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President of the Ulster Medical Society

2019–20
2020–21

Presidential Opening Address
Ulster Medical Society
3rd October 2019

DIAGNOSTICS IN THE FUTURE

So welcome everyone, to the 2019/20 year of the Ulster Medical Society. It is my honour to be the President for this year. So just to start, before we do anything else, these are the members who have passed away within the last year, so I would like to ask you first to take one minute's silence for them, please. Thank you.

So I would like to address you tonight about Diagnostics, and I hope I'll take you on a journey on the diagnostic pathway that we all as medics undertake. So Hippocrates is, of course, the father of modern medicine, and Hippocrates argued that the causes of diseases, or the diagnosis, were physical, and could be determined by observing a patient's symptoms. These ideas of diagnosis and treatment underpin medicine still today.

Disease in those days was thought to be the result of an imbalance between the four humours, or fluids in the human body: black bile, yellow bile, phlegm and blood. If you were lethargic, you had too much phlegm, and the treatment was citrus fruit, but we go on from there: these are my children, and I am the doctor in the house, and much to my embarrassment from time to time, my children have great faith in me as the diagnostician. From anywhere in the world—if you have observed some symptom or sign, you ring mum—so you get a phone call. Therefore I had, "I was out last night, and I think I bit my tongue, and now my face looks funny." "So smile at the mirror." "My face is all twisted" "You've a Bell's palsy." That was right. The same child, a phone call, "I've this awful pain in my chest after playing football, and my friends are going to take me to hospital." I don't know what I'm supposed to do about it, because I'm in Portugal, and he was in England, but that's what happened. So later on you get a text, because they do texts: "Sorry to tell you" (always a bad sign, when your child starts with, "Sorry to tell you"), "Sorry to tell you, but they say I'm having a heart attack, as the heart tracing is abnormal." "What?"—says I, "You're 25!"—and I text back, "You have pericarditis", which was shown to some poor F2, who said, "Yes, that probably is the diagnosis", and she did have… and of course, the worst one—"Mum"—a phone call, it's always a phone call—"I feel awful and shivery all night, and now I have bruises all over me." That was scary, so the instructions were "Move, and get help now", that was right. She did have meningococcal meningitis, and she's fine, but of course, as a haematologist, I first wanted to know what her white cell count was, because I actually had a worse diagnosis in mind.

So this is all about hearing something, and you immediately go down and get a diagnosis, but of course we go further than that. We are all schooled in this, in that we learn and practise the mantra: inspect, palpate, percuss and auscultate, and learn to recognise the signs and make diagnosis until it becomes inherently second-nature, but in order to develop diagnostic skills, we have aids. A prime example is the stethoscope in our generation of medics, where as the 20th century doctor, we all use to listen and interpret and make a diagnosis. My quotation is actually from Middlemarch, which was a very interesting book, which was written for 50 years earlier than the time when she was actually writing it, and it explains about how this new-fangled stethoscope was being used to make the diagnosis.

But the diagnosis in former times involved very careful description of clinical findings, and this is actually fascinating when we think about it. Ronald Ross in his memoirs describes the fever characterised by regular occurrences every two or three days, quotidian, tertian or quartan fever, starting with chills, and then succeeded by high temperature, and the clinicians described this "The disease was recognised from the pattern of fever, and treatment with quinine could be instituted." So we got from that to the treatment, but in the second half of the 19th century, with pathological science, the malarial parasites, of course, were seen with their life cycle, and described, and to this day, in the lab over there, if the diagnosis is suspected of malaria, the first step is microscopy, looking for the parasites to make the diagnosis.

Typhoid fever is another old example, where doctors describe the rose-coloured spots and the high fever. Typhoid was believed to have killed one-third of the population of Athens, including Pericles, in 430 BC, and after this the balance of power actually shifted to Sparta, but it wasn't until the 1880s that again the microscope came into play, where the

causative organism, Salmonella typhimurium, could be identified. Once the organism is identified, this leads to a better understanding of bacterial transmission, and of course, things like the 26-year quarantine of Typhoid Mary, who refused to have her infected gall bladder removed.

So after entering medicine, I decided, when I was a fourth-year medical student, that I wanted to be a haematologist, and for some odd reason I never changed my mind. The attraction for haematology was the mixture of science and medicine, leading to a diagnosis. The haematologist starts with access to the microscope, where the blood is examined, and hopefully a diagnosis made—and of course, blood is very easy to get your hands on to actually look at down the microscope—and I've found, and have continued to find, this fascinating. You not only see the patient, take a history and examine them, but then the blood is investigated and then hopefully a diagnosis arrived at, and we can see this process back in the 19th century.

John Hughes Bennett, was reputed to be the first to describe leukaemia in 1845 (although Virchow discovered similar results six weeks later, so even in those days there were disputes). But John Bennett, in 1845, at the age of 33, was already a Fellow of the Royal Society, though he was described as a man of brilliance, but short temper; certain of his own virtues, pugnacious and unable to suffer fools—a great team member, that! But he described the microscope findings in a very sick patient, of what appeared to be huge numbers of colourless corpuscles, which were then pus, in other words, blood cells, and actually this patient probably had chronic myeloid leukaemia.

This was the beginning, and over the years leukaemia was sub-typed and defined by the microscopic findings, as were many other haematological disorders. Acute myeloid leukaemia was sub-classified by a group called the FAB Group. This was the French/American/British group, and it was actually, it took till 1976 before this was done, and what happened here was a group of the great and the good assembled, sat round the microscope, looked at cases and decided that there were seven different groups of acute myeloid leukaemia, which could be defined on the basis of their clinical appearance. One of these, acute promyelocytic leukaemia, or M3, is perhaps the clearest example, because you can see easily these big, big lots of granules in the promyelocytes, and this is where you get a definitive picture of heavily granulated promyelocytes, where the morphological appearance defines the sub-type, so we've gone through symptoms, signs, and now the microscopic appearance, but there are many other examples of the use of the microscope to arrive at a definitive diagnosis. I will always give you haematological ones, but there are other ones.

One fascinating piece of research is peptic ulceration. When I was a JHO in the Mater Hospital in 1980, we had a surgical ward full of people who had had major surgery for ulcers. Medical therapy in the form of acid-blockers, and later proton-pump inhibitors initially came along that year, but it was the work of Barry Marshall and Robin Warren, for which they won the Nobel Prize in 2005, that showed the Helicobacter infection was the cause, and Barry Marshall drank the H pylori, and developed symptoms of peptic ulceration within five days, and had inflammation and bacteria in his stomach, and then of course you could see in the samples, the Helicobacter.

But back in haematology, there were lots of other attempts to define diseases by looking at the pattern recognition, and this is a particularly interesting example which developed from 1951, so the American haematologist, William Dameshek, published in 1951 a very short paper—it's one page in Nature—where he described and identified the myeloproliferative diseases. These were individuals with elevated red cells, white cells and/or platelets, and these he described as polycythaemia vera, where the red cells were primarily the issue; essential thrombocythaemia, when it was the platelets, and chronic myeloid leukaemia, where it was the white cells, and essentially all he was doing was looking at the clinical picture, the blood count, and what he saw down the microscope, and he divided them up, but it was seminal in what he did.

In order to define it further, what polycythaemia and essential thrombocythaemia and all of them were, they actually produced complicated diagnostic criteria at that stage, where you listed all the different things that you would expect; a raised haemoglobin, white cell count, and platelet count, and the same for essential thrombocythaemia, so at that point, you had a diagnosis which you had to define by a number of very complicated criteria.

But fascinatingly, the other disease that he put in the script was chronic myeloid leukaemia, and this is where the white cell count is increased, and in this case you see on the peripheral blood smear, lots of white cells. The bone marrow is the same, hypercellular, lots and lots and lots of cells, but research got further in this quicker, and the next thing that was observed in these patients, that people with chronic myeloid leukaemia had a funny chromosome 22, down here at the bottom, and a funny chromosome 9, and in fact this is what's called the Philadelphia chro-

mosome, as it was first described in Philadelphia and Edinburgh, at the same time, but it's always been known as the Philadelphia chromosome, and over the decades, this chromosomal change has been dissected at a molecular level, where the reciprocal translocation … so what you get is the two bits of the chromosome have two genes. The two genes come together, and then the genes form RNA, and the RNA is called the BCR-ABL fusion gene, and this RNA makes an abnormal protein, which drives the disease. So, two bits of the chromosome switch over, you get a new fusion gene and a new fusion protein, and that drives the disease.

This is really important, because we're now down from the cytology to the molecular level, because you then can develop a drug to block the action of this new protein, and guess what?—that gets rid of the disease; and these are the STI, or Tyrosine kinase inhibitors, and have changed the treatment of this disease, so you get a detailed diagnosis right through to treatment.

But there were other people who did other things as well, looking at diagnosis. This is Sir John Dacie, who was considered the father of British haematology, and I went to work in the Hammersmith in 1989 as a senior registrar, when he was still around, from time to time. Incidentally, one of my mentors, Dr Brian Mullally, informed me, when I said I was going to get a job in the Hammersmith, he had never actually spoken to a doctor before who was going to be paid to work in the Hammersmith. Everybody else had just gone to observe, but Sir John Dacie was around, although he was long retired, and was still a great influence, and one of the things that he and his colleagues had described world-wide was the rare and fascinating disorder, paroxysmal nocturnal haemoglobinuria, where very occasional patients were seen who had produced red urine in the morning, and often had devastating haemolysis. Now, these were very rare patients, but they collected up these patients from all over the world, did their laboratory studies, and spent a long time showing how the red cells were lysed in an acidified serum, which is what you're supposed to see in the diagram at the bottom. And they collected the patterns of disease in great detail, and that's why some people described these people as stamp-collectors, because they were actually collecting up very clear patterns of disease, but again, in the 1980s and '90s, the molecular lesion was described, and what you found was that these people had acquired mutations in a particular gene, the PIGA gene. Approximately 100 mutations were described, and then you see what happens; in normal cells, there's an anchor onto the red cell membrane which binds various proteins which are required on to the red cell surface, but the patients with PNH have a mutation in that gene, therefore no anchor, the anchor proteins are not synthesised, they float off, and the red cells are then broken down by complement, because they don't fix as they normally do. So again, once you get to the molecular lesion, you can actually work out what is going on, so these are just examples.

But let us look now at how the diagnosis has developed in some of the other cases. This is acute myeloid promyelocytic leukaemia. If you remember, I had that nice morphology at the beginning, but again they found the genetic lesion, a 15/17 translocation, and then they found the two genes that were fused together, the promyelocytic leukaemia gene, and the retinoic acid receptor gene, and this gives a new fusion gene, new RNA, new protein, and again you can treat the disease by giving these patients a tablet called ATRA, and that actually blocks the action of the protein and the cells mature, so again you get a full diagnostic pathway, and then through leading to treatment.

So cytogenetics and molecular diagnostics have led to a much greater understanding of acute myeloid leukaemia, I've given you examples, but this is the WHO 2016 classification of leukaemia. Do you remember the FAB classification had seven types? It now goes on for about four pages, with all the different subtypes, and what I've shown you at the top is many of the ones where the specific molecular lesion is defined. And this is important, because of course we're now developing therapies against these, and this is where we're getting to precision medicine; but there are many types, as you can see at the bottom, where you're still relying on the description, and the molecular lesion is not yet defined.

And what about myeloproliferative neoplasms? Molecular genetics have contributed quite an amazing amount in the diagnosis of these in this century. So this was discovered in 2005 in patients with myeloproliferative neoplasms, where they were discovered to have a mutation in a gene called JAK2, or Janus kinase 2, and that's a picture of the god Janus up at the top, because Janus is the god of doors, and therefore looks in both directions, and these genes are called after them.

And what they discovered was that in many of these patients, they had a single point mutation in this JAK2 gene, and this picture shows the base which has changed is highly conserved across species. That tells you this must be important, and in fact it is, because when you look at JAK signalling, you can see

how this leads to cell proliferation. So this is a normal cell sitting resting, then you get a cytokine coming along, and fixing to the surface, auto-phosphorylation of JAK and then signalling, but if you have a mutated JAK with the B617F mutation, you get what's called a constitutively active protein. It's turned on all the time, and it's signalling all the time, and this actually leads to the pattern that you see in the disease, where with the turned-on protein, you then get the signal and you get increased production of cells. So you see, you get from finding the lesion back to why there's too many red cells, too many white cells or too many platelets.

So the discovery of the JAK2 mutation, and then subsequent mutations in MPL and CALR genes, has meant that the diagnostic criteria for polycythaemia vera and essential thrombocythaemia could be simplified and clarified, and this is what we've got now for polycythaemia vera. All you need is a raised haematocrit or a raised haemoglobin, and the presence of the mutation, and that's enough to know that you have an acquired disease; essential thrombocythaemia the same, but the question is not over there, because that then raises the question, why are we dividing these up? Is there a difference between PV and ET, if all you need is an abnormal blood count and the mutation, and that actually is still up for debate, and this is where we are on the diagnostic pathway. Is this one biological disease with an acquired mutation, or are there other factors that come into play?—and this suggests some of the factors that may come into play that we don't know about yet, there may be further mutations, but the question is, what do you call the patient, do you call them PV or ET, or does it matter?

So now I want to take you sideways to think, I've shown you lots of nice pathways of things that we do know the diagnosis, but what about some other things, and I'm going to give you some examples of things that we might need to look at further. In haematology, we always have a nice time, because these patients come in and they tell you, I'm all aches and pains, and I've got fibromyalgia. I have to say, we need a disease like that in haematology as well, one where you can, that's what you've got, that's why you're tired, go away. But anyway, they all have fibromyalgia, so this interests me. So I looked this up, and the explanation on the NHS website says, you have lots of aches and pains—yes, we have that—and this is the definition on the NHS website; severe pain in three to six different areas of the body; a milder pain in seven or more; symptoms at a similar level for at least three months, and no other reasons found. So in my book, there's a long way to go with the diagnosis there—we need more [?] tests, but that's perhaps a little facetious, but there are other things that cause the same sort of problem, and this is one that we get in haematology again. And what you see in this bone marrow aspirate is a phenomenon called haemophagocytosis, where you can see here a macrophage is eating the red cells, and then destroying them, and you can see that in bone marrow, but there is a phenomenon where patients present with this scene in their bone marrow, and catastrophic illness, which is said to be a rare immune disorder where the body reacts inappropriately to a trigger, such as infection. The microscopic phenomenon of haemophagocytosis is seen. In children, this is clearly described with an associated genetic disorder, but in adults, they usually don't have that, and we end up with diagnostic criteria, as you can see on the other side of the slide. The people ringing us on call get very excited about the high ferritin, but there's lots of reasons why the ferritin can be high, and you're supposed to have haemophagocytic lymphohistiocytosis if you have five out of eight of these things. Most of them are tests we don't usually do, and there are lots of other reasons for this phenomena. If you have a lymphoma, you will often have some of this in the bone marrow, so I think this is not sorted out, we do not know what this disorder is, or what we are dealing with.

So that's where we are, so what I want to do now is look to the future, but the problem we have is that things come along, and they become absorbed into our zeitgeist without us noticing, so let's look at some examples of some things that have changed in my lifetime. So first of all, cars, so when I was houseman in the Mater, I got one of these—the orange Beetle thing—and that was your raison d'être. As soon as you were 17, you got a driving licence, you wanted to get a car, because that was the way of getting around, but where's it going in the future? Well, electric cars are cars like this, where you don't have to drive at all, so the machine does it for you, and that will change everything. My children can drive, but only because I kicked them hard to learn to drive, and they live in cities and they're not that worried about it, whereas we had to learn to drive, because that was the way to get a car and to get around. Think of other things—phones. Alexander Graham Bell, a wonderful invention—we got our first phone in my house at home when I was 16, and it looked like that one there. They haven't changed for 30 years. I was actually already a consultant for several years, when somebody gave me one of the bricks—fairly useless, it was—to contact people, and now, of course, we all have these things in our pockets, which are absolutely phenomenal. The

Encyclopaedia Britannica at your fingertips, they're everything else, but we don't work out how these have changed our lives. They just come along and we absorb the technology, and we don't think anything of it, and we can't really think back about what it was before we had our mobile phone. Younger members of the audience have no concept of not having a mobile phone in your pocket, and there are lots of other examples with this.

Do you remember the car journeys that used to go, "You can't drive and you can't read the map"?—and now, of course, all you do is put it in the phone, and the phone gives you the diagnosis. It tells you where to go with your GPS. It'll even talk to you, to do this, so these are all examples of how things come in and how they change things, without even us really noticing, so what I wanted to think a little bit is about, in medicine, how things will change and how they might change, so in medicine, we were all brought up on the stethoscope, but one of the issues is, is the stethoscope of the 21st century actually going to be point-of-care ultrasound?

Should we be teaching the medical students all how to use this?—because this enables us to look rather than listen, that's if you could use one of them, and the patient can actually share the experience. So the use of the ultrasound will become a core competency for physicians, so imagine a future where, instead of getting your stethoscope to go on your ward round, which we actually very rarely do now, that you have a small ultrasound machine in your pocket.

But back to the microscope, my beloved microscope, so the microscope is moving on. There are lots of technology where you do this automated image analysis, so instead of me looking down, the machine looks at thousands of cells and analyses them, and can tell you what sort of cells there are, so that may be where things go, but is it good enough? Well, the debate in haematology is when will the microscope be dead? When will it be redundant? And of course, that will be an ongoing debate, but the idea is, the microscope is basically giving you the phenotype—that's as far as you can get. Are you going to get to a biological cause?

There are other things happening as well. We've talked lots about molecular genetics. There will be more and more and more of molecular analysis. This is next-generation sequencing, and this is actually a panel that we run, where we run a number of genes looking at people with erythrocytosis, and we want to know, have they a number of specific genetic types. So instead of doing other tests, you just do the panel, see what genetic defects you've got.

But when you can do this massive amount of genetic technology, lots of things come out. So this is a study actually done four or five years ago now, where 18,000 people had their whole genome sequenced, and what they found was that the older you were, the greater percentage of the population (these are all people with absolutely normal blood counts) who had acquired mutations that were associated with haematological malignancy. And in fact if you look at this, the graph takes up as you go towards the end, and people over the age of 90, 10% of them had nasty-looking mutations.

Now, nobody knows what to do with these. Nobody knows yet, because this is not disease, although there are age-related clonal haematopoiesis clinics being run in some places, but nobody actually knows whether this will bring about disease, or will we have treatment at some point that will remove these clones? So we will get more and more information, but what are we going to do with it?

And again, we can take this much grander, so the stamp collectors, I'll get killed for calling Sir John Dacie a stamp collector, but the stamp collectors, basically what they did was, they collected data, and of course, we're in the age of big data. I was actually at a meeting recently in Sweden, and some guy was standing up talking about how he was going to collect all the information from the population, and all their laboratory information, and he was going to have data lakes, he was going to fish data out of the lakes. He would have a bucket, a central bucket and a shared data lake. The point is that huge amounts of data, with computing power to deal with it, and of course that takes us to algorithms, because this all leads into algorithms, and finally, of course, to artificial intelligence, so that is where we're going. What it's going to actually do with some of our diagnostic pathways remains to be seen, but I would make the point that better diagnostics is absolutely crucial, as this leads to better treatment, and I've already made this point, but I would like you to think about this as a last thought, so for many centuries, blood-letting, purging, was what doctors did. They did this because their understanding of disease was that if you took out the bad, that would help. It was awful, it was barbaric, although we still do venesect people in haematology quite a lot, but we're quite nice about it.

But what we do in other diseases at the moment, may well, in a hundred years, appear absolutely barbaric. We take patients apart, and the oncologists do it as well, and give them chemotherapy, and then basically wait for them to get better, and this is a picture of somebody with graft-versus-host disease. It is

quite old, and it is pointed out to me that it's not really as bad as that now, but that's fairly debatable, but I just wonder if we have different diagnostics, will we look at the things we are doing now, and will they appear as bad in a hundred years as bleeding and purging to get rid of the humours appears to us?—I don't know, but I suspect there will be changes. So with all this in mind, I have taken as my theme for the year, Diagnostics in the Future. I have invited people working in various fields, and asked them to look at how their work will lead to new and different diagnoses.