

<Grob over diagram>

Right, I see.

<Green over diagram>

So that you come back to stage 1 where you've got a small amount of free warfarin to give its effect.

<Grob over diagram>

So, they're stable like that, but when you reduce the…

<Green over diagram>

The second drug or if you reduce the amount of protein in somebody's blood.

<Grob over diagram>

You upset it again.

<Green over diagram>

You'll upset it again.

<Grob over diagram>

I see.

<Green over diagram>

So let's withdraw the drug and, as you see, all the free warfarin promptly goes back on to the albumin and there is no free warfarin; the patient is effectively not taking warfarin.

<Grob over diagram>

I see, so to get back to the final state, you have to increase the amount of warfarin again.

<Green over diagram>

And there we are again with free warfarin allowed to go back to the liver and your patient is anticoagulated.

<Grob>

Well, what other drugs may be protein bound? We mentioned phenylbutazone.

<Green>

I think the most important and worrying is aspirin or any salicylate because the patient may put themselves on it and you know nothing about it, so we would ordinarily warn the patient specifically about aspirin.

<Grob>

Taking aspirin, that sort of thing. Well, what other drugs can affect the clotting mechanism? You mentioned vitamin K synthesis.

<Green>

Well, this is important. The broad spectrum antibiotics are partly protein bound, but of course they do stop bacterial synthesis in the gut. And it's from those bacteria that vitamin K comes, so if somebody's on warfarin, say, a chronic bronchitic might be on it for some weeks – will have a sterile gut and no vitamin K. And their warfarin dosage will gradually shrink over that time.

<Grob>

I see. Quite simple things like liquid paraffin can affect you.

<Green>

Yes, of course, because vitamin K, as you know, is fat soluble, so if you swallow a lot of liquid paraffin…

<Grob>

It gets taken out. What about the rate of catabolism of anticoagulant drugs. What affects that?

<Green>

I think the best known one of these is any of the barbiturates, really, or their analogues.

<Grob off camera>

I see.

<Green>

These, mostly people who go on barbiturates need an increase in their warfarin.

<Grob>

Well, that's reasonably clear. What sort of situations may we be running into trouble?

<Green>

Whenever you put people on something like phenylbutazone, you're going to be in trouble, full stop.

<Grob off camera>

Right.

<Green>

The other places are in old people, sclerotic people...

<Grob off camera>

What liver damage?

<Green>

… nephrotic people, these people with low plasma albumins, I'm thinking of. These people are going to be more sensitive to warfarin anyway, so you'll need to be very careful with these.

<Grob>

So the loading dose is a bit…

<Green>

Yes, you've got a problem here with loading dosage. I often see people of 80 with a post-op DVT, who were given 30 milligrams of warfarin and they go straight down with very little protein.

<Grob>

Go straight down. How quickly do these changes take place though?

<Green>

Well, this is one of the problems. In fact, it's gonna take about 48 / 72 hours. In a way it helps because you have that amount of time to adjust the dose, but on the other hand, it can creep up on the patient and they'll be in trouble before you've forgotten, perhaps, you've put them on the dose, the set of tablets even.

00:19:50:09

<Grob >

I see. So this is a problem really of communication: the patient should know what they should or should not take. They certainly should be informed by their general practitioner what drugs he's giving them. How does this information get across to the pathologist who may be controlling their anticoagulation?

<Green off camera>

Yes.

<Grob>

What do you do in your area?

<Green>

Well, as in most areas, we give the patient a personal dosage record card. And we encourage the patient and any doctor that they meet, or dentist come to that, actually to write little messages to us on it…

<Grob off camera>

I see.

<Green>

… and that they've gone on such a tablet, and then to tell them to come up, say, 5 days later for their first test.

<Grob off camera>

And this works moderately effectively?

<Green>

It works pretty well.

<Grob>

I think it's a very good idea to put the onus on the patient because they're really concerned about this and they don't lose the bit of card, do they?

<Green>

Yes, although we can get into trouble. I had a patient in last week who had suddenly gone out of control after 4 years. Found he was on both ampicillin and phenylbutazone. His blood was unclottable.

<Grob>

I see. What happens when you're greeted with such a situation there and they really do need some dramatic therapy?

<Green>

Well, having seen paraplegia from cerebral haemorrhage in this sort of situation, I treat them very seriously. Stop the warfarin, but that's going to take 72 hours before the clotting factors get up, give them vitamin K to push the metabolic system, but in fact, in this case, give them clotting factor concentrate.

<Grob>

This is what, a sort of whole blood, or got out of fresh blood or …?

<Green>

We tend not to use whole blood very often these days in blood banking. This, in fact, was a factor IX preparation, which we use on our Christmas diseases. It happens to be high in some of the other clotting factors and this man was back to normal within about 6 hours.

<Grob>

Well, we get a lot of data about the various drugs that we're prescribing. We've got MIMS which is very useful preparation. Also each particular drug has a data sheet sent to us. I know you're mentioning a book that you felt was useful to have in the surgery, […]

<Grob over slide>

<Slide>

"Drug Interaction"

Philip Hansten

[…] I think it's this one, *Drug Interaction*.

<Green over slide>

Yes, it sounds a rather sort of specialist book, but there are so many drug interactions nowadays that I think it's worth having around the surgery to look up problems.

<Grob>

So this is one you advise? Well finally, at the beginning of the programme, you mentioned that there were certain path tests which you found very difficult to interpret if we'd been giving different therapeutic agents. B12 assays are difficult, aren't they?

<Green>

Yes, when we were talking about trimethoprim, you remember I said it killed bacteria by blocking folate? Now when, in fact, we do a B12 or folate assay, it is in fact a bacterial assay.

<Grob off camera>

Yes.

<Green>

And you find how much B12 or folate there is in a given serum by how much growth of organism it causes. And if you have a high blood level of trimethoprim or really any antibiotic, you suppress the growth of your testing organism, which will give you a false nil result.

<Grob>

And the antibiotics include things like anti-tuberculous drugs.

<Green off camera>

Yes, the whole range of them.

<Grob>

I see. What about cortisones? They're always worrying, aren't they?

<Green>

Yes, well of course, these – one of the things I find is referred quite often, although not a laboratory test, is this patient who's bruising rather a lot and it's usually the senile type of purpura, particularly on the backs of hands. And these occur in people on prednisolone because of thinning of skin collagen. In fact, it's nothing to worry about; I've never seen it give any major bleeding effect, but of course, whenever anybody gets purpura, you have to look to see whether the platelets are normal. When you take blood counts on people on prednisolone, they always have a neutrophil leucocytosis.

<Grob off camera>

From the drug?

<Green>

From the drug. You know, you may think, oh, they've got a bacterial infection, but about 14 000 white count is standard…

<Grob off camera>

That's fine.

<Green>

… with prednisolone over about 10 milligrams a day.

<Grob>

I know some haematologists don't like us to put our patients on iron without first doing a blood test. I mean, we see an immense number of patients who perhaps are a little bit iron deficient anaemia from menstruation or something like that; what do you advise?

<Green>

Well, I think that, as you say, if it's a very obvious clinical situation, we, in fact, couldn't cope with that number of blood tests. What I would say is that if you're going to do a blood test, I'd rather it be, say, 2 months later when the haemoglobin's come up and they're back to normal so that we can pick out the ones that don't respond to iron, say. Because at round about 10 days, when the blood's responding to iron, it can mimic so many small print bits of haematology, you know – lots of young cells, you think it's a haemolytic anaemia or new cells with hyperchromic cells, you think this is sideroblastic anaemia. It can be a real problem to interpret.

<Grob>

So, you'd like us to wait 8/10 weeks and then you'd be happy, would you?

<Green>

Yes, assuming the patient's obviously doing better.

<Grob>

Sure. Well, Alan, if for your final message … ?

<Green>

Yes. I think I'm very lucky where I work in that the general practitioners know us and we know them, and I think what I would say to any general practitioner is that if the lab doesn't take the initiative to get to know you, you go into the lab and meet the haematologist.

<Grob>

Oh, I see. Well, it's a question of communication. Communication with the patient, communication with the hospital pathologist and also, I guess, maintaining a high index of clinical suspicion, being aware that these side effects may occur and when they do occur, taking rapid and appropriate action. Alan Green, thank you very much.

<Grob>

Thank you, Paul.

<End credits>